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

Xavier Benarous,1,2* Vladimir Ferrafiat,3,4 Jessica Zammis,3,4 Angèle Consoli,1,5 Priscille Gérardin,3,4 Jean-Marc Guillé,2,6,7 and David Cohen1,8

1 Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France
2 INSERM U1105 Research Group for Analysis of the Multimodal Cerebral function, University of Picardie- Jules Verne (UPJV), Amiens, France
3 Department of Child and Adolescent Psychiatry, Charles Nicolle Hospital, Rouen, France
4 Department of Child and Adolescent Psychiatry, URHEA, CH Le Rouvray, Sotteville les Rouen, France
5 Group of Clinical Research-15, Dimensional approach of child and adolescent psychotic episodes, Sorbonne University, Paris, France
6 Child and Adolescent Psychiatry Services, Amiens University Hospital, Amiens, France
7 Department of Psychiatry, McGill University, Montreal, Canada
8 CNRS UMR 7222, Institute for Intelligent Systems and Robotics, Sorbonnes Universités, UPMC, Paris, France

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Introduction

Despite the significant disease burden associated with disruptive mood dysregulation disorder (DMDD), very little is known about effective treatments. 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. 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. In children and adolescents, anecdotal 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. 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.

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

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

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.
The most striking finding of this study was that ATX could have a positive effect on emotional dysregulation symptoms was based on empirical data from adults with ADHD. 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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