



CASE REPORT OPEN ACCESS

Unanticipated Pathological Laughter Following Atomoxetine Administration in a Child With Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Introduction: Atomoxetine, a selective norepinephrine reuptake inhibitor (NRI), is commonly prescribed for attention-deficit/hyperactivity disorder (ADHD) and has shown effectiveness in children with autism spectrum disorder (ASD). Although mood disturbances and psychiatric symptoms are recognized side effects, pathological laughter has not been previously reported.

Case Presentation: We present the case of a 6-year-old boy diagnosed with both ASD and ADHD who developed sudden, uncontrollable episodes of pathological laughter after beginning low-dose atomoxetine (5 mg/day, ~0.25 mg/kg). The child had a history of hyperactivity and aggression, managed with risperidone and clonidine. Within 5 days of initiating atomoxetine, he exhibited frequent, spontaneous laughter lasting 2–5 min without any apparent emotional trigger. These episodes resolved within 10 days despite continued atomoxetine treatment, coinciding with a minor increase in risperidone dosage. Following this period, the child displayed noticeable improvements in attention, eye contact, and overall cooperation. Atomoxetine was later increased to 10 mg/day, with no recurrence of pathological laughter.

Conclusion: This case suggests that pathological laughter may be a rare but temporary side effect of atomoxetine, even at low doses. Given the child's familial history of bipolar disorder and the influence of catecholamines on mood regulation, clinicians should be vigilant in monitoring mood-related side effects in children with neurodevelopmental disorders. This report emphasizes the need for personalized treatment approaches and further investigation into the mechanisms and risk factors underlying this phenomenon.

1 | Introduction

Atomoxetine, an norepinephrine reuptake inhibitor (NRI), is widely used for attention-deficit/hyperactivity disorder

(ADHD) treatment and enhances cognitive function by increasing norepinephrine and dopamine levels in the prefrontal cortex (PFC) [1]. Its therapeutic effects are dose-dependent, as excessive catecholamine levels may negatively impact

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cognitive performance [1]. Originally developed as an antidepressant, atomoxetine has been primarily prescribed for ADHD since its approval in 2002 [2–5] and is particularly effective for managing hyperactivity and inattention in pediatric patients [6].

ADHD frequently co-occurs with ASD, with approximately 60% of children with ADHD exhibiting social challenges similar to those seen in ASD [7]. Although atomoxetine has shown some efficacy in children with ASD [6, 8], response rates appear lower compared to neurotypical children [9]. Common adverse effects of atomoxetine include irritability, aggression, insomnia, cardiovascular complications, hepatotoxicity, and psychiatric symptoms such as mania or psychosis [10–12]. However, pathological laughter has not been previously documented as a side effect in pediatric patients.

Pathological laughter is characterized by sudden, inappropriate, and involuntary laughter episodes occurring independently of emotional stimuli [13]. It has been associated with neurological disorders, epilepsy, toxic exposures, and psychotropic medications [14]. Here, we report a case of a child with ASD and ADHD who exhibited pathological laughter following atomoxetine initiation, providing insight into a previously unrecognized adverse effect.

2 | Case Presentation

A 6-year-old boy diagnosed with ASD at age three presented with speech delays, social communication difficulties, repetitive behaviors, and restricted interests. Despite receiving speech and occupational therapy, his developmental progress remained limited. He exhibited symptoms consistent with ADHD, including hyperactivity and distractibility. At age four, he was prescribed risperidone and clonidine for behavioral regulation; however, his hyperactivity and aggression persisted, leading to his hospitalization in September 2023 at a university pediatric psychiatry unit in Tehran, Iran.

The patient had a maternal family history of psychiatric disorders, including generalized anxiety disorder (GAD) and bipolar II disorder (B2D), suggesting a genetic predisposition to mood dysregulation. At the time of admission, he was receiving clonidine (0.3 mg/day) and risperidone (1.5 mg/day).

During hospitalization, he exhibited significant restlessness, poor eye contact, stereotyped behaviors, and difficulty communicating his needs. His mother noted worsening hyperactivity following disrupted sleep. Melatonin (3 mg) was introduced, resulting in mild improvement in restlessness, but his ADHD symptoms remained pronounced.

