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LETTER TO THE EDITOR

# Effective use of atomoxetine to treat six inpatient youths with disruptive mood dysregulation disorder without attention deficit disorder

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## Introduction

Despite the significant disease burden associated with disruptive mood dysregulation disorder (DMDD), very few are known about effective treatments.[1] Atomoxetine (ATX) is a nonstimulant presynaptic inhibitor of the norepinephrine (NE) transporter. Current pharmacological guidelines suggest that ATX should be considered as a second-line treatment for ADHD, especially when anxiety or mood disorder co-occurred.[2] While the efficacy of ATX on affective symptoms has never properly been investigated in children or adolescents, two meta-analyses of RCTs in adults with ADHD showed its positive impact on emotional lability in addition to ADHD symptoms.[3,4] In children and adolescents, anecdotic reports stress a possible positive impact of ATX in patients with neurodevelopmental disorder associated with cognitive difficulties, such as sluggish cognitive tempo, dyslexia, and pervasive developmental disorder.[5] Recently, based on evidence mainly from adult patients, we used ATX in six resistant inpatient cases with severe chronic irritability and matching DMDD criteria. Five showed a dramatic clinical improvement.

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## Methods

We conducted a retrospective review of psychiatric inpatients who were challenged with ATX for the management of DMDD between October 2016 and October 2018 in two child and adolescent psychiatric departments in tertiary care university hospital. Given the large overlap between ADHD and DMDD symptoms (50–80%), only youths with DMDD and without ADHD diagnosis were eligible. By doing so, we ensured that the treatment efficacy could not be due to the effect of ATX on ADHD symptoms. DMDD diagnosis was established from symptoms reported by the patient and his/her family. Psychiatric diagnoses were based on discharge diagnoses after the assessment of all information available. Clinical improvement was based on clinical measures routinely used in both departments: (i) the Clinical Global Impression Improvement scale (CGI-I), (ii) the difference in the Affective Reactivity Index score (ARI), the Buss-Durkee Hostility Inventory score (BDHI), and the Children-Global Assessment Functioning (C-GAF) at entrance and at discharge; (iii) changes in the number of weekly physical restraints; and finally (iv) changes in the number of weekly as needed (PRN) medications. To determine the specific impact of the medication, we defined the week prior to ATX initiation as the baseline period for the weekly use of physical restraints and PRN medications. Changes were assessed and reported

**Table 1. Case descriptions**

| Patient | Age (y = years, m = months) | Gender | Diagnoses associated with DMDD | C-GAF at entrance | CGI-S at entrance | Medication history before hospitalization | Medications at discharge | ATX initial dose | Titration duration for full dose treatment | ATX discharge dose (mg/[kg/d]) | Follow-up | Confounding medication changes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 14y 0m | M | ANX: panic disorder<br>MLD: dyspraxia + dyslexia<br>IQ 100 | 25 | 6 | RIS, HAL, CYA, LOX | ATX 80 mg qam<br>LVP tid<br>DVP bid | 10 mg/d = 0.13 mg/kg/d | 4 weeks | 80 mg/d = 0.95 mg/kg/d | 5 months | Minor |
| 2 | 12y 7m | F | ANX:<br>MLD: dyspraxia + dyscalculia + dysorthography<br>no IQ available | 30 | 6 | RIS, ARI, CAR, | ATX 80 mg | 25 mg/d = 0.4 mg/kg/d | 4 weeks | 80 mg/d =1.2 mg/kg/d | 10 months | None |
| 3 | 11y 9m | M | ANX:<br>MLD:<br>dyslexia + dyspraxia + dyscalculia + dysorthography<br>Chromosome aneuploidies 47, XYY)<br>borderline cognitive function | 25 | 6 | RIS, CAR, MEL, CYA, | ATX 50 mg<br>MEL 2 mg | 25 mg/d = 0.71 mg/kg/d | 4 weeks | 40 mg/d =1.14 mg/kg/d | 48 months | None |
| 4 | 10y 4m | F | ANX;<br>Dyspraxia<br>no IQ available | 30 | 5 | RIS, LOX, | ATX 60 mg<br>MEL 2 mg | 25 mg/d = 0.55 mg/kg/d | 4 weeks | 60 mg/d =1.33 mg/kg/d | 24 months | None |
| 5 | 10y 7m | M | ANX: MLD: dyslexia + dyspraxia + dyscalculia + dysorthography<br>IQ: 70 | 30 | 5 | LAM, DVP, LVP | ATX 30 mg | 10 mg/d = 0.4 mg/kg/d | 3 weeks | 60 mg/d =1.2 mg/kg/d | 7 months | None |
| 6 | 11y 2m | M | ANX:<br>MLD: dysorthography + dyspraxia<br>ASD<br>IQ: 107 | 25 | 6 | RIS, ARI, SER, | ATX 60 mg | 25 mg/d = 0.57 mg/kg/d | 5 weeks | 60 mg/d =1.36 mg/kg/d | 6 months | None |

