The Role of Pharmacogenetic Testing in the Amelioration of Antidepressant-Related Motor Disturbances in 2 Young Adult Men With Major Depressive Disorder

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ABSTRACT

This report describes the cases of 2 young adult men with depressive symptoms who experienced severe and disruptive motor disturbances while taking serotonin reuptake inhibitors. Both patients had a long history of medication failures and complex presentations. Genetic testing was utilized to guide effective treatment plans and to provide insight into previous medication failures. Most notably, testing in these patients revealed variations in the serotonin transporter protein and cytochrome P450 2D6 and 2C19 enzymes. These cases demonstrate the utility of genetic testing in clinical practice to help identify effective treatment plans in psychiatric patients.

Prim Care Companion CNS Disord 2015;17(1):doi:10.4088/PCC.14br01723

Submitted: *September 26, 2014; accepted October 7, 2014.*
Published online: *January 8, 2015.*
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Serotonin neurotransmission contributes to the etiology of psychiatric disorders via regulation of sleep, food intake, pain, vascular tone, platelet function, and motor activity.[1] The serotonin transporter protein (*SLC6A4*) is the primary mechanism for terminating serotonin signaling.[1] Variations in *SLC6A4* alter synaptic serotonin levels, ultimately affecting downstream signaling, which may lead to increased risk for side effects or medication inefficacies. Selective serotonin reuptake inhibitors (SSRIs) cause a wide range of side effects including sexual dysfunction, insomnia, agitation, and weight gain[2]; patients with variations in *SLC6A4* are at a higher risk for adverse events with SSRIs due to altered serotonin signaling.[1,3] In addition, genes that encode for cytochrome P450 enzymes are responsible for the metabolism of many psychotropic agents, and variations can affect medication serum levels, leading to varied response/tolerability.[3]

While side effects are common among patients taking antidepressants, some of these are more severe, such as motor disturbances, which add to the burden of mood disorders and often constitute a major therapeutic challenge.[4] Movement disturbances are very uncomfortable for patients and can impact medication compliance. Increased levels of serotonin, caused by reuptake-blocking agents, may communicate and interact with dopamine, producing effects similar to dopamine-blocking agents, which disturb γ-aminobutyric acid (GABA) outflow, ultimately leading to movement disturbances.[5] Periodic limb movements are a type of motor disturbance that have been observed in patients receiving SSRI/antidepressant treatment. Venlafaxine and a number of SSRIs have been shown to induce periodic limb movements, and these are thought to be related to excess synaptic serotonin.[6,7] While dopamine's role in movement is widely accepted, the role of serotonin is less well understood. The full mechanism is most likely much more complex; however, 1 theory indicates the interplay between serotonin and dopamine is important, with serotonin suggested to have an inhibitory effect on the dopamine-rich substantia nigra.[5] Animal data also point to serotonin effects on motor function.[8] It is reasonable that patients with variations in genes involved in serotonin neurotransmission may be at greater risk for motor disturbances and other serotonergic side effects. Here, we present 2 reports of patients who experienced severe motor disturbances in response to SSRI treatment and whose clinicians utilized genetic testing to help inform treatment decisions.

CASE PRESENTATIONS

Two men in their early 20s with major depressive disorder, treated since adolescence (aged 15 and 17 years), present with ongoing depression and a history of failures with SSRIs. Upon examination, both patients reported impaired cognition, sleep disturbances, fatigue, social anxieties, and difficulty completing college course work.

Specifically, Mr A, diagnosed with recurrent major depressive disorder (*DSM-IV* 296.33), began psychotherapy at age 15 years followed by an unsuccessful trial of fluoxetine, which produced jittery sensations, and was later started on a trial of escitalopram 10 mg, which resulted in an initial

Clinical Points

- Pharmacogenetic testing aided in choosing effective treatments, leading to complete remission in 2 men who previously failed multiple medication trials.
- Genetic test results explained severe motor disturbances in response to past medications and informed treatments that would not produce this debilitating side effect.

partial response but led to neuromuscular irritability. These symptoms were so severe that Mr A, who was an avid track runner, was unable to join his college team. Escitalopram was discontinued as symptoms became unbearable but was restarted when his depression returned. After the dose was titrated to 20 mg, Mr A decompensated and experienced intense suicidal ideation. Intensive treatment with a psychiatrist was initiated. The psychiatrist discontinued escitalopram and started Mr A on a trial of sertraline 25 mg for depression and anxiety and mirtazapine 7.5 mg to improve sleep continuity. Sleep continuity returned; however, Mr A's anxiety still remained problematic. Olanzapine was added for anxiety but was subsequently discontinued due to severe sedation.

