

HYPOMANIA ASSOCIATED WITH ADJUNCTIVE LOW-DOSE ARIPIPRAZOLE: TWO CASE REPORTS AND A BRIEF REVIEW OF THE LITERATURE

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INTRODUCTION

Aripiprazole is one of the newest atypical antipsychotic medications. It has proven to be effective in the treatment of schizophrenia (Hasan et al. 2012, 2013), bipolar manic and mixed states (Yatham et al. 2013, Grunze et al. 2013) and, recently, as an adjunctive agent in patients with treatment-resistant major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) (Wright et al. 2013, Pessina et al. 2009, Muscatello et al. 2011, Sayyah et al. 2012).

Despite the proven efficacy in treating mania, several cases have been reported in which aripiprazole may have contributed to recurrence of manic symptoms or induction of the first ever mania (Barnas et al. 2009, Padala et al. 2007, Traber et al. 2007, Ducroix et al. 2008, Donohue 2009, Viikki et al. 2011, Lin et al. 2012). We report two patients that exhibited reversible hypomania after prescription of low-dose aripiprazole for treating bipolar depression (case one) and unipolar depression with comorbid OCD (case two). All psychiatric diagnoses are based on the Diagnostic and Statistical Manual of Mental Health Disorders, Fourth Edition, Text Revised (DSM-IV-TR).

CASE REPORTS

Case one

The first case involved a 40-year-old Caucasian woman with a diagnosis of Bipolar Disorder type II, who experienced her first severe major depressive episode at age 35, following a mild hypomanic episode. She had recurrent, episodes of hypomania and depression. Episodes followed a seasonal pattern and she was euthymic between episodes. She reported a stable mood, with minimal mood swings, while receiving lithium 600 mg per day (serum lithium levels: 0.51 mmol/L at her last evaluation) and venlafaxine 150 mg per day, for almost three years. Medical history was significant for hypothyroidism, treated with levothyroxine, 75 mcg/die, for more than one year. Her TSH was regularly checked every six months, and prior to the episode was within the reference range (1.63 mcU/mL). She was stable for nine months before developing a

depressive episode, characterized by depressed mood, anhedonia, insomnia, thoughts of death and feeling guilty about being unable to fulfill her role in the family and at work. Venlafaxine was discontinued and bupropion, 150 mg/die was given for five weeks, but this showed no efficacy.

The patient was hospitalized and aripiprazole was added to her medication regimen at 7.5 mg a day, while bupropion was discontinued. Serum lithium levels were 0.58 mmol/L at admission and lithium dose was maintained unchanged; TSH value was 1.76 mcU/mL. The patient denied substance use and a drug screen was not performed. She complained of mood changes four days after starting aripiprazole. Symptoms included elation, racing thoughts, decreased need for sleep and buying sprees, within one week from the initiation of aripiprazole. She did not report akathisia. Aripiprazole was stopped and lithium was titrated up to 900 mg/die (serum lithium level: 0.81 mmol/L). Two week after these interventions, her euphoric mood subsided and she maintained euthymic state.

In this first case, the hypomanic reaction could have represented the natural course of her illness, as she had prior hypomanic episodes. However, previous cycles of the patient were characterized by hypomania first, followed by depression and then euthymia; the possibility that hypomania was caused by the addition of aripiprazole to the medication regimen is then compelling, although the previous use of venlafaxine and later bupropion could also be a factor. Antidepressant medications are controversial in the treatment of patients with Bipolar Disorder and venlafaxine may be more likely to precipitate mania than other antidepressants (Post et al. 2006).

Another contributing factor could have been that the patient may have been suboptimally treated with lithium, being on the lower end of the therapeutic range (Wijeratne & Draper 2011).

Case two

The second case involved a 56-year-old Caucasian woman with a history of OCD and recurrent MDD. She had symptoms of OCD since she was 25-years-old and this disorder represented her greatest source of distress

and dysfunction. She had no family or personal history of Bipolar Disorder. Her Yale-Brown Obsessive Compulsive Scale score (Y-BOCS) (Goodman et al. 1989) was 28, placing her symptoms severity in the “moderate” range, when she first started an antiobsessional treatment (sertraline titrated to 100 mg/die). She slowly responded to this treatment and maintained sub-clinical obsessive-compulsive symptoms with sertraline 100 mg/die for years.

