First Manic Episode in a 55-Year-Old Man After Initiation of Aripiprazole

by ANDREW DONOHUE, DO
Dr. Donohue is a Forensic Psychiatrist, Delaware Psychiatric Center, New Castle, Delaware.

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ABSTRACT

Aripiprazole is a novel antipsychotic medication that is used to treat a number of psychiatric conditions, including schizophrenia, bipolar disorder, and major depressive disorder. Although not specifically indicated for this, novel antipsychotics including aripiprazole are also used for treatment of obsessive compulsive disorder. The following case involves a 55-year-old man with refractory obsessive compulsive disorder who developed his first manic episode after taking aripiprazole. The author reviews other cases of aripiprazole-induced mania and discusses the possible pharmacodynamic mechanisms of this reaction.

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The treatment of bipolar disorder (BD) involves the reduction and prevention of symptoms and episodes of mania and depression. A decade ago, the core treatment involved the use of mood-stabilizing medications, such as lithium, as well as adjunctive sedatives, antipsychotic medications, and perhaps antidepressants. Treatment also employed psychosocial

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ADDRESS CORRESPONDENCE TO: Andrew Donohue, DO, Delaware Psychiatric Center, 1901 N. DuPont Highway, New Castle, DE 19720; Phone: 302-778-6924; Fax: 203-778-6901; Email: Andrew.Donohue@state.de.us

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interventions, hospitalization, and electroconvulsive therapy. In recent years, a number of novel antipsychotic medications have received indications for treatment of different phases of BD. For treatment of mania, the use of novel antipsychotics is now commonplace, often supplanting the use of more traditional mood-stabilizing medications.[1]

Aripiprazole is among the newest of the novel antipsychotic medications. It has proven to be effective in the treatment of schizophrenia, bipolar manic and mixed states, and as an adjunct for major depressive disorder (MDD). Aripiprazole is believed to function as a partial agonist at the D2 and 5-HT1A receptors, and as an antagonist at the 5-HT2A receptor. The following case involves a middle-aged man who developed a first episode of mania after the initiation of aripiprazole.

The patient was a 55-year-old Caucasian man with a history of obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), MDD recurrent, moderate and a remote history of alcohol abuse. He had no known history of BD or any manic symptoms. He had symptoms of OCD since childhood and this disorder represented his greatest source of distress and dysfunction. Symptoms included obsessive thoughts of derogatory sexual terms and images of a sexual nature, accompanied by compulsive tapping and other behaviors. His Yale-Brown obsessive compulsive scores (YBOCS)[2] were 30 to 33, placing his symptom severity in the "severe" to "extreme" range.

He was treated with a combination of medications including fluvoxamine 400mg daily, which is above the United States Food and Drug Administration (FDA) maximum dosage but still within the range sometimes utilized for OCD,[3] bupropion sustained release (SR) 150mg daily, and clonazepam 1mg twice daily (BID). His medication regimen had been unchanged for over six months.

Bupropion SR was discontinued due to a lack of efficacy and 5mg aripiprazole was added, due to its demonstrated benefit in treating OCD with comorbid MDD.[4,5] After initiation of aripiprazole, the patient developed euphoria, an expansive affect, rapid speech, increased goal-directed behavior, a reduced need for sleep, grandiosity, excessive spending, and more interest in sexual activity. His young mania rating scale (YMRS)[6] score was 31. His mother rated him at 30 on the parent version of the YMRS.

A first episode of acute mania at age 55 is highly unusual and the course and timing of the episode suggests that the initiation of aripiprazole 5mg may have been the precipitant. This conclusion is of interest, given aripiprazole's antimanic properties.[7–9]

Aripiprazole was discontinued and lithium carbonate 300mg BID prescribed in its place. Laboratory data included an unremarkable thyroid stimulating hormone level, complete blood count, electrolytes, liver function tests, and a negative drug screen. Lithium level was 0.4mmol/L once steady state was reached. Magnetic resonance imaging (MRI) of the brain without contrast revealed enlarged ventricles and greater than expected cortical atrophy for age, but no masses or focal lesions. Symptoms improved, with a YMRS score of 12 at one week and 4 at two weeks postdiscontinuation of aripiprazole and initiation of lithium.

A first episode of acute mania at age 55 is highly unusual and the course and timing of the episode suggests that the initiation of aripiprazole 5mg may have been the precipitant. This conclusion is of interest, given aripiprazole's antimanic properties.[7–9] There have been previous case reports of mania occurring during treatment with other novel antipsychotics[10,11] and two previous case reports of mania occurring during treatment with aripiprazole.[12,13] The first case occurred in a 45-year-old man with a history of BD and previous manic episodes, whose index manic symptoms worsened after beginning aripiprazole on an outpatient basis.[12] The second case involved a 35-year-old man with a history of schizophrenia, but no history of mania, who developed a manic episode when starting aripiprazole during hospitalization for an exacerbation of psychotic symptoms.[13]

Padala et al[12] hypothesized that the combined antagonism of 5-HT1A and partial agonism of D2 receptors could cause frontal dopamine release, contributing to manic symptoms. Traber et al[13] hypothesized that their patient had become accustomed to dopamine blockade due to his chronic exposure to D2 antagonists to treat schizophrenia. Thus, exposure to aripiprazole, a partial D2 agonist, could have resulted in a state of relatively high dopamine activation. Furthermore, they proposed that aripiprazole's 5-HT2A receptor antagonism and its resultant disinhibition of the dopaminergic system could have been a contributor to a relative increase in D2 activation and therefore a contributor to mania.

This is the first case report of mania associated with aripiprazole initiation in a patient over age 50. A first episode of mania in this population with no known prior episodes would be unusual. Unlike previous case reports, this case did not involve a patient with a psychotic disorder who was accustomed to chronic dopamine blockade and thus potentially predisposed to the relative dopaminergic activation of aripiprazole. In this case, the patient was also receiving a high dose selective seratonin reuptake inhibitor (SSRI), which could also have been a factor, considering aripiprazole's 5-HT2A antagonism and its potentiation of SSRI serotinergic activity.[14] In addition, fluvoxamine is a potent inhibitor of the cytochrome P450 isoenzyme 3A4 and a weak inhibitor of 2D6, which could significantly increase the aripiprazole blood level when taken together. The finding of

generalized cortical atrophy and enlarged ventricles is nonspecific, but could be relevant in this patient with no known clinical signs of dementia or psychosis. It may be related to his history of alcohol abuse (which could have masked prior manic episodes), and it might have predisposed him to this unusual clinical reaction to aripiprazole.

This case demonstrates the potential for aripiprazole, an agent with proven antimanic efficacy, to paradoxically precipitate a manic episode. Aripiprazole has been shown to be effective at augmenting antidepressants in patients with MDD. This case and the cases by Padala et al[12] and Traber et al[13] suggest that, like traditional antidepressants, aripiprazole might also have the potential to precipitate a manic episode in certain patients.

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