Intermittent explosive disorder: A study in personalized psychopharmacotherapy

Laura G. Leahy, DrNPc, APRN, PMH-CNS/FNP-BC

Intermittent explosive disorder (IED) is categorized under the disruptive, impulse control, and conduct disorders section of the newly published Diagnostic and Statistical Manual for Mental Disorders (DSM-5). The symptoms of this disorder include recurrent behavioral outbursts that are grossly out of proportion to any provocation or psychological stressors and are not related to any other physical or mental disorder or substance use. These outbursts are not premeditated, and they contribute to significant impairment in the individual’s social, occupational, and interpersonal functioning. IED has a high comorbidity with other mental health disorders, such as mood, anxiety, and substance-related disorders. These episodes may result in verbal and/or physical aggression carried out on people, animals, and/or property, and many patients have reported disruption of their daily work and personal lives.

IED treatments

Approximately 4% to 7% of Americans are diagnosed with intermittent explosive disorder. One way to help identify effective treatments for individuals with all types of diagnoses (psychiatric or medical) is to apply personalized medicine techniques. Personalized medicine is defined by the National Cancer Institute as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.” Patients may present with similar disease symptomatology but vary greatly in treatment response, which can be attributed at least in part to variations in genetics. The Human Genome Project fueled the expanse of personalized genomics, and soon after the sequencing of an individual’s genome became possible, genome-wide association studies were launched to identify common genetic variants and how these variants associate with disease.

Conventionally, treatment has been applied in a “one-size fits all” fashion. Medications have been standardized to target a specific disease or symptom, allowing for minimal individual variation in response to treatment. Personalized genetic information can allow a clinician to adjust therapeutic doses, predict responses, decrease the instances of adverse drug reactions, and create a personalized health plan. This is particularly important with psychiatric illnesses, as many prescribed treatments can have serious adverse effects. Personalized genomics allows a patient and clinician to determine the likelihood of how that person may respond to different treatment options and to choose an individualized treatment plan.

Case

An 18-year-old male presented to the author’s outpatient psychiatric practice for medication evaluation and psychotherapy due to recurrent, violent outbursts with no identifiable precipitant or psychosocial stressor. The patient described “blacking out” and had “no recollection” of the events surrounding these episodes. The outbursts had become increasingly frequent and violent over the last 6 months and ranged from extreme verbal aggression to physically assaulting family members. Family members said these episodes occurred three to four times weekly. Symptoms had been present for years, and family members reported...
that the patient experienced oppositional and defiant behavioral issues as early as elementary school. In more recent years, the patient’s mood had become increasingly “dark,” although without symptoms characteristic of depression.

This collection of symptoms led to a primary psychiatric diagnosis of IED. The patient was adopted at 3 weeks of age with no psychiatric or medical history known about his biological parents.

On initial examination, the patient’s medications included lisdexamfetamine 60 mg in the morning, guanfacine 2 mg twice per day, and quetiapine 300 mg at bedtime. The lisdexamfetamine and guanfacine were prescribed to manage symptoms of impulsivity, inattention, and aggression, which were contributing to his explosive behaviors. The patient reported using quetiapine only intermittently due to excessive sedation. The patient had significant medication trials in his history, including multiple psychostimulant agents, with lab studies and blood draws to monitor drug levels and potential alterations in the functioning of the liver and pancreas as well as white blood cell counts. Fluoxetine and escitalopram produced restlessness and diarrhea. Risperidone, aripiprazole, and ziprasidone caused irritability and weight gain.

Patients with similar disease symptomatology may vary greatly in treatment response.

Genetic testing
Given the lack of symptom stabilization, despite the various psychotropic medication trials, genetic testing was instituted to develop a more...
personalized treatment plan. Genetic testing can be a valuable tool to help determine why a patient exhibits a poor response or adverse effects when prescribed certain medications. Genetic testing was performed using the Genecept Assay to address the need for targeted therapy. The Genecept Assay, Genomind’s core product, is a saliva-based genetic test that helps inform clinician treatment decisions. Once a patient has been identified for testing and consent is obtained, the patient provides a teaspoon of saliva into the saliva collection tube. After the sample is received at Genomind’s lab, the clinician receives the results within three to five business days. (See Genetic variants identified using the Genecept Assay.) The assay is reimbursed by many insurance providers and can be covered through a self-pay option or Genomind’s Patient Assistance Plan. Genomind has a list of preferred providers on their website for patients in search of a clinician who utilizes this type of testing.

The assay revealed the patient to be a carrier of a short serotonin transporter (SLC6A4) allele and a risk variant in the dopamine receptor subtype D2 (DRD2). The patient was also found to be homozygous for a variant in serotonin receptor subtype 2C (5-HT2C).