Eventually, this patient experienced an exacerbation of her MDD. Symptoms included markedly depressed mood, anhedonia, insomnia; she concurrently developed an intense and irrational fear of a worsening of obsessive-compulsive symptoms. She also reported poor appetite, lack of energy, and diminished interests. Sertraline was titrated up to 200 mg/die for eight weeks and then it was gradually discontinued due to lack of efficacy. Paroxetine up to 60 mg/die was started in substitution of sertraline. Given the poor efficacy of paroxetine monotherapy after six weeks, aripiprazole 5 mg/die was added, due to its demonstrated benefit in treating OCD with comorbid MDD (Pessina et al. 2009, Muscatello et al. 2011, Sayyah et al. 2012). After three days from aripiprazole augmentation, she developed an elevated and expansive mood, inflated self-esteem, decreased need for sleep, distractibility and more interest in sexual activity. The characteristics were in stark contrast to her reserved character. Aripiprazole was first reduced to 2.5 mg/die and then stopped, and her hypomanic symptoms remitted without recurrence of depressive symptoms in approximately one week. She remained on paroxetine 60 mg/die for five months without obsessive-compulsive symptoms, or further mood instability.

None of the two women showed extrapyramidal syndromes, akathisia, or other physical adverse effects during treatment with aripiprazole. Results of blood biochemistry, electrolyte panels and thyroid function tests were all within reference ranges. Patients claimed regular medical adherence and denied abusing alcohol or illicit drug use during treatment.

DISCUSSION

To our knowledge, there have been to date 10 cases of aripiprazole-associated hypomanic or manic episodes. Reported cases have different diagnoses: treatment-resistant unipolar Major Depression, Bipolar Disorder, Schizoaffective Disorder, Bipolar and Unipolar type, and Obsessive-Compulsive Disorder. Aripiprazole doses employed when aripiprazole was added to the main medication were between 2.5 and 20 mg/die (Table 1). It is of note that in three cases it was clearly stated that the individual had no history of prior (hypo)mania (i.e. first ever episode associated with the use of aripiprazole).

Our two cases add to the existing literature in demonstrating the potential for aripiprazole, an agent

with proven antimanic efficacy, to paradoxically precipitate a hypomanic or manic episode. Our cases meet several of the eight criteria proposed by Aubry and colleagues (Aubry et al. 2000) to evaluate a causal relationship between atypical antipsychotic use and initiation of hypomanic/manic symptoms, suggesting that aripiprazole was the proximate cause of hypomanic symptoms. In particular, in both cases prior to initiation of aripiprazole no active symptoms of hypomania or mania were evident (first criterion), classical DSM-IV symptoms of hypomania developed (second criterion) within few days from aripiprazole initiation (short interval from starting a medication and onset of hypomania – third criterion), dosages and titration of aripiprazole were standard (criterion four), none of the other medications either prior to (criterion five) or at the time (criterion six) of aripiprazole treatment contributed, in our view, to the induction of hypomania (less clear in case one), and finally a rapid remission of symptoms (in few days) after aripiprazole discontinuation was evident in both patients (criterion eight).

Aripiprazole acts as a high-affinity partial agonist to dopamine D2/D3 receptors and serotonin 5-HT1A receptors as well and as an antagonist to 5-HT2A receptors; these mechanisms of action are speculated to play a role in its antidepressant effect (Pae et al. 2008), and might contribute, in susceptible individuals, to the recurrence of (hypo)manic symptoms (as in case number one) or induction of the first ever (hypo)mania (as in case number two). The finding of first episode of acute hypomania at age 56 (case number two) is highly unusual and the course and timing of the episode suggests that the initiation of aripiprazole 5mg/die may have been the precipitant.

Unlike some previous case reports (Barnas et al. 2005, Padala et al. 2007, Traber et al. 2007, Ducroix et al. 2008, Viikki et al. 2011, case number four), our cases did not involve patients with a psychotic disorder who were accustomed to chronic dopamine blockade and thus potentially predisposed to the relative dopaminergic activation of aripiprazole. In the second case, the patient was receiving a moderate dose selective serotonin reuptake inhibitor (SSRI), which could also have been a contributing factor to the onset of hypomania, considering aripiprazole’s 5-HT2A antagonism and its potentiation of SSRI activity (Boothman et al. 2006).

Our cases received a lower starting dose of aripiprazole as an adjunct to depression treatment compared to that used in some previous cases (Barnas et al. 2005, Traber et al. 2007, Ducroix et al. 2008), and hypomanic symptoms still occurred; aripiprazole in fact seems to exert its adjuvant antidepressant effect at a minimal dosage. These cases showed that aripiprazole, an effective adjunctive antidepressant agent, has a risk of initiating manic/hypomanic symptoms despite its antimanic properties at higher dosage (Lin et al. 2012).

