Results From 2 Proof-of-Concept, Placebo-Controlled Studies of Atomoxetine in Children With Attention-Deficit/Hyperactivity Disorder

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Background: Atomoxetine is a nonstimulant drug being studied for the treatment of attention-deficit/hyperactivity disorder (ADHD). Atomoxetine is a highly specific inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or other neurotransmitter transporters or receptors. Results of 2 proof-of-concept studies are reported that tested the hypothesis that a selective inhibitor of presynaptic norepinephrine uptake would be effective for the treatment of ADHD in school-aged children.

Method: Two identical 12-week, stratified, randomized, double-blind, placebo-controlled trials were conducted in children who met DSM-IV criteria for ADHD. The primary efficacy outcome measure was the mean change from baseline to endpoint in the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) total score. Secondary efficacy measures included the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S) and the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S).

Results: A total of 291 patients were randomized in the 2 trials combined (Study 1, N = 147; Study 2, N = 144). Stimulant-naive patients were randomized to atomoxetine, placebo, or methylphenidate. Patients with prior stimulant exposure were randomized to atomoxetine or placebo. Atomoxetine significantly reduced ADHD RS total scores compared with placebo in each study ($p < .001$). Changes in the CGI-ADHD-S (Study 1: $p = .003$; Study 2: $p = .001$) and CPRS-ADHD Index (Study 1: $p = .023$; Study 2: $p < .001$) also showed atomoxetine to be statistically significantly superior to placebo in reducing ADHD symptoms. Atomoxetine was found to be well tolerated in this population of pediatric patients.

Conclusion: Two studies of atomoxetine early in its development confirmed that atomoxetine, a specific and selective inhibitor of noradrenergic uptake, was effective for the treatment of children with ADHD. In addition, atomoxetine was found to be well tolerated.

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Attention-deficit/hyperactivity disorder (ADHD) is an early-onset, neurobehavioral disorder characterized by the symptom cluster of inattention, impulsivity, and hyperactivity. Recognition of ADHD, as well as pharmacologic treatment of this disorder, has significantly increased during the past decade.[1,2] Epidemiologic studies report a range of prevalence rates that has led the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition-TR (DSM-IV-TR) to estimate that 3% to 7% of school-aged children may have ADHD, and the recently published American Academy of Pediatrics ADHD treatment guideline suggests a prevalence rate of 8% to 10%.[1,3–5] ADHD is associated with a high level of comorbidity, such as learning disabilities and mood and anxiety disorders, and it is estimated that as many as 65% of children with ADHD will have 1 or more comorbid conditions.[5]

The 2 primary treatment modalities for ADHD are pharmacotherapy and behavioral interventions, with psychostimulant treatment considered the primary pharmacotherapy for ADHD.[6] While psychostimulant agents are generally efficacious, a significant number of patients exhibit an inadequate response or cannot tolerate their use.[7] Green[8] reports that approximately 25% to 30% of patients

do not have satisfactory responses to stimulant medication. Greenhill[9] estimated that 10% to 40% of children with ADHD do not improve on stimulant treatment or experience adverse events that result in discontinuation of treatment. Late afternoon and evening dosing with stimulants may lead to nighttime sleep disturbances, which in turn may lead to medication discontinuation or a lack of full-time medication coverage. The resulting lack of medication coverage may lead to recurrence of ADHD symptoms after school when the child is at home or engaged in extracurricular activities. Since all stimulants are currently controlled substances, there has been considerable interest in the development of medications without abuse liability. Although some nonstimulant medications that are not approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD have been used to successfully treat ADHD symptoms, none are currently approved for the treatment of the disorder.[10] In addition, the data from double-blind studies are limited, and there have been very few multicenter, randomized, placebo-controlled trials of these medications in pediatric ADHD.

