

# Case Report

## Atomoxetine Induced Hypomania in a Patient with Bipolar Disorder and Adult Attention Deficit Hyperactivity Disorder

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### ABSTRACT

Comorbidity of bipolar disorder (BD) with attention deficit hyperactivity disorder (ADHD) is frequent. The management of comorbid ADHD and BD is complicated by the risk of induction of (hypo) mania by the medications used for ADHD treatment. Earlier reports in children and adolescents with ADHD-BD suggest that the possibility of (hypo) mania induction is low when atomoxetine is used along mood stabilizers or antipsychotics. Here, we report induction of hypomania by atomoxetine when used for the treatment of comorbid ADHD in a BD patient while on prophylactic treatment with mood stabilizers. This report indicates that atomoxetine carries the risk of induction of (hypo) mania even in stabilized BD patients. Clinicians should closely monitor such patients for (hypo) mania symptoms.

**Key words:** Atomoxetine, attention deficit hyperactivity disorder, bipolar disorder, hypomania, mania

### INTRODUCTION

Bipolar disorder (BD) is an episodic mood disorder and has a significant psychiatric comorbidity.<sup>[1]</sup> Attention deficit hyperactivity disorder (ADHD) persists in adulthood in about two-third of patients, affecting 2.5–4.4% of adults.<sup>[2]</sup> Concomitant BD and ADHD are frequent with 10–21% of adults with BD having ADHD and 5–20% of adults with ADHD having BD.<sup>[2,3]</sup> Subjects with comorbid ADHD and BD have poorer outcomes, and the management is further complicated by the risk of induction of (hypo) mania with the

medications used for ADHD treatment.<sup>[2,4]</sup> Here we report induction of hypomania by atomoxetine, a selective norepinephrine reuptake inhibitor when used for the treatment of comorbid ADHD in a patient with BD.

### CASE REPORT

Mr. A, a 22-year-old male, with diagnosis of BD (age of onset 20 years) and borderline personality

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disorder (BPD) was stable on sodium valproate 1000 mg/day and quetiapine 400 mg/day since a year. He was adherent with medications and had adequate serum valproate levels (95 µg/ml). He then had an impulsive deliberate self-harm attempt following a stressor and was admitted for in-patient care. During the in-patient evaluation, he reported significant inattention since childhood (age of onset 6–7 years). On further exploration, he was found to have features suggestive of impulsivity and hyperactivity, causing significant impairment in his academic and interpersonal functioning. On structured evaluation, he fulfilled the DSM-5 criteria for adult ADHD and scored 24 on the conners' adult ADHD rating scale. We educated the patient and his caregivers about ADHD, and added tablet atomoxetine 18 mg/day to his treatment regimen and increased it to 25 mg/day after 5 days (0.4 mg/kg body weight). After the 2<sup>nd</sup> day of receiving 25 mg/day of atomoxetine, he was noted to be more talkative than usual and irritable over minor issues. From the following day, he started reporting expansive ideas and appeared overfamiliar with treating team members. His need for sleep decreased and psychomotor activity increased. On rating with Young's Mania Rating Scale, he scored 14. These symptoms were consistently noted for about 3 days while he was on atomoxetine 25 mg/day. After discussing with the patient and his family, atomoxetine was stopped and other medications were continued at the same dose. Hypomanic symptoms resolved over next 4–5 days and he became euthymic. The patient also had family history of BD in a second-degree relative and history of manic switch with imipramine. The score on the Naranjo adverse drug reaction probability was 8, suggesting that atomoxetine-induced hypomania was probable.

