

Improvement of ADHD by Atomoxetine in Children with Tic Disorders

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ABSTRACT

Objective: Assess efficacy of atomoxetine versus placebo for treatment of attention-deficit/hyperactivity disorder (ADHD) in children with Tourette's syndrome or chronic motor tics.

Methods: Study subjects (7–17 years old) with ADHD and Tourette's syndrome or chronic motor tics were randomly assigned to double-blind treatment with placebo ($n=72$) or atomoxetine (0.5–1.5 mg/kg/day, $n=76$) for approximately 18 weeks.

Results: Atomoxetine patients showed significantly greater improvement on the ADHDRS-IV-Parent:Inv Total (-10.9 ± 10.9 versus -4.9 ± 10.3 , $p=.002$) as well as the Inattentive ($p=.019$) and Hyperactive/Impulsive ($p=.002$) subscale scores. Similarly, the atomoxetine group showed greater improvement in CGI severity of ADHD/psychiatric symptoms (-0.8 ± 1.1 versus -0.3 ± 1.0 , $p=.015$). Atomoxetine treatment was associated with greater numerical reduction of tic severity on the Yale Global Tic Severity Scale total score (-5.5 ± 6.9 versus -3.0 ± 8.7 , $p=.063$) and achieved significance on CGI tic/neurological severity (-0.7 ± 1.2 versus -0.1 ± 1.0 , $p=.002$). Atomoxetine patients had greater increases in heart rate ($+8.3\pm 12.0$ versus -1.2 ± 12.7 bpm, $p<.001$) and decreases of body weight (-0.9 ± 1.9 versus $+1.6\pm 2.3$ kg, $p<.001$). Rates of treatment-emergent decreased appetite and nausea were significantly higher for atomoxetine patients. Discontinuation rates from both groups were low. No other clinically relevant differences were seen in any other safety parameter.

Conclusions: Atomoxetine is efficacious and well tolerated in children with ADHD and comorbid tic disorders and may decrease tic severity.

INTRODUCTION

- Approximately 10% to 35% of children with attention-deficit/hyperactivity disorder (ADHD) have a comorbid tic disorder.
- Approximately 30-65% of children with Tourette's syndrome have ADHD.
- Treatment of ADHD has traditionally relied on the use of psychostimulants, but these drugs may exacerbate tics or produce little benefit in a portion of ADHD patients.

METHODS

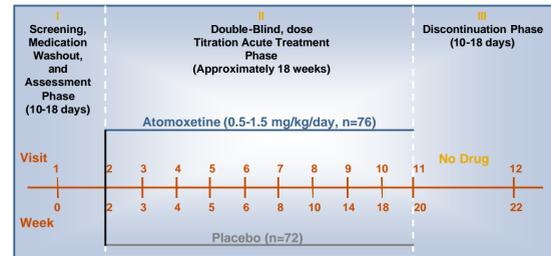
- Primary Hypothesis:** Atomoxetine does not cause significant worsening of tic severity relative to placebo in children with ADHD and comorbid Tourette's syndrome or chronic motor tics.
- Secondary Hypothesis:** Atomoxetine treatment results in significant improvement of ADHD symptoms relative to placebo in children with ADHD and comorbid Tourette's syndrome or chronic motor tics.

Study Design

- 2-week screening/washout period
- 18-week double-blind, parallel group, placebo-controlled acute treatment phase
- Atomoxetine titration up to 1.5 mg/kg/day, administered b.i.d.
- "Clinical non-responder" (CGI-Overall-S ≥ 4 for 2 consecutive visits) beginning at V9 (Week 12) permitted entry into an open-label extension study.

Subjects

- 7 – 17 years old
- 20 – 80 kg
- Tourette's syndrome or chronic motor tic disorder
 - YGTSS total score ≥ 5 at V1, V2



- ADHD, any subtype
 - ADHDRS-IV-Parent:Inv Total score ≥ 1.5 SD above age and sex norm for ADHD subtype at V1, V2
- Able to swallow capsules

Exclusion Criteria

- Severe OCD or depression
 - OCD requiring medication
 - CY-BOCS total score >15
 - Depression requiring medication
 - CDRS-R total score >40
- History of Bipolar I or II, psychosis, organic brain disease, seizure disorder, substance abuse, mental retardation
- Serious medical conditions

Efficacy Assessments

- ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv)
- Clinical Global Impressions
 - Tic/Neurological Severity (CGI-Tic/Neuro-S)
 - ADHD Psychiatric Severity (CGI-ADHD/Psych-S)
 - Overall Severity (CGI-Overall-S)
- Yale Global Tic Severity Scale (YGTSS)
- Tic Severity Self-Report (TSSR)
- Multidimensional Anxiety Scale for Children (MASC)
- Children's Depression Rating Scale- Revised (CDRS-R)
- Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)

Statistical Methods

- For continuous parameters (with the exception of the ADHDRS-IV-Parent:Inv measures), between treatment group differences in mean change from baseline to endpoint (last observation carried forward) scores were assessed using an analysis of variance (ANOVA).
- Since a significant baseline treatment group difference was observed for the ADHDRS-IV-Parent:Inv measures, between treatment group differences in mean change from baseline to endpoint (last observation carried forward) scores were assessed using an analysis of covariance, adjusting for baseline.
- Effect size (ES) was computed by subtracting the atomoxetine mean change from baseline from the placebo mean change from baseline and dividing that difference by the square root of the mean square error (from an ANOVA model with a treatment effect).
- For categorical measures, between treatment group differences were assessed using Fisher's exact test.