Although the etiology of ADHD is unknown, its pathophysiology appears to involve a dysregulation in central dopaminergic and noradrenergic pathways associated with modulation of higher cortical functions including attention, alertness, vigilance, and executive function.[11–15] Atomoxetine is a highly specific inhibitor of presynaptic norepinephrine reuptake with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Similar to the metabolism of desipramine and other commonly prescribed medications, the metabolism of atomoxetine is genetically determined and is influenced by the cytochrome P450 2D6 isoenzyme (CYP2D6) pathway, resulting in extensive and poor metabolizers.[16]

The specificity and selectivity of atomoxetine for the norepinephrine transporter, along with data from a study of desipramine[17] in children with ADHD, led to an interest in a study that would confirm the hypothesis that a specific and selective norepinephrine reuptake inhibitor would be effective for the treatment of ADHD. Although desipramine inhibits uptake at the norepinephrine transporter, it is neither specific nor selective in its activity. Prior to the start of the studies reported in this article, limited data from an open-label pharmacokinetic study in children with ADHD[18] and a pilot, placebo-controlled study in adults with ADHD[19] suggested that atomoxetine could be an attractive treatment for ADHD.

Two proof-of-concept, randomized, double-blind, placebo-controlled studies were undertaken to fully test the hypothesis that atomoxetine would be efficacious for the treatment of ADHD. The primary objective of each study was to evaluate the efficacy of atomoxetine as compared to placebo in all patients randomized to atomoxetine or placebo. Efficacy was to be determined by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD RS). The secondary objective was a comparison of safety of atomoxetine and placebo. We report here the results of these 2 early-phase, double-blind, placebo-controlled studies that assessed the safety and efficacy of atomoxetine as compared with placebo in school-aged children with ADHD.

METHOD

Study Population

Two multicenter trials were conducted concurrently at a total of 17 investigational sites (Study 1 = 7 sites, Study 2 = 10 sites) in the United States beginning in November 1998 and continuing until February 2000. Patients were at least 7 years of age but less than 13 years of age at the initial visit and were determined to be of normal intelligence based on the Wechsler Intelligence Scale for Children-Third Edition (WISC-III).[20] Patients were required to meet DSM-IV diagnostic criteria for ADHD, as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia,[21] and have a score on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS)[22] at least 1.5 standard deviations above the age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype. Patients with the combined type met DSM-IV criteria, i.e., minimum of 6 inattentive and 6 hyperactive/impulsive symptoms.

Patients were excluded from this study if, based on their genotype, they were characterized as poor metabolizers of CYP2D6. The assessment of tolerability and safety of atomoxetine in poor metabolizers was ongoing at the time of study initiation. In addition, patients were ineligible to participate in this study if they weighed less than 25 kg (55 lb) at study entry; had a documented history of bipolar I or II disorder or any history of psychosis; had any organic brain disease or a history of any seizure disorder; were taking any psychotropic medication; had any history of alcohol or drug abuse within the past 3 months; or had significant prior or current medical conditions. Patients with comorbid anxiety and/or depressive disorders were eligible to participate.

Patients were recruited by referral and by advertisement. After a description of the procedures and purpose of the study was provided, written informed consent was obtained from each patient's parent or guardian and written assent was obtained from patients, if applicable, prior to entering the study. This study was conducted in accor-

dance with the ethical standards of each of the investigative sites' institutional review boards and with the Declaration of Helsinki 1975, as revised in 1983.

Study Design

Eligible patients were enrolled in 1 of 2 double-blind, randomized, multisite, placebo-controlled studies. The study designs were identical (Study 1 or Study 2) and were conducted as separate trials to conclusively test the noradrenergic hypothesis. Each was sufficiently powered to meet the primary analysis of detecting treatment differences between atomoxetine and placebo. There were 3 study periods: study period I (visits 1 through 3) was a 2-week medication washout, screening, and assessment phase; study period II (visits 3 through 12) was a 9-week, double-blind, acute treatment phase; and study period III (visits 12 through 13) was a 1-week, single-blind study drug discontinuation phase. Prior to randomization, patients were stratified into 2 groups, as determined by their previous exposure to psychostimulants. Patients with a prior exposure to psychostimulants (stimulant-prior-exposure stratum) were randomized to 9 weeks of double-blind treatment with atomoxetine or placebo. Randomization was balanced between the 2 groups.

Patients with no prior history of treatment with psychostimulants (stimulant-naive stratum) were randomized to 9 weeks of double-blind treatment with atomoxetine, placebo, or methylphenidate. Randomization was intentionally unbalanced in this stratum with a randomization ratio for atomoxetine, placebo, and methylphenidate of 3:3:2.