On the tenth day of hospitalization, atomoxetine was initiated at 5 mg/day (~0.25 mg/kg) to address his ADHD symptoms. By the fifth day of treatment, he began experiencing frequent episodes of spontaneous, uncontrollable laughter lasting 2–5 min. These episodes occurred primarily in the afternoon and evening and had no identifiable environmental or emotional trigger.

Risperidone was increased to 1.75 mg/day on the seventh day after atomoxetine initiation. Atomoxetine was continued, and close monitoring revealed a gradual decrease in the frequency and intensity of laughter episodes. By the tenth day, the pathological laughter had fully resolved. Simultaneously, improvements in attention span, eye contact, and cooperation were observed. Atomoxetine was later titrated to 10 mg/day, with no recurrence of symptoms.

At discharge, the patient exhibited reduced restlessness, hyperactivity, and aggression. One month post-discharge, follow-up assessments by his parents and therapist confirmed sustained improvements in attention and social engagement, with no further episodes of pathological laughter or mood instability (Figure 1).

3 | Discussion

This case highlights a rare adverse reaction—pathological laughter—following the initiation of atomoxetine in a child with ASD and ADHD. Notably, the episodes occurred at a low dose (5 mg/day) and resolved spontaneously within 10 days without discontinuing the medication. This suggests a transient neurochemical imbalance rather than a persistent mood disorder. Based on a Naranjo Adverse Drug Reaction Probability Scale score of 5, the reaction was classified as “probable” [15].

Pathological laughter, as observed in this case, was episodic, involuntary, and lacked an apparent emotional trigger. This distinguishes it from alexithymia, in which laughter may arise due to emotional misinterpretation [16]. Additionally, differentiating these episodes from ASD-related stereotyped behaviors is crucial. The laughter’s sudden onset following atomoxetine initiation and its resolution contrast with the typically persistent nature of stereotypies in ASD [17].

Mood instability, including hypomanic symptoms, has been reported as a side effect of atomoxetine, particularly in individuals with a family history of mood disorders [3, 10, 18, 19]. Prior literature describes activation syndrome, characterized by increased energy, aggression, and manic-like symptoms [18, 20]. However, only one previous case—reported by Park et al. [21]—has linked atomoxetine to pathological laughter, occurring in a 55-year-old patient with post-stroke cognitive impairment. Unlike that case, our patient’s symptoms resolved without discontinuation, suggesting a different underlying mechanism.

Pathological laughter has been associated with dysregulation of the PFC and monoaminergic neurotransmission, particularly involving serotonin, dopamine, and norepinephrine [21–23]. The catecholamine hypothesis of affective disorders proposes that dopamine fluctuations in the forebrain may contribute to mood disturbances [21, 24, 25]. Given that atomoxetine increases catecholamine levels in the PFC, it is plausible that these neurochemical changes triggered the pathological laughter observed in our patient [21].

Interestingly, previous reports indicate that mood-related side effects of atomoxetine typically emerge at doses ≥ 0.8 mg/kg