Patient Demographics and Other Characteristics

Variable	Atomoxetine (N=76)	Placebo (N=72)	p-Value
Age (years): Mean (SD)	10.9 (2.5)	11.5 (2.4)	.126
Sex: n (%)			.200
Female	6 (7.9)	11 (15.3)	
Male	70 (92.1)	61 (84.7)	
Origin: n (%)			.785
Caucasian	65 (85.5)	65 (90.3)	
African descent	5 (6.6)	2 (2.8)	
Hispanic	3 (3.9)	3 (4.2)	
Other	3 (3.9)	2 (2.8)	
Weight (kg): Mean (SD)	39.9 (13.1)	44.8 (15.3)	.037
Prior stimulant exposure: n (%)	55 (72.4)	46 (63.9)	.293
Poor metabolizers: n (%)	4 (5.3)	5 (7.0)	.740

RESULTS

Patient Diagnoses

Characteristic	Atomoxetine (N=76) n (%)	Placebo (N=72) n (%)	p-Value
Tourette's syndrome	61 (80.3)	56 (77.8)	.840
ADHD subtype			.487
Combined	50 (65.8)	40 (55.6)	
Inattentive	24 (31.6)	29 (40.3)	
Hyperactive/Impulsive	2 (2.6)	3 (4.2)	
ODD	17 (22.4)	15 (20.8)	.844
MDD	0 (0)	1 (1.4)	.486
GAD	2 (2.6)	3 (4.2)	.675
OCD	2 (2.6)	2 (2.8)	1.00

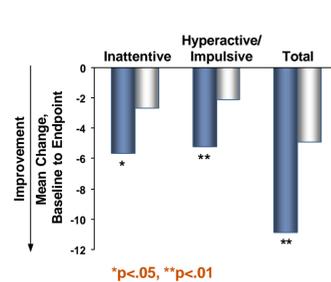
Baseline ADHD and Overall Severity

Measure	Atomoxetine (N=76)		Placebo (N=72)		p-Value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
ADHDRS-IV-Par:Inv					
Hyper/Imp	17.1 (6.8)	14.5 (7.1)			.025
Inattentive	21.7 (4.1)	20.5 (5.0)			.128
Total	38.8 (9.0)	35.0 (9.5)			.015
CGI-S					
ADHD/Psych-S	4.7 (0.8)	4.5 (0.8)			.086
Tic/Neuro-S	3.7 (0.9)	3.6 (0.8)			.438
Overall-S	4.5 (0.7)	4.3 (0.7)			.077

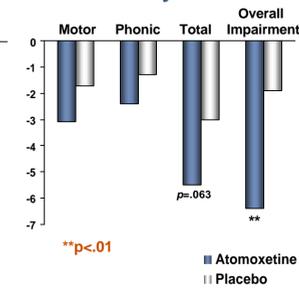
Baseline Severity of Comorbid Disorders

Measure	Atomoxetine (N=76)		Placebo (N=72)		p-Value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
YGTSS					
Motor	13.2 (3.9)	12.9 (4.1)			.582
Phonic	8.4 (5.7)	9.5 (5.2)			.212
Total	21.6 (7.8)	22.4 (8.4)			.563
Overall impairment	21.5 (11.0)	20.1 (11.5)			.445
TSSR Total	12.5 (11.0)	11.3 (8.7)			.496
MASC Total T-score	50.8 (12.8)	50.6 (11.7)			.925
CDRS-R Total	22.6 (4.8)	24.1 (5.8)			.098
CY-BOCS Total	3.0 (4.7)	2.5 (4.3)			.477

ADHDRS-IV-Parent:Inv



Yale Global Tic Severity Scale



Safety: Adverse Events

Event	Atomoxetine (N=76)		Placebo (N=72)		p-Value
	n (%)	n (%)	n (%)	n (%)	
Headache	16 (21.1)	14 (19.4)			.840
Vomiting	12 (15.8)	6 (8.3)			.211
Upper abdominal pain	7 (9.2)	9 (12.5)			.601
Decreased appetite	12 (15.8)	2 (2.8)			.010
Cough	4 (5.3)	9 (12.5)			.151
Nausea	12 (15.8)	1 (1.4)			.002
Fatigue	9 (11.8)	3 (4.2)			.131
Pharyngitis	3 (3.9)	9 (12.5)			.073
Diarrhea	3 (3.9)	8 (11.1)			.123

Adverse events with an incidence $>10\%$ or significantly different between treatment groups.

Safety: Discontinuations

- Discontinuations due to adverse events were rare and rates were not significantly different between treatment groups (Atomoxetine, 2.6%; Placebo, 1.4%; $p=1.0$).
- No subject discontinued due to exacerbation of tics.

Safety: Vital Signs / ECG

Event	Atomoxetine (N=76)		Placebo (N=72)		p-Value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Blood pressure (diastolic)	3.3 (11.0)	0.5 (8.0)			.083
Blood pressure (systolic)	2.9 (10.4)	0.4 (10.5)			.147
Pulse	8.3 (12.0)	-1.2 (12.7)			<.001
Body weight (kg)	-0.9 (1.9)	1.6 (2.3)			<.001
ECG QT _c ^a	-5.7 (12.4)	0.2 (12.3)			<.001

Data are expressed as mean change, baseline to endpoint. ^aIncreases in QT_c may be associated with an increased risk of torsade de pointes. Decreases in QT_c are not a clinical concern.

CONCLUSIONS

- Atomoxetine significantly decreased ADHD symptoms in patients with comorbid tic disorders compared with placebo (ADHD RS Total ES = 0.6).
- Atomoxetine did not worsen tics. A trend towards decreased tic severity was observed (YGTSS Total ES = 0.3).
- Treatment appeared to be safe and well tolerated.
 - No subject discontinued due to exacerbation of tics.
 - Only decreased appetite and nausea were observed to be significantly increased over placebo rates of adverse events.
- Atomoxetine appears to be a useful treatment option for ADHD children and adolescents with comorbid tic disorders.