The Genecept Assay was able to identify variations in genes essential to neurotransmission, neurotransmitter function, and drug metabolism. These pathways impact many different psychiatric disorders from depression to schizophrenia. By identifying where these pathways are being disrupted, clinicians will be able to determine a more appropriate treatment plan and intervention to improve the patient’s symptom management and quality of life.

SLC6A4 is responsible for transporting serotonin from the synapse back to the presynaptic cells. Variants in this gene can alter transcription levels and result in reduced expression of SLC6A4, and ultimately, reduced reuptake of serotonin. Genotyping found this patient to possess one short allele and one long allele variant. The short allele is the risk variant and

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<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Functional significance</th>
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<tr>
<td>Serotonin transporter (SLC6A4)</td>
<td>Long/short (rs63749047)</td>
<td>Reduced serotonin reuptake</td>
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<tr>
<td></td>
<td>A&gt;G (rs25531)</td>
<td></td>
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<tr>
<td>Serotonin receptor subtype 2C (5HT2C)</td>
<td>-759 C&gt;T (rs3813929)</td>
<td>Altered satiety signaling</td>
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<tr>
<td>Dopamine receptor subtype 2 (DRD2)</td>
<td>141 C INS/DEL (rs1799732)</td>
<td>Altered binding of dopamine and antipsychotics</td>
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<tr>
<td>Voltage-dependent calcium channel L-type,</td>
<td>G&gt;A (rs1006737)</td>
<td>Altered neuronal depolarization</td>
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<tr>
<td>alpha 1c subunit (CACNA1C)</td>
<td>C&gt;T (rs10994336)</td>
<td>Dysregulation of sodium channels</td>
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<tr>
<td>Catechol-O-methyltransferase (COMT)</td>
<td>158 Val&gt;Met (rs4680)</td>
<td>Altered dopamine degradation</td>
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<td>Methylene tetrahydrofolate reductase</td>
<td>677 C&gt;T (rs1801133)</td>
<td>Impaired folic acid metabolism</td>
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<td>(MTHFR)</td>
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<td>Cytochrome P450 2D6 (CYP2D6)</td>
<td>Active alleles: *1, *2</td>
<td>Variants can lead to poor metabolism, intermediate metabolism, or ultra-metabolism of certain medications</td>
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<td></td>
<td>*10, *17, *41</td>
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<td>Cytochrome P450 2C19 (CYP2C19)</td>
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<td>Variants can lead to poor metabolism, intermediate metabolism, or ultra-metabolism of certain medications</td>
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<td>Variants: *2, *3, *17</td>
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<tr>
<td>Cytochrome P450 3A4/5 (CYP3A4/5)</td>
<td>Active allele: *1</td>
<td>Increased metabolism of certain medications</td>
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<td></td>
<td>Variants: *3</td>
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has been demonstrated in large meta-analyses to be correlated to slow response, poor response, and a greater risk of adverse reactions with SSRI medications. The patient’s poor response and significant adverse reactions with fluoxetine and escitalopram may be partially explained by this genetic variation. Antidepressant agents that do not primarily target the serotonin transporter may be beneficial in patients who display this variation.

**Neuroleptics**

Neuroleptics antagonize the D2 subtype of the dopamine receptor (DRD2) to produce antipsychotic activity by inhibiting dopamine signaling. This patient has the -141C Ins/DEL variation, which results in reduced in vitro gene expression. Clinical studies have shown that this variation leads to increased risk for poor response and adverse events with antipsychotic medications. The patient’s history of poor response and intolerability to multiple antipsychotic medications is consistent with this genetic variation. Similar to DRD2, the 2C subtype of the serotonin receptor (5HT2C) is antagonized by various neuroleptics. Serotonin influences satiety signaling via this receptor, and antagonism of 5HT2C can lead to increased food intake, hyperlipidemia, glucose intolerance, and obesity. The C allele at the -759C/T polymorphism is linked to weight gain and metabolic syndrome in patients taking atypical antipsychotics. The patient’s symptoms markedly decreased. He and his family reported that over the 3 months since initiation of the new psychopharmacologic therapies based on the results of the Genecept Assay, he experienced only two brief episodes of anger, both of which were less severe in both duration and intensity.

**Moving forward**

Upon achieving a therapeutic level of 1.0 on lithium 600 mg twice daily, this young man’s symptoms markedly decreased. He and his family reported that over the 3 months since initiation of the new psychopharmacologic therapies based on the results of the Genecept Assay, he experienced only two brief episodes of anger, both of which were less severe in both duration and intensity.

**REFERENCES**


The author has disclosed that she has no financial relationships related to this article.