Since these were hypothesis-testing, "proof-of-concept" studies, methylphenidate treatment was included in the stimulant-naive stratum in both studies to validate the study design in the event that atomoxetine failed to separate from placebo. Study design validation of a novel compound in early clinical trials has become increasingly important in the development of new psychiatric drugs. One means of validating the study design is to include as a treatment option a medication proven to be effective, e.g., methylphenidate, for the disorder under study, in this case ADHD. A comparison of the efficacy of atomoxetine with methylphenidate was neither a primary nor a secondary objective of these studies. Had atomoxetine failed to separate from placebo in either study, data from the methylphenidate treatment group, compared with placebo, would be available to ensure that the hypothesis had been fairly tested and would have been essential in determining further development of atomoxetine for ADHD.

In the stimulant-naive stratum, patients assigned to atomoxetine treatment received active drug before school and in the late afternoon or early evening, as well as a midday dose of placebo. Patients assigned to treatment with methylphenidate received study drug before school and at midday, as well as a dose of placebo in the late afternoon or early evening. Since a methylphenidate treatment arm was not needed in the prior-stimulant-exposure stratum, patients were randomized to double-blind treatment with either atomoxetine or placebo, each administered before and after school, in the late afternoon or early evening.

Study drug dose was titrated based on clinical response and was administered as equally divided doses. In the stimulant-naive stratum, the double-blind dosing schedule for patients randomized to atomoxetine allowed patients to be titrated to a maximum dose of 2 mg/kg/day or a total dose of 90 mg/day based on therapeutic response and tolerability. The double-blind dosing schedule for patients randomized to methylphenidate in the stimulant-naive stratum allowed patients to be titrated to a maximum dose of methylphenidate of 1.5 mg/kg/day or a total daily dose of 60 mg/day, also based on therapeutic response. Package label information for methylphenidate limits the maximum daily dose to 60 mg.[23] Since some flexibility with dosing was needed for work and school schedules, it was recommended that the morning dose be given between 0630 and 0800 hours; the midday dose be given 3 to 4 hours after the morning dose, usually between 1030 and 1200 hours; and the after school dose be given 3 to 4 hours after the midday dose, usually between 1430 and 1700 hours. In the stimulant-prior-exposure stratum, study drug was administered before and after school.

In an effort to develop a weight-based dosing schedule for future studies and to address the considerable variability in patients' weights, a weight-based dose titration schedule was used. All atomoxetine-treated patients achieved their maximum dose no later than week 7 of treatment, and all methylphenidate-treated patients achieved their maximum dose no later than week 6 of treatment. The amount of dose increase at each visit was determined by clinical response following investigator assessment and by each patient's baseline weight.

Study drug materials for all treatment groups were manufactured to be identical in appearance, and no evidence of unblinding during the studies was uncovered. Randomization schedule information was not released until the final database was cleaned and locked. Treatment codes were provided to the investigational sites in a sealed manner for emergency purposes and were returned unopened by the investigational sites at the conclusion of the trials.

Outcome Measures

The primary efficacy measure for this study was the ADHD RS,[22] an 18-item scale with 1 item for each of the 18 symptoms contained in the DSM-IV diagnosis of ADHD. Each item on this scale is scored 0 to 3 (0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). This rating scale assessed symptom severity over the previous week and was administered and scored by qualified and

trained personnel at the investigative site during every visit, based on an interview with the parent and child, if the child was able to participate in the interview. The total score was computed as the sum of the scores on each of the 18 items. In addition to the total score, scores were computed for inattention and hyperactivity/impulsivity subscales of the ADHD RS. The ADHD RS administered and scored by trained clinicians has been shown to be a reliable and valid measure of ADHD symptom severity.[24] Acceptable interrater agreement was observed at a rater training session conducted prior to the start of the trials (interclass correlation coefficients of 0.76 to 0.85).

