Pharmacogenomics in practice: a case report of personalized inpatient psychiatric care

Given variable response to psychotropic intervention, this case highlights the potential of pharmacogenomics to inform medical decision-making in a male with atypical psychosis and depression with longer-standing attentional difficulties. Likely because of his specific COMT polymorphism and intermediate metabolizing liver enzymes, when the patient’s stimulant medications were titrated to affect for attentional needs, he became psychotic secondary to a hyperdopaminergic state. Past prescriptions of dopaminergic antidepressant agents (e.g., bupropion) likely would have exacerbated further the problem. The patient’s serotonin transporter polymorphism also potentially was associated with SSRI inefficacy and increased side effects. Knowledge of the patient’s genetically influenced departure from average response allowed for personalization of pharmacology with clinical improvement across measures of functioning.

Keywords: inpatient psychiatry • pharmacogenomics • psychosis • psychotropic medications

Case presentation

History of presenting illness
The patient is a 33-year-old single Caucasian male with previous psychiatric diagnosis of attention deficit/hyperactivity disorder, depression and anxiety admitted for comprehensive psychiatric assessment in the context of failed multiple previous medication trials, inpatient treatment and significant disability. He was diagnosed with attention deficit/hyperactivity disorder when he was 12 years old, was first prescribed antidepressants at age 15 and was psychiatrically hospitalized at 16 years for suicidal ideation and self-harm. He reported that at higher doses of stimulants he became psychotic. At admission he was no longer taking stimulants; however, mild psychotic symptoms continued to persist. He had ideas of reference which interfered in his social life and work opportunities due to suspicions that he was being tracked and discerning patterns that led him to believe others were conspiring against him. He experienced anxiety about leaving his home and consequently went grocery shopping at 6 am to avoid seeing other people. He attributed some of his social avoidance to embarrassment associated with his lack of progress in life. However, he also acknowledged finding others annoying.

At admission, his depression was significant including anhedonia, sadness, isolation, guilt, fatigue, hopelessness, intrusive thoughts, ruminations, a recent 20 pound weight gain (which the patient attributed to a recent decrease in physical activity, i.e., staying in bed much of the day) and poor concentration. There was no history of mania. Patient described himself as being anxious and feeling trapped. He denied any history of trauma. He reported intermittently engaging in psychotherapy but nothing intensive. Substance abuse assessment revealed the patient had previous use of marijuana – multiple times daily for several years. He reportedly stopped using marijuana three years prior to the index hospitalization secondary to it ‘not working’ anymore. The patient met criteria for cannabis dependence in full sustained remission. The patient had a history of binge-
type drinking, which included drinking 7–10 beers in one sitting on the weekends. The six months prior to admission, the patient had engaged in drinking 1–2 beers 2–3 times per week. He did meet a criterion for alcohol abuse due to driving after binge episodes.

Past medication trials included: fluoxetine up to 60 mg (discontinued because caused tiredness); duloxetine hcl unknown dose which helped him feel ‘great’ (discontinued for unknown reasons); risperidone up to 2 mg (discontinued because caused sedation); bupropion (unknown does, unknown effect and unknown reason for discontinuing); sertraline 100 mg may have been potentially helpful (discontinued for unknown reasons); possibly buspirone hcl (unknown dose, unknown effect and unknown reason for discontinuing); and amphetamine/dextroamphetamine 30 mg was helpful but at 60 mg associated with psychotic symptoms. Of note, the treatment team at the study hospital was not responsible for any historical medication trials. This was their first exposure to this patient, and all historical medications and responses were based on patient self-report of trials under the supervision of myriad previous psychiatrists. At admission, the patient was taking none of his previously prescribed psychotropic medications; he was solely taking omeprazole 20 mg for gastroesophageal reflux disease. Consequently, there was no immediate provider to contact for corroborative details.

Medical evaluation
The patient presented with primary mood and attention complaints, while the most intrusive observed symptoms were psychosis manifested by paranoia, ideas of reference and delusions. To have a primary psychotic disorder present in a male 33 years of age without noted prodromal symptoms is atypical and concerning for an organic process underlying the symptomatology. The patient was assessed for atypical seizures with a routine EEG (within normal limits [WNL]). Toxins were another possible source of the patient’s presentation and this was thoroughly evaluated with a 24-h urine heavy metal screen and urine drug screen (both were negative). As important as assessing external sources of toxins, it is also important to assess internal sources of toxins, such as Wilson’s disease and porphyria. These disorders were eliminated as a source of symptoms with a normal ceruloplasmin and normal urine porphobilinogen. Assessment for an anatomic anomaly was evaluated with a noncontrast MRI of the brain (no abnormalities). Infectious etiologies that may present with psychiatric symptoms were assessed and found to be negative including urinalysis, hepatitis B and C, syphilis and HIV. The patient’s general health was also assessed with blood counts, metabolic panels, thyroid function and vitamin B12 and folic acid levels (WNL). Total cholesterol was 226 (high-density lipoprotein 30, triglycerides 267, low-density lipoprotein 143). Total iron was normal, iron binding capacity was slightly elevated at 433, percent saturation was slightly low at 17. Ferritin was normal. Complete metabolic panel and blood count were essentially WNL. Thyroid-stimulating hormone was normal. Antinuclear antibody was negative. Amylase and lipase were normal. Genomic analysis was also performed and revealed polymorphisms which did elucidate the patient’s symptoms and his prior response to medication trials.