In the second case, Mr B was diagnosed with major depressive disorder, single episode, moderate, and attention-deficit/hyperactivity disorder without hyperactivity (*DSM-IV* 296.22 and 314.00). Mr B reported ongoing depression that forced a leave of absence from college along with difficulties concentrating, staying on task, and sleeping, as well as mood disharmony and periods of intense sadness. Mr B underwent a trial of escitalopram, which was subsequently discontinued due to reported jaw pain. He was then switched to sertraline and concurrent bupropion extended release 300 mg. Sertraline led to headaches, and Mr B was switched back to escitalopram with continued concurrent bupropion. His fatigue and restlessness still remained problematic, and a sleep study was conducted. This study revealed severe periodic limb movements, 67 per hour, and a paucity of rapid eye movement sleep. Pramipexole was initiated to help control periodic limb movements, but Mr B's symptoms still remained problematic.

Genetic testing was employed to inform treatment strategies for both patients. Testing revealed both patients to have variations in the serotonin transporter (*SLC6A4*) and in cytochrome P450 2D6 (CYP2D6) and 2C19 (CYP2C19).

DISCUSSION

Two variations are commonly tested for within the promoter of *SLC6A4*, which may confer altered transcription and activity of the protein. Both patients inherited 2 risk alleles associated with decreased *SLC6A4* function and altered serotonin signaling. These variations help explain prior histories of SSRI failures including movement disturbances experienced with SSRIs such as escitalopram. The patients' genetic profiles indicate that medications that do not primarily target the serotonin transporter sites may be better tolerated. Both patients were also at risk for reduced metabolism of psychiatric medications processed by the CYP2D6 and CYP2C19 enzymes.[9] Previous trials of many medications were unsuccessful (Mr A: olanzapine, fluoxetine, sertraline, mirtazapine, and nortriptyline; Mr B: escitalopram, sertraline, and mirtazapine). Mr A was found to have CYP2D6 poor metabolism, and Mr B was found to have intermediate metabolism for CYP2D6 and 2C19. Genetic polymorphisms leading to slower metabolism of psychiatric medications can lead to increased serum levels of drugs and an increased risk for side effects. These patients possessed variations in *SLC6A4* and CYP450 enzymes and may be at an even greater risk for side effects and/or intolerability with SSRIs due to a combination of altered signaling at the target site (*SLC6A4*) and altered blood levels of medications related to impaired metabolism.

In response to these genetic results, sertraline was replaced with the tricyclic antidepressant nortriptyline, along with aripiprazole, in Mr A. Neither of these medications acts selectively on the serotonin transporter; however, both are metabolized by CYP2D6, and given Mr A's impaired metabolic capacity, these medications were initiated at low doses and titrated slowly. Mr A became stable on a relatively low dose of aripiprazole (2.5 mg). With these changes to his medication regimen, Mr A restarted his college coursework and reengaged in social activities.

In the case of Mr B, escitalopram was discontinued due to the *SLC6A4* variations. The periodic limb movements stopped with this discontinuation, and Mr B reported improved sleep and a reduction in fatigue. Pramipexole was discontinued, and periodic limb movements remained controlled. Mr B was initiated on mirtazapine, which produces serotonergic effects independent of the serotonin transporter. Mirtazapine is partially metabolized by CYP2D6, and the patient was monitored closely for any adverse effects before titrating up the medication. Mirtazapine was titrated up to 45 mg, and a robust reduction in depressive symptoms was seen. Mr B's academic performance improved, and he has remained stable while obtaining his advanced degree and beginning his career.

CONCLUSION

The severe side effects in these patients can be better understood in light of the presence of multiple variations impacting medication response. With the guidance of genetic testing, both patients were initiated on medication regimens personalized to their genetic background, resulting in complete remission of symptoms. Examination of genetic information alongside clinical presentations can help clinicians and patients gain a better understanding of treatment outcomes and side effect risks.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), pramipexole (Mirapex and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Prim Care Companion CNS Disord
2015;17(1):doi:10.4088/PCC.14br01723

Potential conflicts of interest: **Ms Gardner** is an employee of Genomind, Inc. Drs Rhea and Petrie report no conflicts of interest related to the subject of this article.
Funding/support: None reported.

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