

A Study of Atomoxetine in Adolescents with ADHD and Major Depressive Disorder

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ABSTRACT

Objective: Recent attention has focused on the safety of drugs labeled for the treatment of depression in pediatric patients. Because attention-deficit/hyperactivity disorder (ADHD) may co-occur with depression, we examined the efficacy and safety of atomoxetine, a norepinephrine reuptake inhibitor, in adolescents with ADHD and major depressive disorder (MDD).

Methods: Adolescents aged 12 to 17 with DSM-IV diagnoses of both ADHD and depression confirmed by persistently elevated scores on the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) ≥ 1.5 SD above the norm and Child Depression Rating Scale (CDRS ≥ 40) were randomly assigned to either atomoxetine (ATX, n=72) or placebo (PBO, n=70) and treated for up to 9 weeks. Treatment-emergent mania was defined as a Young Mania Rating Scale total score ≥ 15 postbaseline 8 baseline was ≤ 15 .

Results: Mean ADHD RS total score decreased significantly from baseline to endpoint for the atomoxetine group (-13.3, SD 10.0) relative to placebo (-4.1, SD 13.0; $P < .001$). Mean CDRS improved for both groups but did not differ between groups (ATX -14.8, SD 13.3; PBO -12.8, SD 10.4; $P = .34$). Treatment-emergent mania did not differ between groups (ATX 2.9%, PBO 3.0%, $P = .99$). Adverse events that occurred significantly more frequently in the atomoxetine group were nausea and decreased appetite. No adverse events involving suicidal ideation or suicidal behavior occurred in either group.

Conclusion: Results suggest that atomoxetine is effective for the treatment of ADHD and is safe and tolerable for adolescents with ADHD and MDD.

INTRODUCTION

- Attention-Deficit/Hyperactivity Disorder (ADHD)
 - Affects 3% to 7% of school-aged children in the United States¹
 - Characterized by inattention and/or hyperactivity and impulsivity
 - Hypothesized that dopaminergic and noradrenergic pathways are involved

- Atomoxetine
 - A highly selective inhibitor of the presynaptic norepinephrine transporter
 - FDA-approved for ADHD treatment in children, adolescents, and adults

- ADHD and Comorbid Depression
 - ADHD and mood disorders are frequently comorbid.^{2,3}
 - Atomoxetine was associated with greater reductions in depression rating scale scores in a trial aimed primarily at ADHD.⁴

- Study Objective
 - This study compared atomoxetine with placebo in the treatment of adolescents with ADHD and MDD.

METHODS

- Subjects**
 - Adolescents ≥ 12 and < 18 years old who met DSM-IV criteria for both ADHD and MDD

- Inclusion Criteria**
 - Patients with ADHD RS scores 1.5 standard deviations above age and gender norms
 - Child Depression Rating Scale (CDRS) score ≥ 40

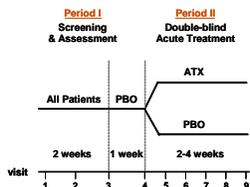
- Exclusion Criteria**
 - Patients beginning structured psychotherapy of ADHD and/or depression less than 1 month prior to trial entry

- Study Design**
 - Randomized, double-blind, placebo-controlled trial
 - Patients randomly assigned to approximately 9 weeks of atomoxetine or placebo
 - The target atomoxetine dose (1.2 mg/kg/day) could be increased to 1.8 mg/kg/day for patients not responding adequately
 - All daily doses were administered once daily
 - Visits 1 and 2 were screening and baseline assessment visits followed by a placebo lead-in phase at Visits 3 through 4.
 - At the beginning of Visit 4, patients began double-blind treatment with placebo or atomoxetine followed by assessments at Visits 5 through 9.

- Primary Efficacy Measures**
 - ADHD RS, investigator-rated and -scored based on Secondary Measures
 - Children's Depression Rating Scale-Revised (CDRS-R)
 - Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales
 - Young Mania Rating Scale (YMRS)

- Statistics**
 - ADHD RS and CDRS-R Total scores
 - Postbaseline scores analyzed by repeated measures analysis.
 - Change from baseline to endpoint scores analyzed using a last-observation-carried-forward (LOCF) analysis.
 - CGI-S and CGI-I scales
 - Change from baseline to endpoint scores analyzed using a LOCF analysis.
 - YMRS Total score
 - Change from baseline to endpoint scores analyzed using a LOCF analysis.
 - Post-hoc categorical analysis of treatment-emergent mania: YMRS Total Score < 15 at baseline and ≥ 15 postbaseline.⁵

