

Pharmacogenomic testing: aiding in the management of psychotropic therapy for adolescents with autism spectrum disorders

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Abstract: Adolescents with autism have higher rates of anxiety than the general adolescent population. They often struggle to express psychological symptoms verbally where their symptoms may manifest as withdrawal and agitation. Adolescent patients with autism have higher rates of polypharmacy and high-risk psychiatric medication use (eg, atypical antipsychotics) than other patients with psychiatric illness. Primary care pediatricians are at the front lines of psychiatric management for patients with autism. Yet, they have inadequate access to pediatric psychiatry for complex medication management. Pharmacogenomic testing can provide personalized drug metabolism profiles for a majority of psychotropic medications. Primary care based pharmacogenomic testing for adolescents with autism on one or more psychiatric medications may help individualize and optimize complex medication regimens, while promoting drug safety.

Keywords: autism, pharmacogenomic, pharmacogenetic, pharmacotherapy, anxiety, depression, psychiatry, pediatrics

Introduction

Pharmacogenomic testing is a genetic test that helps assess and provide possible explanations for a patient's response or lack thereof, therefore aiding drug selection and dosing for improved outcomes. Although pharmacogenomics testing has been a crucial part in the personalized medicine movement, there is little clarity on how much it will benefit patients with autism spectrum disorder (ASD).

Pharmacogenomics

"Pharmacogenomics," (also referred to as pharmacogenetics) is a relatively new field, which studies how a patient's genes influence drug therapy response. Clinical pharmacogenomics testing has evolved from benchwork to direct patient care testing. It has received increased public attention since President Obama's call for personalized medicine in his 2015 State of the Union Address. Gene testing to understand a patient's genetic makeup permits tailoring the choice of medication therapy and/or dosing to an individual's determined drug metabolism. The patients will benefit through having fewer side effects and lower drug-related costs as a result of shorter hospital stays, reduced medical visits, and reduced medical absence days.¹ Genetic testing assessing common polymorphisms affecting selective serotonin reuptake inhibitors (SSRIs) metabolism may provide guidance to prescribers about individual drug metabolizing patterns for specific psychotropic medications.² Genetic differences have increasingly been shown to play a vital role in the variability of treatment response, optimal dosage,

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and tolerability.³ For example, an ultrarapid metabolizer phenotype to a particular drug can be a cause of therapeutic inefficacy, whereas a poor metabolizer phenotype to a drug carries an increased risk of toxicity.²

The use of pharmacogenomics in ASD

Side effects of psychotropic medications (some of which mimic anxiety-related symptoms such as irritability and insomnia), are related to individual pharmacogenetics influencing drug metabolism.⁴ With the profound side effect profile of atypical antipsychotics, pharmacogenomic testing could serve as a beneficial tool for reducing polypharmacy and negative side effects related to their use among adolescents with ASD. In adult medicine, it is likely that this testing modality will be ordered preemptively to aid in the selection and dosing of psychotropic medications in the near future.⁵ For adults, the Clinical Pharmacogenetics Implementation Consortium Guidelines from 2015 strongly recommends SSRI dosing adjustment based on the rate of metabolism through the CYP2C19 pathway (sertraline, citalopram, and escitalopram) and the CYP2D6 pathway (fluvoxamine).⁶ While specific pharmacogenomic guidelines have not been established for pediatrics or autism, there is precedence for use in these populations. For example, CYP2C19 testing in patients with autism identified a clear disparity in tolerability of SSRI dose titration between ultrarapid and normal metabolizers.⁷ At the same time, studies looking at how drug metabolism rates affect dosing at different stages of pediatric and adolescent development are needed to further refine their clinical application in adolescents with and without autism.⁸ Pharmacogenomic testing has already been specifically applied to the pediatric population for medications other than SSRIs. It has been used to identify patients who are at higher risk of respiratory depression from codeine,² predict toxicity in pediatric patients receiving 6-mercaptopurine and azathioprine, and predict risk for Stevens–Johnson syndrome in patients receiving carbamazepine treatment.^{9,10} There have been case reports where pharmacogenomics testing results were successfully utilized resulting in improved symptom management and overall quality of life among children and adolescents with complex behavior health issues.^{11,12} There is, therefore, precedence in pediatric care for pharmacogenomic testing in high-risk populations. While pharmacogenomic testing must be carefully researched and monitored prior to broad generalization to general adolescent populations, implementing pharmacogenomic testing in adolescents with

autism on one or more psychotropic medications may be warranted because of their high-risk profile.^{12,13}