Secondary efficacy analyses using the primary efficacy variable included the percentage of responders (defined a priori as a ≥ 25% reduction in ADHD RS total score) and analyses of changes over time using repeated-measures mixed models. In addition, changes in the Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S)[25] and Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S)[26] scores were assessed as secondary analyses. The CPRS-R:S is a validated parent-scored scale with a large normative sample that includes the ADHD Index as a subscale (CPRS-ADHD Index). This subscale was developed to differentiate children with and without ADHD. The CGI-ADHD-S is a single-item rating of the clinician's assessment of the severity of ADHD symptoms in relation to the clinician's total experience with ADHD patients. Severity is rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill patients). The CGI has been widely used in both child and adult patient populations in a variety of psychiatric disorders including ADHD.[27–29]

The safety and tolerability of acute treatment with atomoxetine were assessed by unsolicited adverse events, laboratory values, changes in vital signs, and electrocardiogram (ECG) intervals.

Statistical Analysis

All statistical tests were performed using a 2-sided test at .05 significance level. For the ADHD RS and CGI-ADHD-S scores, change from baseline to endpoint of the double-blind treatment period was computed for all patients who had a baseline and at least 1 postbaseline measurement using a last-observation-carried-forward approach. Treatment differences in mean change scores were assessed using an analysis of variance (ANOVA) model with terms for baseline, treatment, and investigator. The ADHD RS scores over time were also assessed using a repeated-measures mixed model. The model included terms for baseline, treatment, investigator, strata, visit, and treatment-by-visit interaction, while the within-patient covariance matrix selection was based on Akaike information criteria.

Treatment differences in percentages of unsolicited treatment-emergent adverse events were assessed using Fisher exact test. Treatment differences in changes from baseline to endpoint for laboratory data, vital signs, and ECG intervals were assessed using an ANOVA model.

Table 1. Patient Demographics and Baseline Characteristics

Demographic	Atomoxetine (N = 129)	Placebo (N = 124)
Male, N	98	103
Female, N	31	21
Age, mean (SD), y	9.7 (1.6)	10.0 (1.5)
Diagnostic subtypes, N (%)		
Inattentive	24 (18.6)	24 (19.4)
Hyperactive/impulsive	1 (0.8)	2 (1.6)
Combined	104 (80.6)	98 (79.0)
Comorbid diagnoses, N (%)		
Oppositional defiant disorder	53 (41.1)	45 (36.3)
Elimination disorders	10 (7.8)	15 (12.1)
Phobias	16 (12.4)	13 (10.5)
Dysthymia	7 (5.4)	5 (4.0)
Generalized anxiety disorder	4 (3.1)	3 (2.4)
Major depressive disorder	4 (3.1)	4 (3.2)
Assessment scale scores, mean (SD)		
WISC Full Scale IQ	103.0 (13.7)[a]	106.9 (15.4)
ADHD RS Total	39.5 (8.6)	39.5 (8.2)
CGI-ADHD-S	4.9 (0.8)	4.9 (0.8)
Weight, mean (SD), kg	36.9 (12.2)	37.4 (10.7)
Height, mean (SD), cm	138.2 (10.0)	139.2 (9.6)

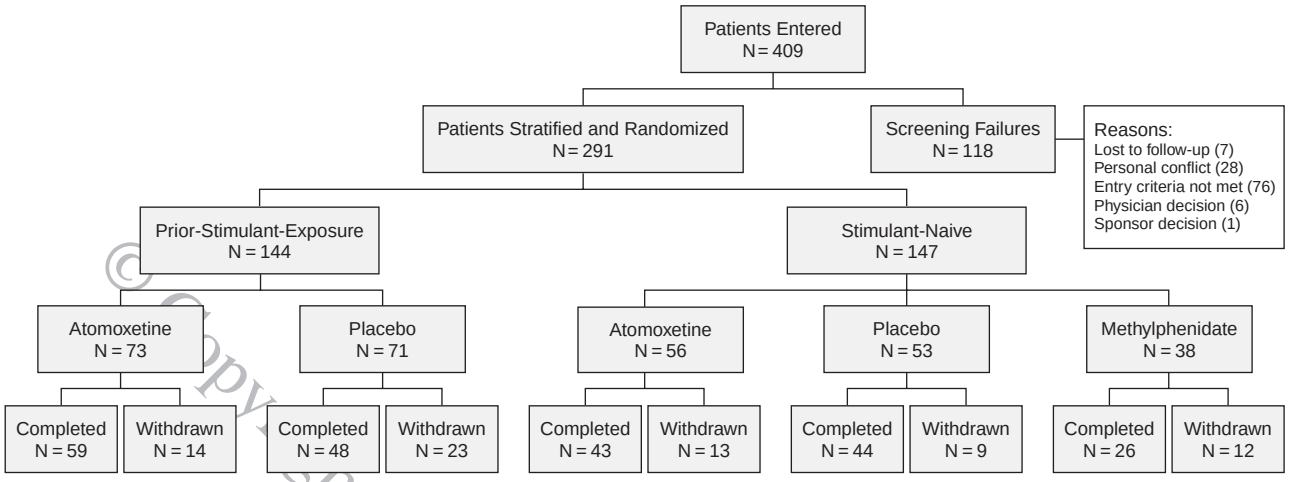
[a]The mean baseline WISC IQ score for the atomoxetine group was statistically significantly lower than for the placebo group (p = .021).
Abbreviations: ADHD RS = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and -Scored; CGI-ADHD-S = Clinical Global Impressions of Severity of ADHD; WISC = Wechsler Intelligence Scale for Children-Third Edition.

