

An Aripiprazole Discontinuation Syndrome

TO THE EDITOR:

Major depression is a common and debilitating illness. Over recent years, new pharmacologic treatments have been approved for this disorder, including the atypical antipsychotics. One of the benefits of these medications is their significant efficacy as augmenting agents for unipolar, nonpsychotic major depressive disorder (MDD).¹ Aripiprazole (marketed as Abilify, Bristol-Myers Squibb/Otsuka Pharmaceuticals) was the first medication of this class approved for adjunctive treatment of MDD, and is the 5th most commonly prescribed medication in the United States in 2010.² However, despite the frequency of its use, little has been described regarding events surrounding aripiprazole discontinuation. Here I describe what is, to my knowledge, the first reported case of an aripiprazole discontinuation syndrome. While directly relevant to psychiatrists and behavioral specialists, the symptoms described here are pertinent for internists and neurologists who may encounter this medication in their clinical practice.

Noah S. Philip, MD

Assistant Professor of Psychiatry and Human Behavior (clinical),
Alpert Medical School of Brown University, Butler Hospital

KEYWORDS: akathisia, Aripiprazole, major depression

CASE REPORT

Ms. L, a 20-year-old Caucasian woman with MDD, was admitted to the inpatient psychiatry service for depression and suicidality. Admission physical examination and laboratory measures were normal. Admission medications were aripiprazole 15 mg/day, clonazepam 1 mg three times a day, citalopram 80 mg/day, trazodone 50 mg at bedtime, and topiramate 100 mg twice daily for migraines. There had been no changes in her medications in 4 months, which indicated that the current regimen provided little or no relief from her depression. On further evaluation, the patient reported that she had been feeling “restless inside” since aripiprazole initiation, and that this symptom contributed to severe anxiety. Aripiprazole was tapered over 48 hours and her akathisia resolved. Over the following three days her citalopram was tapered to 40 mg, in anticipation of a medication switch.

On the fourth day after aripiprazole discontinuation, she reported anxiety, irritability, “feeling shaky and jittery,” which increased in intensity throughout the day. Physical and motor examinations were unremarkable and vital signs were stable. A diagnosis of serotonin reuptake inhibitor discontinuation syndrome was made, and a one-time dose of fluoxetine 20 mg was given. Lorazepam 1mg *prn* was provided.

These symptoms continued over the following 24 hours. Citalopram was subsequently increased up to 60 mg with no effect. Lorazepam was only moderately effective, at doses up to 4 mg/day. A presumptive diagnosis of aripiprazole discontinuation syndrome was made. She was given aripiprazole 5 mg, which resulted in prompt symptomatic improvement.

DISCUSSION

To my knowledge, this is the first report of an “aripiprazole discontinuation syndrome,” characterized by anxiety and restlessness without psychomotor findings. Aripiprazole is a dopamine partial agonist, with high affinity for the D2 and 5-HT_{1A} receptors, and antagonism at the 5-HT_{2A} receptor.³ Elimination half-lives of aripiprazole and its metabolite, dihydro-aripiprazole, are 75 and 94 hours, respectively. Although the aripiprazole package insert does not report side effects that occurred after discontinuation of the medication during registration trials,⁴ there have been previous reports

of withdrawal dyskinesias with atypical antipsychotics with prominent motor symptoms.⁵ Internet searches of lay-person message boards describe aripiprazole withdrawal, with similar reports to those described here. While aripiprazole has a high rate of discontinuation due to akathisia,⁶ this is the first case of discontinuation-induced symptoms.

I hypothesize these symptoms are etiologically related to akathisia, within the spectrum of withdrawal dyskinesias induced by an abrupt loss of antagonism at nigrostriatal D2 receptors.⁷ The patient's presentation, with symptoms emerging at approximately the elimination half-life of aripiprazole, lack of effect of other interventions, and prompt response to re-initiation of treatment support this observation. I hope that my experience is useful, in that caution should be employed when abruptly discontinuing this frequently prescribed medication.

References

1. Philip NS, Carpenter LL, Tyrka AR, Price LH. Pharmacologic approaches to treatment resistant depression: a re-examination for the modern era. *Expert Opin Pharmacother*. 2010;11(5):709-722.
2. IMS Institute for Healthcare Informatics, April 2011.
3. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. *J Pharmacol Exp Ther*. 2002;302(1):381-389.
4. Aripiprazole (Abilify) Package Insert, Otuska Pharmaceuticals, Tokyo, Japan 2011.
5. Urbano M, Spiegel D, Rai A. Atypical antipsychotic withdrawal dyskinesia in 4 patients with mood disorders. *J Clin Psychopharmacol*. 2007;27(6):705-707.
6. Gao K, Kemp DE, Fein E, et al. Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. *J Clin Psychiatry*. 2010;72(8):1063-1071.
7. Tranter R, Healy D. Neuroleptic discontinuation syndromes. *J Psychopharmacol*. 1998;12(4):401-406.

Disclosures

The author has received research/grant support from Neosync, Inc. and Neuronetics, Inc.

Correspondence

Noah S. Philip, MD
345 Blackstone Boulevard
Providence RI 02906
401-455-6632
Fax 401-455-6686
Noah_Philip@brown.edu