Genetic analyses of select SNPs (specific marker[s]): frequently observed variation from anticipated clinical response
- **SLC6A4 S/S (RS25531 & RS6379047):** associated with a poor response, slow response and/or adverse events with SSRI medications;
- **5HT2C C/C (RS3813929):** associated with increased incidence of weight gain with atypical antipsychotics;
- **DRD2 INS/DEL (RS1799732):** associated with reduced efficacy and increased incidence of side effects with antipsychotics;
- **CACNA1C G/A (RS1006737):** common variation associated with altered function of brain calcium channels, changes in neuronal excitability and clinically with conditions characterized by mood instability or lability;
- **COMT Met/Met (RS4680):** associated with reduced COMT activity and increased synaptic dopamine;
- **CYP2C19 intermediate metabolizer (RS12248560, RS4244285, RS4986893):** associated with reduced efficacy and increased incidence of side effects with citalopram, escitalopram, diazepam, and most tricyclic antidepressants.

Pharmacogenomics-informed medical decision-making
The pharmacogenomics profile of this patient helped to elucidate his atypical presentation with mood symptoms and psychosis in respect to predicted prodromal symptoms and natural course of his psychiatric disorder. Upon receiving the results of the genomic testing, the patient’s symptoms were informed from another perspective. The observed polymorphism (S/S) of the patient’s serotonin transporter gene *(SLC6A4)* helped
to understand his past susceptibility to side effects associated with trials of fluoxetine and sertraline, persistent and worsening symptoms on the medications, which led to its discontinuation. The S/S or ‘short short’ polymorphism has been associated with SSRI medications being ineffective, as well as increased susceptibility to side effects—all of which have been more consistently implicated among Caucasians samples [1–3]. Prolonging the medication trial was unlikely to produce benefit and increasing the dosing often causes intolerable side effects with gastric distress, headaches, sleep disturbance and low-grade symptoms of serotonin syndrome, such as tremor, tachycardia and heat intolerance in addition to increased anxiety.

The COMT and DRD2 polymorphisms provide important data with respect to the patient’s psychotic symptoms. The Met/Met polymorphism was plausibly linked to decreased degradation of synaptic dopamine, which may enhance cognitive functioning; in the context of stimulant treatment with the SSRIs, the patient experienced instead symptoms of a hyperdopaminergic state/psychosis. In addition, antipsychotic medications were less likely to be effective and have increased side effects due to the patient’s observed polymorphism at DRD2 of INS/DEL [4,5]. Because antipsychotics could not effectively block the dopamine receptor and the patient had a genetic tendency toward increased dopamine further enhancement from the stimulant and likely the sertraline, the patient likely developed psychosis on the medication cocktail selected to treat his depression and attention deficits.

While the CACNA1C was analyzed and a polymorphism was noted, these findings were not used to inform medical decision-making. The extant literature suggests that this polymorphism is associated with neurological signaling in key areas of the brain associated with psychiatric disease including the amygdala, hippocampus and mesolimbic system and has been most consistently implicated with genome wide association studies of bipolar disorder [6]. The clinical presentation of this patient did not include any historical or current manic symptoms in support of a bipolar disorder diagnosis.

Pharmacogenomics helped guide diagnosis and treatment. The patient had a prior successful treatment response on duloxetine, an SNRI, which some studies suggest is less influenced by the serotonin transporter polymorphism [7]. As such, the patient was started on duloxetine and titrated up to 60 mg at discharge with the next level of care provider given follow-up recommendations to titrate further (up to 120 mg) as indicated to achieve therapeutic response.