## DISCUSSION

There are no randomized controlled trials that have evaluated any treatment in adult patients with ADHD-BD, and no definitive treatment recommendations are available.<sup>[5]</sup> The consensus is to follow staged or hierarchical approach by treating BD first and then treat ADHD.<sup>[2,6]</sup> It is believed that mood stabilizers provide protection against the possible risk of (hypo) mania induction with the medications used for ADHD.<sup>[2,7]</sup> In the above scenario, our patient was euthymic and on adequate doses of two mood stabilizers when we commenced pharmacotherapy for ADHD. Several experts suggest avoiding these medications in BD patients, especially in those having risk factors such as family history of psychosis or BD.<sup>[8-10]</sup> However, earlier reports in children and adolescents with ADHD-BD suggest that the possibility of (hypo) manic switch is low when atomoxetine is used along with mood stabilizers or antipsychotics.<sup>[11]</sup> In the

patient described above, as the dose of atomoxetine was increased, we witnessed hypomanic symptoms. These hypomanic symptoms disappeared within few days of stopping atomoxetine.

To our knowledge, this is the second report of atomoxetine-induced mania/hypomania in an adult patient. The first report was published in 1985, in a 46-year-old patient with major depressive disorder having family history of postpartum depression.<sup>[12]</sup> An important point in this report is that the hypomania occurred while the patient was on treatment with two mood stabilizers at adequate doses. This is probably the first report of atomoxetine-induced hypomania in an adult patient stabilized on mood stabilizers. Conversely, the literature on children and adolescents with ADHD has several documented reports of atomoxetine-induced (hypo) mania.<sup>[13-18]</sup> In an uncontrolled open trial, about one-third (33%) of ADHD children receiving atomoxetine reported irritability, hypomania, mania, and aggression. In this study, the majority of the affected children experiencing above-mentioned adverse effects had family or history suggestive of mood disorder or symptoms.<sup>[13]</sup> The salient features of published case reports on atomoxetine-induced (hypo) mania in children and adolescents are summarized in Table 1.<sup>[14-18]</sup> A family history of affective disorder was commonly seen in these case reports, similar to the findings from the trial described above.<sup>[13]</sup> In addition, the findings from these case reports suggest atomoxetine-induced hypo (mania) to be a dose-dependent phenomenon with a higher probability at the dose range of least 0.8–1.7 mg/kg of body weight. The patient, in this case, developed hypomania at a dose of 0.4 mg/kg. However, it is to be noted that he was a known case of BD. The dose of atomoxetine required to induce hypo (mania) in adults with BD and the role of comorbid conditions such as BPD need further investigation.

## CONCLUSION

Atomoxetine carries the risk of induction of (hypo) mania even in stabilized patients with BD. Clinicians should closely monitor such patients for (hypo) manic symptoms. Further systematic research is required on the predictors and pathophysiology of atomoxetine-induced hypo (mania) in children and adults.

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### Conflicts of interest

There are no conflicts of interest.

**Table 1: Summary of published reports on atomoxetine induced (hypo) mania in children and adolescents with ADHD**

Sex/age in years	Diagnosis	Co-morbidity	Family history	Dose of atomoxetine at the point of induction of mania	Induction of mania after increasing the dose of atomoxetine	Management of induced mania
Male/11 <sup>[14]</sup>	ADHD	None mentioned	Bipolar disorder	0.8 mg/kg	Induction occurred at the starting dose; could not be commented	Atomoxetine discontinued
Female/12 <sup>[15]</sup>	ADHD	ODD	Depressive disorder	1.2 mg/kg	Yes (0.5 to 1.2 mg/d)	Atomoxetine discontinued
Male/8 <sup>[16]</sup>	ADHD	Tic disorder	ADHD, Tourette's disorder Atomoxetine induced mania	1.7 mg/kg	Yes (1.1 mg/kg to 1.7 mg/kg)	Atomoxetine dose decreased to 25 mg/d
Male/10 <sup>[17]</sup>	ADHD	Social anxiety disorder	None	Not mentioned	Yes	Atomoxetine discontinued
Female/14 <sup>[18]</sup>	ADHD	None mentioned	Depressive Disorder Multiple substance use disorder	0.8 mg/kg	Yes (0.4 mg/kg to 0.8 mg/kg)	Added lamotrigine (50 mg/d) and aripiprazole (15 mg/d) Atomoxetine dose decreased to 25 mg/d

ADHD – Attention deficit hyperactivity disorder; ODD – Oppositional defiant disorder

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