CASE REPORT

Psychiatry and Clinical Psychopharmacology 2020;30(4):464-466
DOI:10.5455/PCP.20201009072139

Atomoxetine-Induced Mania in a 6-year-old Child with Autism Spectrum Disorder

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Abstract

Atomoxetine, a selective norepinephrine (noradrenaline) reuptake inhibitor, is an effective and safe medication in the treatment of attention-deficit hyperactivity disorder (ADHD) with or without autism spectrum disorder (ASD) in children. However, unusual side effects may occur during the course of the treatment. In this case study, we present a 6-year-old child diagnosed with ASD comorbid with ADHD who developed atomoxetine induced mania during his treatment for ADHD.

ARTICLE HISTORY

Received: Oct 06, 2020
Accepted: Nov 18, 2020

KEYWORDS: atomoxetine, mania, autism spectrum disorder, child

INTRODUCTION

Autism spectrum disorder is a neurodevelopmental disorder characterized by early-onset social communication deficits and repetitive sensory-motor behaviours [1]. Irritability is a common symptom of ASD and it be observed with or without comorbidity with ADHD. However, when distinct periods of irritability is observed, one must consider the possibility of bipolar disorder comorbidity. In clinical studies, the prevalence of bipolar disorder in children and adolescents with ASD ranged from 0.7% to 27 % [2]. Genetic influences, environmental factors, comorbid neurodevelopmental disorders and drug-induced conditions are frequently mentioned in the etiology of bipolar disorder. In line with this, having a parent diagnosed with bipolar disorder was found to be the strongest factor in the development of bipolar disorder in children and adolescents [2]. Atomoxetine, a selective norepinephrine (noradrenaline) reuptake inhibitor, was documented to be effective in treating ADHD symptoms in ASD patients [3]. However, atomoxetine-induced psychiatric adverse effects have been observed in adult [4] and adolescent patients [5,6,7,8]. Hence, we report the case study of a 6-year-old boy ASD and comorbid ADHD, and an intense psychiatric family history, who developed mania after increasing the atomoxetine dose to 25mg/d).

CASE

A is a 6-year-old boy who was diagnosed with autism spectrum disorder (ASD) based on DSM-5 criteria at the age of four in a university hospital child and adolescent psychiatry department. In his very recent examination, he exhibited severe social and verbal deficits, was unable to maintain eye contact and communicate meaningfully. His parents complained about high levels of irritability, hyperactivity and impulsivity for a year. He was diagnosed with comorbid ADHD and started taking aripiprazole 1 mg/day (with titration to 7 mg/day) before bedtime and within 2 months his symptoms improved without any considerable side effects. In the third month of aripiprazole treatment, his ADHD symptoms mildly improved. Therefore, atomoxetine 10 mg/day was added to his treatment (0.5 mg/kg initial dose). Atomoxetine was gradually increased to 25 mg/day during the first 6 weeks of treatment. The parents did not report any significant side effects until the dose was increased to 25 mg/day. Two weeks after the increase of atomoxetine to 25 mg/day, he had a significant decrease in need for sleep to 2 hours a day along with increases in irritability, energy and activity level, masturbation, and stereotyped behaviors. Although he was a non-verbal child, he started muttering and talking to himself with a desire of leaving the house at inappropriate times. According to the parental reports, these behavioral changes appeared one week after the atomoxetine dose was increased to 25 mg/day and they continued for a week until the next examination. These behavioral changes were

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To cite this article: Tanir Y, Turkmen G. Atomoxetine-Induced Mania in a 6-year-old Child with Autism Spectrum Disorder. Psychiatry and Clinical Psychopharmacology 2020;30(4):464-466, DOI: 10.5455/PCP.20201009072139

diagnosed as atomoxetine induced manic episode. Due to these side effects, aripiprazole and atomoxetine were discontinued, and olanzapine was started at 5 mg/day. Follow-up examination showed that manic symptoms had regressed. Approximately 7 months the parents reported that the patient had frequent crying episodes followed by fits of laughter, his irritability and sexual desire increased (increase in masturbation, kissing dolls by the lips) as well as his attempts to leave the house at inappropriate times, he urinated in his hand and drank it, which indicated that symptoms of mania returned. Olanzapine dose was increased from 5 to 7.5 mg/day and valproic acid 400 mg/day was added to the treatment. After two weeks following the dose increase, manic episodes completely disappeared. For the last 3 months, monthly examinations revealed that his manic symptoms have been under control.

In addition, the Naranjo adverse drug reaction (ADR) probability scale was developed to assist clinicians in standardizing the assessment of causality for ADRs. The ADRs are assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4, and unlikely if the score is 0. The patient's ADR score was 7, indicating a probable effect [9]. Therefore, atomoxetine was a likely cause of mania in this case.

Patient's family history revealed that his grandmother was diagnosed with schizophrenia and his uncle and aunt were diagnosed with bipolar disorder. In addition, his father, had experiences of severe mood swings and euphoria, especially in the spring months, which hampered his work performance significantly, although no psychiatric diagnosis was assigned to his symptoms.

DISCUSSION

In the present case, clinical symptoms or signs of mania or hypomania and medication prior to the treatment were absent. This, combined with the onset of manic symptoms shortly after the initiation of atomoxetine treatment, and improvement of manic symptoms following the discontinuation of atomoxetine indicate that mania symptoms were induced by atomoxetine. This was in line with the previous findings in the literature [5,6,7,8]. To our knowledge, the present study was the first to report the link between a manic episode and atomoxetine use in a patient ASD comorbid with ADHD where family history revealed bipolarity. It is known that positive family history in terms of mood disorders is one of the biggest risk factors for developing manic symptoms after atomoxetine treatment [6]. According to past research, presence of mood disorders in relatives (especially bipolarity in first degree relatives) was related to higher chances of BD comorbidity in ASD [10]. In addition, BD is more commonly observed in younger patients with ASD [11]. Therefore, in the present case, a positive family history for bipolar disorder, schizophrenia, and an accompanying neurodevelopmental disease (ASD) might have catalyzed the manic episode, which was already triggered by atomoxetine treatment.

It should be noted that there are difficulties to reach differential diagnosis of manic episode induced by atomoxetine in ASD patients. The differential diagnosis of bipolar disorder and ADHD is challenging because bipolar disorder accompanying ASD is seen with intense irritability and patients diagnosed with ASD cannot express feeling of elevated mood [11].

In addition, after the use of atomoxetine to help with the differential diagnosis, the increase in the intensity in ASD symptoms, e.g., stereotypes and destructive irritability, should warn clinicians about the possibility of bipolar disorder. Also, recent onset of sleep problems, masturbation, avoidance of the previously feared objects, increase in the amount of speech or in nonverbal gestures, amount of sounds produced, and new-onset attention problems should be evaluated in terms of bipolarity in the family history [11].

In our case, despite antipsychotic treatment, the development of a manic episode following increased atomoxetine doses suggest that atomoxetine triggers mania [8]. Therefore, when starting atomoxetine treatment in cases with ASD comorbidity, clinicians should take into account different factors. Mainly, in the presence of bipolar disorder or any other mood disorder, the medical history of first-degree relatives should be taken into consideration. Also, atomoxetine dose should be increased gradually to avoid side-effects, and symptoms over the course of treatment should be closely monitored to prevent episodes of mania or hypomania. In cases where bipolarity is suspected, discontinuation of atomoxetine and addition of a mood stabilizer to the treatment plan could prevent manic symptoms.

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