RESULTS

A total of 291 patients were randomized for treatment (Study 1: atomoxetine, N = 65; placebo, N = 62; methylphenidate, N = 20 and Study 2: atomoxetine, N = 64; placebo, N = 62; methylphenidate, N = 18). Pooled patient demographics and baseline characteristics are presented in Table 1. The majority of patients randomized in both studies combined were male (236/291 or 81%), and the mean age at the time of study initiation was 9.8 years. A statistically significant higher mean WISC IQ score was noted for the placebo as compared to the atomoxetine group. However, inclusion of the WISC IQ score as a covariate in the efficacy analysis models demonstrated that this difference did not affect the efficacy conclusions resulting from these studies.

Combining both study populations, 235/291 patients (81%) met DSM-IV criteria for the combined subtype of ADHD. Fifty-three patients (18%) met criteria for the inattentive subtype, and 3 patients (1%) met criteria for the hyperactive/impulsive subtype. Baseline scores indicated that patients were "markedly ill" based on mean CGI-ADHD-S and mean ADHD RS scores (the latter greater than 2.7 standard deviations above gender- and age-specific norms). The most common comorbid diagnoses were oppositional defiant disorder (N = 107 or

Figure 1. Participant Flow and Follow-Up



36.8%), phobias (N = 34 or 11.7%), and elimination disorders (N = 31 or 10.7%). Comorbid dysthymia (N = 12 or 4.1%), major depressive disorder (N = 8 or 2.8%), and generalized anxiety disorder (N = 7 or 2.4%) occurred less frequently.

The study cohort is summarized in the patient-flow diagram (Figure 1). For Study 1 and 2, respectively, N = 49 (75.4%) and N = 53 (82.8%) of atomoxetine and N = 47 (75.8%) and N = 45 (72.6%) of placebo patients completed the study. The most common reason for early study discontinuation in both studies combined was lack of efficacy (atomoxetine 7.8%, placebo 13.7%). Six randomized patients discontinued the study without any post-baseline ADHD RS measurements (3 due to personal conflicts, 2 due to lack of efficacy, and 1 due to protocol violation) and thus were excluded from the primary efficacy analysis below.

The primary and secondary efficacy measure results are reported by each study (Studies 1 and 2). As stated earlier, methylphenidate treatment was included in the stimulant-naive stratum in both studies to validate the study design in the event that atomoxetine failed to separate from placebo, thus allowing for a conclusive test of the original hypothesis. Double-blind studies of methylphenidate and other psychostimulants have consistently found these medications to be effective for the treatment of ADHD in school-aged children. Since the number of patients treated with methylphenidate was small, data from patients treated with methylphenidate are not included in the results.