Complex mental health issues

Data from the Center for Disease Control and Prevention in 2012 estimate 1 in 68 children have been diagnosed with ASD.¹⁴ Comparing to typical adolescents, young patients with ASD have more complex mental health concerns and frequently suffer from comorbid psychiatric disorders such as anxiety, attention deficit hyperactivity disorder, and obsessive compulsive disorder.¹⁵ Agitation, self-injury, and temper outbursts are often manifestations of anxiety in patients with autism who have difficulty verbally describing their symptoms.¹⁵ A practice parameter published in the *Journal of the American Academy of Child and Adolescent Psychiatry* suggests that pharmacotherapy may be offered to children with ASD when there is a specific target symptom or comorbid condition.¹⁶ While adolescents without ASD often have a hard time expressing psychiatric symptoms,¹⁷ adolescents with ASD may face behavioral and verbal challenges that make it even more difficult to describe symptoms. Adolescents with autism may also have difficulty expressing experienced medication side effects.¹⁸ Moreover, presenting symptoms may also vary by sex in ASD, with females tending to show more internalizing symptoms, such as withdrawal and males showing more externalizing behaviors such as aggression.¹⁹ This combination of complex manifestations of psychiatric symptoms and unrecognized side effects requires high levels of medication management expertise.²⁰

Complicated pharmacotherapy

Almost 1 in 10 patients aged 10–19 years are on some psychotropic medication.²¹ Patients with ASD are commonly diagnosed with anxiety and refractory depression.²² Several randomized clinical trials have been conducted indicating that cognitive behavioral therapy (CBT) is associated with positive treatment responses such as reduced anxiety in children with ASD.^{24,25} SSRIs are first line pharmacotherapy for patients with uncontrolled symptoms after behavioral interventions alone.¹⁶ Along with behavioral therapy, SSRIs have been indicated to reduce repetitive behavior among patients with ASD.²⁶ However, only half of pediatric patients with depression or anxiety who are prescribed a single SSRI have full remission of symptoms after 6 months.²⁷ In comparison, only one third of pediatric patients with autism who have anxiety have remission of symptoms with a single SSRI at 6 months. The remainder of patients either cycle through

numerous psychotropic medications due to side effects or are classified as having SSRI failure.²⁸ The side effect profile of SSRIs (such as increased nervousness) may exacerbate anxiety and depression symptoms.²⁹ Patients with ASD are more likely to be on psychotropic therapy for depression or other mental health conditions.³⁰ At the same time, they are less equipped to express potential side effects of medications or have full remission of symptoms with medication.^{18,31} This results in a higher risk of polypharmacy. Adolescents with ASD have higher prevalence of psychotropic use. Analysis of a national registry reviewing children with ASD indicated that >35% of this patient population use at least one psychotropic medication, and ~10% use psychotropic medications in ≥3 major classes concurrently.²³

Antipsychotics, stimulants, anticonvulsants, and antidepressants are often prescribed in combination for symptom control in these patients at much higher rates than the general population.³⁰ Over the past two decades, these psychotropic medications are increasingly being prescribed to children and adolescents with ASD, making polypharmacy among these patients a concerning issue.³² Teens with ASD are more likely to be on an atypical antipsychotic than those without autism.³³ These medications are often prescribed to manage symptoms related to resistant depression and anxiety, as well as behavioral problems in this population.³³ As superior efficacy of combination therapy has been demonstrated among pediatric patients in past clinical studies, pharmacological interventions are often added on top of behavioral therapy to help patients improve their daily function.^{34,35} Guidelines for adolescent depression in primary care suggest that treatment with antidepressants or psychotherapy such as CBT should be offered to adolescent patients with depression.³⁶ According to a 2011 report published by the Agency for Healthcare Research and Quality, 90% of children taking antipsychotic medications would receive an atypical antipsychotic for mostly off-label indications.³⁷ However, limited clinical data evaluating acute and long-term risks place these adolescents at a greater chance of undertreatment or overtreatment, in addition to long-term side effects.^{30,33} While regulatory approval for new indications depends on large randomized controlled clinical trials, studies in adolescents with autism have been limited in size and scope.³³ Other factors that intensify polypharmacy in this patient population include adolescence, handicap, and group home environment.³⁸ Because it may be very challenging for patients with ASD to express anxiety symptoms resulting intrinsically or from medication, a vicious cycle of chasing behavioral symptoms (unknowingly resulting from medication side effects) further

exacerbates psychotropic polypharmacy. With psychotropic medication's profound side effect profile (such as sedation, weight gain, metabolic disorders, hyperprolactinemia, movement disorders, and QTc prolongation),³⁹ it is imperative to maintain doses as low as possible while optimizing therapy for the best outcome.