LYAX Study Diagram



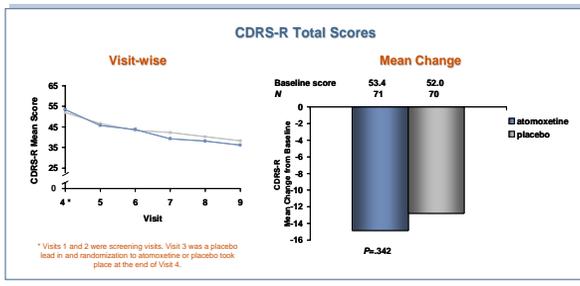
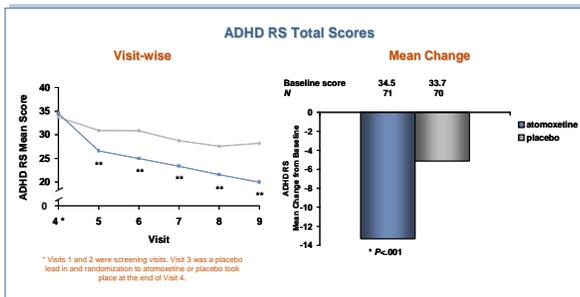
Patient Demographics

	Atomoxetine (N=72)	Placebo (N=70)
Age, mean (SD)	14.6 (1.8)	14.2 (1.5)
Caucasian, n (%)	64 (88.9)	53 (75.7)
Gender, n (%)		
Male	52 (72.2)	52 (74.3)
Female	20 (27.8)	18 (25.7)
ADHD Subtype, n (%)		
Combined	33 (45.8)	28 (40.0)
Inattentive	39 (54.2)	42 (60.0)
Prior Stimulant Exposure, n (%)		
Yes	57 (79.2)	58 (82.9)
No	15 (20.8)	12 (17.1)
CYP2D6 Genotype, n (%)		
Extensive metabolizer	67 (95.7)	64 (92.8)
Poor metabolizer	3 (4.3)	5 (7.2)
Height, cm; mean (SD)	163.7 (11.9)	163.7 (9.8)
Weight, kg; mean (SD)	63.1 (14.3)	58.4 (12.7)

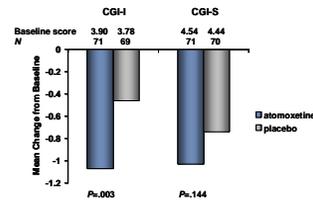
RESULTS

Total Daily Atomoxetine Dose (all Patients Randomly Assigned)

	Atomoxetine (N=72)
Mean final dose	1.51 \pm 0.24 mg/kg/day
Median final dose	1.55 mg/kg/day
Maximum final dose	1.88 mg/kg/day



Mean Change in CGI-I and CGI-S Total Scores



Treatment-emergent Mania Based on YMRS Total Score*

	N	%
Atomoxetine, N=68	2	2.9
Placebo, N=67	2	3.00

At baseline, 5 patients in the atomoxetine group and 2 patients in the placebo group had YMRS scores > 15 . At endpoint, all but 1 patient in the atomoxetine group had YMRS scores < 15 .

* Treatment-emergent mania defined as YMRS Total Score < 15 at baseline and ≥ 15 postbaseline 5.

Treatment-emergent Adverse Events of $> 5\%$ in Either Treatment Group

Adverse Event	Atomoxetine (N=72)	Placebo (N=69)	Fisher's Exact P Value
Headache	12 (16.7%)	7 (10.1%)	.326
Nausea	16 (22.2%)	3 (4.3%)	.002
Vomiting	9 (12.5%)	6 (8.7%)	.588
Targing	3 (4.2%)	3 (4.3%)	.153
Abdominal pain upper	6 (8.3%)	5 (7.2%)	1.00
Dizziness	9 (12.5%)	2 (2.9%)	.056
Diarrhea	1 (1.4%)	6 (8.7%)	.059
Influenza	3 (4.2%)	4 (5.8%)	.715
Pyrexia	2 (2.8%)	5 (7.2%)	.268
Weight decreased	6 (8.3%)	1 (1.4%)	.116
Irritability	4 (5.6%)	1 (1.4%)	.367
Weight increased	1 (1.4%)	4 (5.8%)	.202

There was 1 serious adverse event, worsening of depression, in the placebo group.

CONCLUSIONS

- ADHD scores on the ADHD RS improved significantly in patients in the atomoxetine treatment group.
- Depression scores on the CDRS-R improved for both placebo and atomoxetine treatment groups but the change from baseline was not significantly different between groups.
- The incidence of treatment-emergent manic symptoms was low and not significantly different between groups.
- The incidence of nausea and decreased appetite occurred significantly more frequently in the atomoxetine treatment group compared with the placebo group.
- For adolescent patients with ADHD and MDD, atomoxetine is safe and tolerable, and is effective for symptoms of ADHD. However, there is no evidence of efficacy for MDD.

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