In each study (Studies 1 and 2), atomoxetine treatment resulted in a significantly greater mean reduction in ADHD RS total score ($p < .001$ for both) (Table 2). In addition, a statistically significantly greater percentage of atomoxetine-treated patients than placebo patients met response criteria (at least a 25% decrease in ADHD RS total score from baseline to endpoint) in each study (Study 1: 64.1% vs. 24.6%, $p < .001$; Study 2: 58.7% vs. 40.0%, $p = .048$). Patients treated with atomoxetine also demonstrated statistically significantly greater reductions in scores on both the inattentive and hyperactive/impulsive subscales of the ADHD RS compared with placebo ($p < .001$ for both subscales in both studies except for the hyperactive/impulsive subscale in Study 2 where $p = .002$) (Table 2). Combining the 2 studies, the effect sizes for the total, inattentive, and hyperactive/impulsive scores from the ADHD RS were 0.72, 0.66, and 0.69.

Atomoxetine treatment resulted in a significantly greater mean reduction in CGI-ADHD-S score ($p < .01$ in each study) than placebo (Table 2). In addition, atomoxetine was found to be significantly more effective using the CPRS-ADHD Index in both studies (Study 1, $p = .023$; Study 2, $p < .001$) (Table 2).

Discontinuations and adverse events are presented as pooled data from both studies. Of the 129 atomoxetine-treated patients who were randomized to treatment for both studies combined, 6 (4.7%) discontinued because of an adverse event (2 patients for irritability and 1 patient each for chest pain, aggression, tic-like movements, and vomiting). Discontinuation due to an adverse event occurred in 3 (2.4%) of 124 placebo patients (depression, hyperkinesia, and somnolence). In the placebo treatment group, 3 adverse events were considered serious, in that they resulted in hospitalization. Serious adverse events are defined by the FDA as events that result in hospitalization, disability, or death. These adverse events were not related to the placebo treatment as judged by the investigator.

As Table 3 illustrates, the adverse events reported most frequently across treatment groups were headache, abdominal pain, rhinitis, decreased appetite, and pharyngitis.

Table 2. Results of 2 Placebo-Controlled Studies of Atomoxetine in Children With Attention-Deficit/Hyperactivity Disorder

	Study 1										Study 2									
	Atomoxetine				Placebo						Atomoxetine				Placebo					
		Baseline		Change		Baseline		Change				Baseline		Change		Baseline		Change		
Measure Score	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD	F	df	p Value	N	Mean	SD	Mean	SD	Mean	SD	F	df	p Value
ADHD RS Total	64	41.2	(8.9)	–15.6	(13.7)	61	41.4	(7.9)	–5.5	(11.6)	19.0	1,117	< .001[a]	63	37.8	(7.9)	–14.4	(13.0)	60	37.6	(8.0)	–5.9	(13.0)	12.7	1,113	< .001[a]
CGI-ADHD-Severity	64	4.9	(0.8)	–1.2	(1.4)	61	4.8	(0.8)	–0.5	(1.0)	9.5	1,117	.003[a]	63	4.9	(0.8)	–1.5	(1.4)	61	4.9	(0.8)	–0.7	(1.2)	11.8	1,114	.001[a]
CPRS-ADHD Index	59	27.4	(6.2)	–5.7	(10.4)	54	28.7	(5.8)	–2.6	(8.4)	5.3	1,105	.023[a]	61	26.5	(6.6)	–8.8	(9.8)	60	26.3	(5.7)	–2.1	(9.6)	15.3	1,111	< .001[a]
ADHD RS subscales																										
Inattentive	64	22.0	(3.9)	–7.5	(7.2)	61	22.2	(4.0)	–3.0	(6.6)	15.2	1,117	< .001[a]	63	21.0	(4.0)	–7.6	(7.6)	60	21.1	(3.8)	–3.0	(6.8)	12.0	1,113	< .001[a]
Hyperactive/ impulsive	64	19.3	(6.1)	–8.0	(7.4)	61	19.2	(5.5)	–2.5	(5.9)	20.0	1,117	< .001[a]	63	16.8	(6.5)	–6.9	(6.6)	60	16.5	(6.1)	–2.9	(7.1)	9.7	1,113	.002[a]

[a]p Values are from pairwise tests of treatment differences in mean change from baseline to endpoint (last observation carried forward) scores versus placebo using least squares means from an ANOVA model with terms for baseline, investigator, and treatment.