The patient’s psychosis may be better understood, with consideration to his genetic predispositions. Therefore, it was determined to avoid stimulants in the patient, as well as avoid antipsychotic medications, as it was possible that his psychosis was the result of appropriately applied standard of care resulting in an iatrogenic psychosis, thus negating the patient’s need for antipsychotics. In addition, with the DRD2 polymorphism likely making antipsychotics less effective and the 5HT2C receptor polymorphism of C/C potentially making the patient more susceptible to known metabolic side effects of atypical antipsychotics, the benefit of these medications was likely outweighed by the risk to this patient [8]. The class also should not be considered as augmentation therapy for depression. With regard to the patient’s attention issues, the Met/Met polymorphism observed on the COMT gene was suggestive of inefficient dopamine breakdown with resultant accumulation being associated with psychosis (especially paranoia) in the context of stimulant use/abuse [9]. These results supported past psychotic side effects on higher doses of amphetamine/dextro-amphetamine. It was mutually decided to avoid stimulant mediations at this time. In addition, the patient’s psychological testing indicated that his attention deficits were driven by anxiety rather than a primary attention error. The patient was encouraged to refrain from stimulant abuse and to discuss with his outpatient psychiatrist the possibility of adding guanfacine to help with both attention and anxiety. Patient was prescribed hydroxyzine 25 mg at bedtime to help with anxiety and sleep. Additional medications at discharge included: fish oil 1000 mg twice daily for cholesterol and diocytyl sodium sulfosuccinate 100 mg at bedtime with a full glass of water as needed for constipation.

**Treatment outcomes**

The patient evidenced significant symptomatic improvement during the course of his 17-day hospitalization, especially a reduction in his psychotic symptoms. He evidenced significantly less paranoia and was able to engage with the treatment team and establish relationships with other patients on the unit. Further, objective measures of psychopathology and functioning revealed reduced depressive, anxious and somatic complaints as well as decreased disability. Of note, the patient was able to maintain these treatment gains up to 21 days post hospitalization (see Figures 1 & 2). Based on expert clinical judgment and informed by psychological and pharmacogenomics testing, the patient’s discharge Axis I diagnoses included: major depressive disorder, recurrent, severe without psychotic features; anxiety disorder, NOS; social phobia; and alcohol abuse.

**Discussion**

Individual response to psychiatric pharmacologic intervention is highly variable with inadequate...
response to front-line psychiatric agents range from 50 to 85% depending on the disorder [10–15]. Thus, for a sizable percentage of psychiatric patients, psychotropic medications lack efficacy and/or are associated with intolerable side effects. Algorithms to maximize therapeutic response generally structure a rational sequence of trials of biological treatments, with appropriate augmentation strategies and an emphasis on maximizing patient compliance with medication [16–18]. Despite best practices [19] multiple medication trials often fail, which may lead to adverse polypharmacy.

One promising pathway to improved medication response is the use of genetic testing to identify potentially efficacious treatment options. Though variable drug effects have been linked to genetic differences for greater than half a century [20,21], recent advances in genetic testing and mapping of the human genome have accelerated exponentially discoveries in the field of pharmacogenomics. Pharmacokinetic and pharmacodynamic research appears to be at the cusp of application to personalized medicine [22].

Pharmacogenomics is making inroads into the interaction between psychotropic medications and individually expressed alleles in various transporters, receptors and enzymes as coded by genes. Without this information best standards of practice can fail a subset of the population because response to compounds is not well matched to the individual’s genetic makeup. Patients may have an aberrant response to typical treatment that not only does not ameliorate their psychiatric distress but may worsen it. Thus, ‘personalized prescription’ [23] has become the cornerstone of personalized medicine. Despite its promise to improve patient care, the use of pharmacogenomics data to inform clinical care is not widespread, and the literature supporting its clinical utility is in its relative infancy [22].

This case highlights the potential of pharmacogenomics testing to help inform medical decision-making and personalize psychiatric medicine. This young adult male presented with a new onset psychosis. He admitted to historically feeling socially awkward, anxious and excluded, leading to depression which led to further isolation. The patient also struggled to maintain the typical tasks of an adult in his age group including consistent employment, independent living and setting a functional schedule. The patient admitted situational depression and presented with both typical and atypical signs of a major depressive disorder. The patient was also taking stimulants and high doses caused psychosis; it would be logical to conclude that the primary cause of the patient’s psychosis was stimulant abuse and all the ramifications to the therapeutic alliance that this entails. By using results from pharmacogenomics testing, however, this reasonable and erroneous conclusion was averted. This patient’s unique genetic polymorphisms may have contributed to him processing dopamine more slowly. When a stimulant was titrated to the recommended dosage for his attentional needs, the increased dopamine likely created a burden his COMT could not address. The resultant hyperdopaminergic state lead to psychosis in a patient using his medications as prescribed. This would be exacerbated by more dopaminergic antidepressant agents such as bupropion and sertraline. Pharmacokinetically, the patient’s liver enzymes (CYP450 system) processing stimulants were also slower, resulting in potentially a longer half-life of stimulants further exacerbating the effects. In addition, the patient’s serotonin transporter gene polymorphism may be associated with SSRI inefficacy [1–3] and increased side effect burden, even when used as prescribed.