Table 1. Reported manic/hypomanic cases induced by aripiprazole

Author, year	Previous Diagnosis	Sex, Age	Aripiprazole Dose	Mania/Hypomania (recurrence/first induction and YMRS score if specified)
Barnas et al. 2005	Schizoaffective, bipolar type	Female, 57	20 mg/d (started at 10 mg/d)	Mania (recurrence)
Padala et al. 2007	Schizoaffective, bipolar type	Female, 45	10 mg/d	Mania (recurrence; YMRS: 31)
Traber et al. 2007	Paranoid Schizophrenia	Male, 35	15 mg/d	Mania
Ducroix et al. 2008	Schizoaffective, unipolar type	N.R.	15 mg/d	Mania
Donohue 2010	OCD, GAD, MDD- recurrent	Male, 55	5 mg/d	Mania (first induction; YMRS: 31)
Viikki et al. 2011	BD II, MDE	Male, 39	15 mg/d	Hypomania (recurrence; YMRS: 13)
	BD II, MDE	Male, 44	7.5 mg/d	Hypomania (recurrence; YMRS: 19)
	Resistant-MDD	Female, 46	5 mg/d	Hypomania (first induction)
	DB I, mixed episode	Female, 19	7.5 mg/d	Mania (recurrence)
Lin et al. 2012	MDD	Female, 62	5 mg/d	Hypomania (first induction)

Author, year	Previous/concomitant treatment	Interval until onset	Management	Result
Barnas et al. 2005	Perphenazine 8 mg/die for 2 years (previous)	14 days	Discontinued aripiprazole; added quetiapine up to 350 mg/d	Remission
Padala et al. 2007	Valproate 1500 mg/die; fluphenazine 15 mg/die (concomitant)	3 days	Discontinued aripiprazole	Manic symptoms reduced in intensity within few days; Complete remission after 15 days
Traber et al. 2007	No concomitant medication	10 days	Discontinued aripiprazole; added quetiapine	Remission in 2 days
Ducroix et al. 2008	Risperidone depot (previous)	N.R.	N.R.	N.R.
Donohue 2010	Fluvoxamine 400 mg/die (concomitant) bupropion 150 mg/die, (previous)	2-3 days	Discontinued aripiprazole added lithium 600 mg/die	Manic symptoms reduced (YMRS: 12) after 7 days, then remission (YMRS: 4) after 14 days
Viikki et al. 2011	Valproate 2000 mg/d (concomitant)	14 days	Discontinued aripiprazole; added olanzapine	Remission in few days
	Valproate 1500 mg/d, lamotrigine 200 mg/d (concomitant); lithium 300 mg/d (previous)	21 days	Discontinued aripiprazole, lamotrigine reduced to 100 mg/die	Remission in few days
	Agomelatine 50 mg/d (previous), pregabalin 225 mg/d, venlafaxine 75 mg/d (concomitant)	7 days	Reduction to 2.5 mg/d	Remission in few days
	Valproate 2800 mg/d, quetiapine 900 mg/d, stable thyroxine dose (concomitant)	28 days	Discontinued aripiprazole; hospitalization	N.R.
Lin et al. 2012	Fluoxetine 40-60 mg/die for more than 9 months (concomitant); bupropion 150 mg/die for 4 weeks (previous) Propranolol 30 mg/die, for decades (concomitant)	7 days	Reduction to 2.5 mg/die, then discontinued	Remission; however, depressive symptoms returned 14 days later Aripiprazole 1.875 mg/d was added and remission occurred within 21 days, euthymic state for 7 months

N.R.: not reported; BD: Bipolar Disorder; MDD: Major Depressive Disorder; YMRS: Young-Mania Rating Scale; MDE: Major Depressive Episode

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CONCLUSIONS

Paradoxical reactions, in which a medication causes the opposite of the intended effect, are not unheard of with psychiatric medications. This paper demonstrates a growing body of literature (see Table 1) describing the paradoxical induction of mania in persons taking aripiprazole, a medication demonstrated to reduce mania (Yatham et al. 2013, Grunze et al. 2013).

This effect could be attributed to the unique pharmacological properties of aripiprazole, of having both dopaminergic antagonistic and agonistic properties at different doses, as well as serotonergic activity". That is, at lower dose (<15 mg) aripiprazole often acts as a full D2 agonist with positive correlation between dosage and dopaminergic agonism, whereas in higher doses more often as an antagonist (Stahl 2008). It may therefore be more likely to induce hypomania/mania

when used in smaller doses (Lin et al. 2012). The likelihood of this paradoxical reaction remains uncertain. Further research would be beneficial to determine the frequency of induction of mania, particularly in patients who have never been manic in the past. Further research could also help illuminate what factors may predispose individuals to develop this unusual reaction to this medication. Given this case series of individuals who became manic, sometimes for the first time, after taking aripiprazole, it would benefit clinicians to be aware of the rare potential of this medication to cause manic states.

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