*Notes*: DMDD, disruptive mood dysregulation disorder; ANX, anxiety disorder; MLD, multiple learning disabilities; CYA, cyamemazine; RIS, risperidone; ARI, aripiprazole; HAL, haloperidol; LOX, loxapine; ATX, atomoxetine; LVP, levomepromazine; DVP; divalproex sodium; CAR, carbamazepine; LAM, lamotrigine; SER, sertraline; MEL, melatonine.
Major, antipsychotic cross taper conducted; Minor, tapered off ineffective antipsychotic with no new drug started.

at 2, 3 and 4 weeks following achievement of concentration steady state at the maximum used ATX dosage. This project was designated as Institutional Review Board (IRB) exempt due to its retrospective design, patient de-identification, and the use of routine questionnaires.

## Results

Six patients aged from 10 to 14 years (mean 11.7) were included (Table 1). Most patients were male ($n = 4$). The most common associated diagnoses with DMDD was anxiety disorder ($n = 6$). Five patients had multiple learning disabilities. The period of treatment on ATX ranged from 5 to 48 months (mean 16.7). Mean ATX starting dosage was 20 mg/d (i.e., 0.46 mg/kg/d) and mean discharge dosage was 63 mg/d (i.e., 1.20 mg/kg/d). The number of weeks to achieve maximum dose ranged from 3 to 5 weeks (mean 4).

During the hospitalization, the score on the C-GAF showed improvement, with average change value of +50.8. Five patients were very much improved and one patient was minimally improved according to the CGI-I following ATX therapy. We noted a 73% reduction of the ARI scores (at entrance mean = 24 (±2.53), at discharge mean = 6.68 (±6.49), $t$ (5) = 7.61, $p < .001$) and a 46% decrease of the BDHI scores (at entrance mean = 102.2 (±13.6), at discharge mean = 54.5 (±19.5), $t$ (5) = 8.27, $p < .001$).

The use of physical restraints for aggressive behavior was reduced during the treatment period (mean = 7.67 at baseline compared to mean = 4.17 after 2 weeks, $p = .01$). The frequency of PRN medications per week decreased after 2 weeks of ATX (mean = 4.83 at baseline compared to mean = 3.67 after 2 weeks, $p = .02$). No patients were readmitted to our facility within 60 days following discharge. ATX was well tolerated. The main adverse effect identified was enuresis in one patient.

## Discussion

We found that five patients were very much improved and one patient minimally improved following ATX therapy. These observations are supported by the reduction of ARI and BDHI scores between admission and discharge, and by the decrease in physical restraints and PRN medications in the weeks following achievement of concentration steady state at the maximum used ATX dosage. As mentioned in the introduction, the assumption that ATX could have a positive effect on emotional dysregulation symptoms was based on empirical data from adults with ADHD.[3,4] The most striking finding of this study is that ATX could also effectively target irritability in non-ADHD youths. Open-label use of medications, the small sample size, the use of other medications, and the absence of blind clinical rating limit our ability to produce firm conclusions. Moreover, all of the six patients had at least one comorbid anxiety disorder. Such finding may partially explain the efficacy of ATX toward chronic irritability by reducing anxiety features. However, we believed that ATX should be investigated through well-designed efficacy and tolerance studies on DMDD in children and adolescents to confirm or reject our observations.

## Disclosures

The authors declare they have nothing to disclose.

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