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Editorial. Beyond Red Light, Green Light: Examining the Role of Pharmacogenomics in Evidence-Based Care in Child and Adolescent Psychiatry

Lisa B. Namerow, MD,

Division of Child and Adolescent Psychiatry at the Institute of Living/Hartford Healthcare and the University of Connecticut School of Medicine, Hartford, CT.

Laura B. Ramsey, PhD,

Division of Clinical Pharmacology, and with the Division of Research in Patient Services at Cincinnati Children's Hospital Medical Center, and the Department of Pediatrics in the College of Medicine at the University of Cincinnati, Cincinnati, Ohio.

Salma Malik, MD, MS,

Division of Child and Adolescent Psychiatry at the Institute of Living/Hartford Healthcare and the University of Connecticut School of Medicine, Hartford, CT.

Samuele Cortese, MD, PhD,

Centre for Innovation in Mental Health, Academic Unit of Psychology, and the Clinical and Experimental Sciences (CNS and Psychiatry), University of Southampton, UK; Solent National Health System Trust (NHS), Southampton, UK; Hassenfeld Children's Hospital at NYU Langone, New York University Child Study Center, New York; Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Nottingham, UK.

Jeffrey R. Strawn, MD

Department of Psychiatry and Behavioral Neuroscience in the College of Medicine at the University of Cincinnati and in the Divisions of Child & Adolescent Psychiatry and Clinical Pharmacology at Cincinnati Children's Hospital Medical Center Cincinnati, Ohio

The role of pharmacogenetics in guiding psychopharmacologic treatment for children and adolescents remains elusive for many clinicians. In the absence of a solid and comprehensive evidence base, sufficient training, education, and consensus guidelines, commercial

Correspondence: Lisa B. Namerow, MD, University of Connecticut School of Medicine, Hartford HealthCare/Institute of Living; lnamerow@connecticutchildrens.org.

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promotion of pharmacogenetic testing panels has the potential to become the main source of information for providers. Commonly, these tests include multigene panels and group medications into color-coded bins. These panels include both pharmacokinetic (PK) and pharmacodynamic genes (PD) and, using combinatorial algorithms, direct clinicians to use medications “as directed,” or caution that “moderate gene-drug interaction(s)” or “significant gene-drug interaction(s)” may exist. Many industry-sponsored studies in adults concluded that that when clinicians select medications based on pharmacogenomic guidance, patients have better outcomes,¹ although some caution against this approach.² To provide evidence on the clinical impact and potential of pharmacogenetic testing panels in clinical practice in child and adolescent psychiatry, in this Issue of the Journal, Vande Voort³ and her colleagues report the results of a prospective trial of pharmacogenetically-guided treatment versus treatment as usual in depressed adolescents. The authors randomized adolescents aged 13-18 with moderate to severe major depressive disorder ($N=176$) to treatment guided by combinatorial pharmacogenetic testing that was either available at the baseline visit (GENE arm, $n=84$) or at the 8-week visit (treatment-as-usual arm, $n=92$). Patients and raters were blinded but the treating psychiatrist was unblinded and could prescribe any medication deemed clinically indicated for the patient. Improvement, side effects and satisfaction were assessed throughout the study and at a 6-month follow-up visit. There was no significant difference in terms of symptom improvement, side effect burden, or satisfaction at 8 weeks or 6 months between patients in the GENE and treatment-as-usual arms, respectively. However, significantly more patients in the treatment-as-usual arm received SSRIs compared to the GENE arm (81.5% vs 66.7%). Therefore, there was no significant clinical impact when clinicians used combinatorial pharmacogenomic testing to guide treatment for depressed adolescents. If anything, this guidance influenced providers to more frequently prescribe medications that are not considered first-line for the treatment of depression in youth (SNRIs, atypical antidepressants) and for which double-blind placebo-controlled trials have failed to demonstrate efficacy in depressed youths.^{4,5}

Adding to similar findings from another study examining the impact of P450 gene testing in depressed youths,⁶ the study by Vande Voort³ et al. serves as a warning to our field that utilization of combinatorial pharmacogenomic test results does not improve outcomes in depressed youth and may, in fact, cause clinicians to deviate from evidence-based treatments. However, it is important to note that there is a growing evidence base for the use of pharmacogenetic results for specific medications. In fact, some of our regularly prescribed psychotropic medications have guidance from the FDA recommending dosing modifications (dose reductions or maximum doses) based on pharmacogenetic results (*e.g.*, paroxetine, clomipramine, aripiprazole, citalopram and atomoxetine).⁷

Indeed, the study by Vande Voort³ et al. should be considered within the framework of the broader body of evidence available so far. In just the last five years, prospective and large retrospective pediatric studies have revealed that variation in pharmacokinetic genes were significantly associated with escitalopram-related weight gain,⁸ the trajectory and magnitude of escitalopram-related improvement in anxious adolescents,⁹ escitalopram-related side effects,^{8,9} and sertraline dose escalation.¹⁰ These studies also demonstrate that pharmacodynamic genes (*e.g.*, *HTR2A* and *SLC6A4*) were associated with response in fluoxetine-treated youths¹¹ and the response dose in sertraline-treated pediatric patients.¹⁰

Further, variation in *CYP2C19* was associated with variation in SSRI plasma concentrations in large samples of sertraline- and escitalopram-treated patients. Finally, youths who were *CYP2C19* poor metabolizers had much higher escitalopram exposure than normal metabolizers, with higher risk for side effects and discontinuation.¹² Studies like these are greatly enhancing our knowledge base regarding relevant medication-gene pairing.

So, is there a role for pharmacogenetic testing in child and adolescent psychiatry or should clinicians avoid such testing? The answer to this question is nuanced. Arguably, providers should be cautious when using multigene panel results combined into colored bins suggestive of the familiar childhood game “red light-green light.” Instead, in our view, a rational approach is that when pharmacogenetic testing is available, clinicians use information from FDA labelling, Clinical Pharmacogenetics Implementation Consortium (CPIC)¹³ and peer-reviewed studies⁸⁻¹⁰ to identify important gene-medication associations. Then, after careful clinical evaluation and review of the evidence-base to select a medication, clinicians may use the relevant gene results to alter their dosing strategy, their level of monitoring, or select a different medication within the same evidence-based category.^{14,15}

Overall, the important trial by Vande Voort³ and colleagues underscores that—as a field—we must shift our approach to integrating pharmacogenetic data into clinical care. Further, this study helps to support a call to arms for clinicians and researchers. We think that the main priorities are:

- To educate our colleagues and trainees regarding the appropriate application of pharmacogenetic information;^{15,16}
- To collaborate, as a field, to develop evidence-based consensus guidelines on the appropriate application of pharmacogenetics;
- To examine which genes are most relevant to which medications, and the interplay between pharmacokinetics and pharmacodynamics;
- To ensure that pediatric psychopharmacologic trials obtain pharmacogenetic information to understand the genetic contributions underpinning the “rapid responders” versus the “poor responders” or those patients that need to withdraw from studies due to adverse events.

Although it is true that we are not there yet, we may finally be developing the foundation to get there.

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