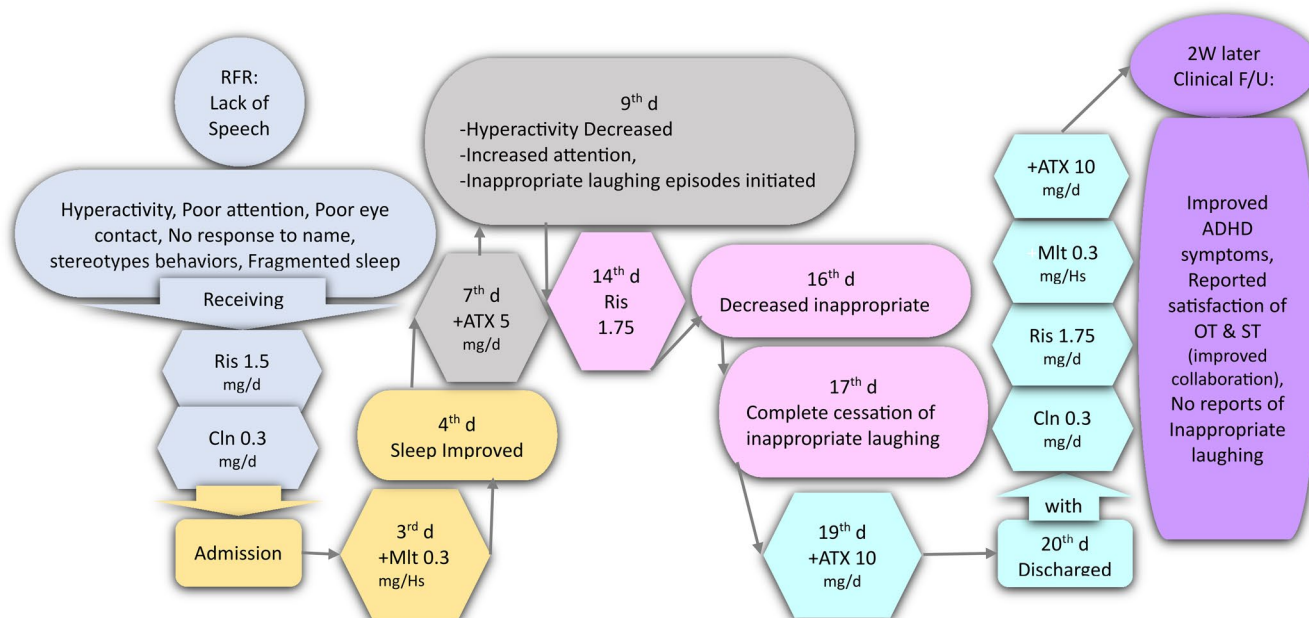


FIGURE 1 | The clinical course of the patient. +, added; ADHD, attention deficit hyperactivity disorder; ATX, atomoxetine; Cln, clonidine; d, day after admission; HS, hour of sleep; Mlt, melatonin; OT, occupational therapist; RFR, reason for referring; Ris, risperidone; ST, speech therapist; W, week.

[26]. However, this case demonstrates that even a lower dose (0.25 mg/kg) can induce such effects, underscoring the importance of close monitoring, particularly in patients with ASD or a family history of mood disorders [10, 19, 26, 27].

Unlike prior reports requiring atomoxetine discontinuation [21], this case illustrates that temporary dosage adjustments—such as increasing risperidone—can effectively mitigate symptoms while preserving atomoxetine’s therapeutic benefits. This suggests that, in some cases, atomoxetine-induced mood disturbances may be self-limiting and responsive to adjunctive pharmacological modifications.

Further research is needed to identify risk factors for atomoxetine-induced pathological laughter and to develop evidence-based strategies for its management. Longitudinal studies are also warranted to assess whether symptom recurrence occurs with prolonged treatment or dose escalation.

4 | Conclusion

This case report describes a rare but clinically significant adverse reaction—pathological laughter—following the initiation of low-dose atomoxetine in a child with ASD and ADHD. Unlike previously documented cases, symptoms resolved without discontinuation, suggesting a transient neurochemical imbalance rather than a persistent mood disorder.

Given the child’s family history of bipolar disorder, this case highlights the importance of monitoring mood-related side effects in children with neurodevelopmental conditions. Clinicians should remain attentive to atypical mood responses,

carefully adjust treatment regimens, and consider individualized approaches to maximize therapeutic benefits while minimizing adverse effects.

These observations provide several important issues, including potential factors related to the vulnerability to develop pathological laughs due to atomoxetine (dose of the drug, age of patients, and etc....). Therefore, the information reported in this paper would add to the refinement of the pharmacotherapy for some of the developmental disorders.

Further research is essential to elucidate the mechanisms underlying atomoxetine-induced pathological laughter and to establish clinical guidelines for its management.

Author Contributions

A.F. contributed to the conception of the work, participation in clinical management of the patient, did the literature search, contributed to drafting the manuscript, and editing the manuscript. A.Z. contributed to drafting the manuscript and editing the manuscript. F.E. did the literature search and contributed to editing the manuscript. E.S. contributed to editing the manuscript. All authors approved the final manuscript.

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Ethics Statement

The research protocols were conformed to the tenets of the Declaration of Helsinki.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data supporting the findings of this case report are included in the main text of the article. No additional datasets were generated or analyzed during the preparation of this report.

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