Struggles of providers

Primary care providers are at the front lines of ASD management in the pediatric population. Families often have longstanding trusting relationships with them and often seek guidance from them both pre- and post-diagnosis.^{40,41} Pediatricians are encouraged to refer more complex patients, including those diagnosed with behavioral health disorders such as ASD, to mental health providers who practice in a multidisciplinary care team; the child and adolescent mental health workforce can currently care for only 10% of these patients, and they have limited tools to guide management during the often long waiting period to establish psychiatric care.^{27,40,42} In a recent study, 63% of pediatric patients with autism reported unmet needs, frequently lacking family services such as mental health and respite care.⁴³ About half of all pediatric patients who are provided a psychiatric referral actually see a mental health provider within 6 months.²⁷ These delays are due to an acute shortage of psychiatric providers who are comfortable providing care to adolescents with autism.⁴⁴

Pharmacogenomic testing in primary care setting

There are positive and negative logistical aspects to ordering pharmacogenomic testing in a primary care pediatrician's office. Over the past few years, the cost associated with pharmacogenomic testing has decreased drastically.⁵ With increased public awareness of such tests, parents and patients may specifically request testing from their provider. Such requests can help caregivers advocate for personalized psychotropic prescribing patterns, but require primary care providers to be familiar with testing. Many pharmacogenomic samples can be collected using a minimally invasive buccal swab, negating the need for venipuncture. Most samples can be processed within 7 days, allowing for real-time medication adjustments. Companies offering these testing services provide a comprehensive decision support analysis to assist in the genomic results interpretation and application to a wide array of medications within the selected therapeutic drug classes. The report is meant to provide guidance in selecting drug therapy based on that patient's specific results. Medicare and Medicaid provide insurance coverage for pharmacogenomic

testing, but many private insurance companies do not currently cover the cost of these tests.⁴⁵ Patients and parents may need to communicate directly with testing companies to determine out-of-pocket costs. These administrative burdens may dissuade patients with autism and their parents from pursuing this testing. Practices may have to facilitate such communication in addition to collecting insurance information for the testing vendor. In addition, outpatient clinics generally need to establish a relationship with specific pharmacogenomic testing vendors to obtain supplies and establish a practice workflow. Individual clinics and providers need to weigh these factors in deciding whether or not to offer these services for psychotropic medication management.

Proposed practice model

While pharmacogenomic testing is an emerging resource, it can be an effective tool for primary care pediatricians to assist in the management of adolescent patients with autism who are on psychotropic medication.¹¹ In our proposed practice, non-invasive gene testings can be offered to patients with autism who are on one or more of these medications. Patients who can potentially benefit from such testings are identified by our clinical staff using electronic health record based population management. Clinical pharmacists then will perform comprehensive medication review and pre-visit planning to further stratify for best candidates. Samples can be collected via buccal swab and are then sent for genetic testing. This testing is used to guide medication changes in patients who have suboptimal control of behavioral symptoms. Standardized behavioral symptom assessments in conjunction with medication monitoring can be used to monitor the impact of medication changes on behavior over time. Psychology practices are already using these tools as part of disease management. Practice guidelines are available, guiding clinicians on the use of pharmacogenomic testing with antidepressants and antipsychotics metabolized through CYP450 2D6 and CYP450 2C19.⁴⁶ Past study on major depression in an outpatient psychiatric practice also demonstrated improved outcomes with the use of pharmacogenomic testing.⁴⁷ While pharmacogenomic testings have been increasingly used for management of psychiatric symptoms in psychiatric practices, they are rarely used in primary care settings. If practices choose to incorporate pharmacogenomic testing, they should collect data on what impact it has on providers and patients so this information can be disseminated. Moreover, concurrent research and policy discussions should be pursued to ensure that this clinical application is optimized for pediatric patients with autism.

Conclusion

Adolescent patients with ASD often suffer from comorbid psychiatric disorders that may be more challenging to manage. They are frequently treated with complex drug regimens and are at increased risk of undertreatment and overtreatment, side effects, and polypharmacy. Although primary care providers are at the front lines of ASD management in this population, they are often overwhelmed and lack the right tools to better care for these patients. Through aiding in drug selection and dose optimization, pharmacogenomic testing may be beneficial in aiding better management of adolescent patients with ASD. Our proposed practice model should be individualized to best meet the needs of each practice.

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Disclosure

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