Clinical trials have tested medications that have demonstrated efficacy based on average responses of patients. In fact, the average, group-level treatment outcomes associated with hospitalization at the study
institution are excellent; however, patients vary in their treatment trajectories and level of response, thus emphasizing the value of a personalized approach [24,25]. This patient’s ability to process SSRIs and stimulants did not correspond to average response. Knowledge of the patient’s genetically-influenced departure from average response allowed for personalization of a psychopharmacologic regimen. During the course of a 17-day hospitalization, the patient was titrated up to effective doses of a genomics-guided medication regimen with options for augmentation in the future, should they be required. The patient demonstrated significant clinical improvement. The patient was no longer psychotic and objective measures of psychopathology revealed significant improvement in depressive, anxious and somatic complaints as well as reduced disability. These treatment gains were maintained 3 weeks post-discharge.

The benefits of stimulant medication are unlikely to outweigh the potential risks. Additionally, should the patient ever again require treatment for psychotic symptoms, the benefits of first-generation antipsychotics likely outweigh the risks associated with them given the patient’s genomic profile with polymorphisms at the D2 receptor and the serotonin 5HT2C receptors making atypical antipsychotics potentially less likely to be effective and of risk for metabolic syndrome. Arguably, the inclusion of pharmacogenomics data is only one component of physicians’ attempts to tailor treatments that are best for a given patient in the context of other available information [26]. In some circumstances polypharmacy, tobacco/alcohol consumption or demographic considerations (e.g., age, gender) may be more relevant to medical decision-making than genetic specificity [27]. Future advances may see the inclusion of additional biomarkers (e.g., neurofunctional) that further personalize treatment [28].

Pharmacogenomics testing has the potential to transform medicine. In the early 2000s, JAMA [29] predicted widespread use of personalized prescription by 2015, and business journals were heralding psychiatry as leading the advance [30]. The end of days of trial and error, frustration and prolonged disability were supposed to be the hallmark of the new millennium. However, the technology advanced more slowly than anticipated, and psychiatric clinicians appear reluctant to integrate pharmacogenomics testing into practice. Current barriers to routine practice include: high costs; limited, if any, third-party payers reimbursement; and the needed 3–5 day turnaround time from sample collection to receipt of test results, which may be impractical for traditional inpatient and emergency department settings. Given the number of barriers to widespread use, many have used racial background as a proxy measure of genetically influenced response to medications. In support

### Executive summary

**Atypical case presentation**
- 33-year-old male presented with primary mood and attention complaints.
- Most intrusive observed symptoms were psychosis, which is atypical given the patient’s age and lack of prodromal symptoms.

**Discontinued past medication trials**
- Because of side effects: fluoxetine (tiredness), risperidone (sedation), amphetamine/dextroamphetamine (psychosis at high dose).
- For unknown reasons: duloxetine hcl, bupropion, sertraline, buspirone hcl.

**Genetic analyses of select SNPs**
- SLC6A4 5/5; 5HT2C C/C; DRD2 INS/DEL; CACNA1C G/A; COMT Met/Met; CYP2C19–IM.

**Medical decision-making**
- Met/Met polymorphism of COMT has been associated with slowed dopamine metabolism. The combination of a stimulant (dopamine agonist) titrated to effect within the context of genetic variation may have resulted in a hyperdopaminergic state and associated psychosis.
- Dopaminergic antidepressant agents (e.g., bupropion) would likely exacerbate psychosis.
- The patient’s liver enzymes were slow to process stimulants, potentially further exacerbating effects.
- SLC6A4 polymorphism has been associated with SSRI inefficacy and increased side-effect burden.

**Treatment outcomes**
- Personalization of a psychotropic regimen with options for augmentation in the future.
- Clinical improvement across objective measures of psychopathology and disability.

**Discussion**
- Pharmacogenomics testing has the potential to end of days of psychotropic trial and error, frustration and prolonged disability.
- Clinicians are reluctant to incorporate testing into practice because of high costs and limited time for obtaining tests results in acute inpatient and emergent settings.
- The potential cost savings of pharmacogenomics testing and improved functioning of patients should be weighed, especially in cases of atypical presentation.
of Hunt and Kreiner [31], we caution the inappropriate use of race and ethnic classifications as proxy indicators of genetically determined drug response. Despite these barriers, the potential cost savings of pharmacogenomics testing and improved functioning of patients may spur use in coming decades, especially when cases of treatment-resistant disorders and atypical presentations are more frequently encountered.

Disclosure
The study follows the guidelines on good publication practice. The study sponsors were not involved in any aspect of the research activities and did not approve the specific protocol or manuscript. Thus, the authors were independent from study sponsors in the context of the research.

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