Table 3. Adverse Events Occurring in ≥ 10% of Any Treatment Group: Combined Stratum

Adverse Event	Atomoxetine (N = 129) %	Placebo (N = 124) %
Headache	30.2	28.2
Abdominal pain	31.0	21.8
Rhinitis	25.6	32.3
Decreased appetite	21.7[a]	7.3
Pharyngitis	16.3	15.3
Vomiting	14.7	12.1
Cough increased	13.2	11.3
Nervousness	13.2	6.5
Somnolence	9.3	8.1
Nausea	10.1	10.5

[a]p < .05 vs. placebo.

A significantly higher percentage of patients treated with atomoxetine compared with placebo reported treatment-emergent decrease in appetite (22% vs. 7%, respectively; Fisher exact p < .01). In addition, a greater percentage of atomoxetine patients compared with placebo patients also experienced weight loss (4% vs. 0%, respectively; Fisher exact p = .060). The mean weight loss in the atomoxetine treatment group was 0.5 kg (1.1 lb), compared with a mean increase of 1.4 kg (3.1 lb) in the placebo treatment group.

There was no statistically significant difference in percentage of patients reporting treatment-emergent insomnia between atomoxetine and placebo (7.0% vs. 8.9%, respectively; $\chi^2 = 0.3$, p = .577). For vital signs, changes from baseline to endpoint in diastolic blood pressure and heart rate were statistically significantly (p < .05) increased in the atomoxetine group compared with the placebo group. Mean change in diastolic blood pressure and heart rate for the atomoxetine treatment group was 2.0 mm Hg and 9.2 bpm, respectively. There were no significant differences between atomoxetine and placebo in laboratory parameters, vital signs, and ECG intervals (Table 4).

During the study drug discontinuation phase (study period III), study medication was discontinued and all patients were assigned single-blind placebo (no tapering). Discontinuation-emergent (posttreatment) adverse events are those events that first occurred in study period III or that worsened in severity following the final visit of the acute treatment phase (study period II). No statistically significant differences between atomoxetine and placebo were observed for any specific event or for the overall percentage of patients with at least 1 discontinuation-emergent event (atomoxetine 18.6%, placebo 22.8%; $\chi^2 = 0.5$, p = .470). No discontinuation-emergent adverse events were reported by ≥ 5% of patients in any group.

At last patient visit, the mean and median doses of atomoxetine in the combined studies were 1.5 and 1.7 mg/kg/day, respectively.

Table 4. Vital Signs Summary: Combined Strata

		Baseline		Change			
Vital Sign[a]	N	Mean	SD	Mean	SD	p Value[b]	p Value[c]
Systolic blood pressure (mm Hg)							
Atomoxetine	127	103.9	11.6	1.8	10.8	.082	.081
Placebo	121	102.7	10.0	0.6	8.6	.302	…
Diastolic blood pressure (mm Hg)							
Atomoxetine	127	63.3	9.0	2.0	9.6	.014	.008
Placebo	121	62.2	8.1	0.2	8.3	.701	…
Heart rate, bpm							
Atomoxetine	127	84.7	11.2	9.2	13.0	< .001	< .001
Placebo	121	85.2	10.0	1.5	12.2	.220	…
Temperature (°C)							
Atomoxetine	127	36.7	0.4	0.01	0.5	.589	.351
Placebo	121	36.8	0.4	0.03	0.5	.238	…
Weight (kg)							
Atomoxetine	127	37.0	12.1	–0.5	1.4	< .001	< .001
Placebo	122	37.8	10.7	1.4	1.4	< .001	…
Height (cm)							
Atomoxetine	113	137.7	9.4	0.8	1.7	< .001	.273
Placebo	110	139.4	9.5	1.1	1.6	< .001	…

[a]All vital signs taken in the sitting position.
[b]Within-treatment group p values are from Wilcoxon signed rank test on change from baseline to endpoint (last observation carried forward) scores.
[c]Between-treatment group p values are from ANOVA F tests on change from baseline to endpoint (last observation carried forward) scores versus placebo.

DISCUSSION

Two proof-of-concept studies were conducted to test the hypothesis that a selective noradrenergic reuptake inhibitor, atomoxetine, would be superior to placebo in reducing the severity of ADHD symptoms in pediatric outpatients with ADHD. As compared with patients treated with placebo, patients treated with atomoxetine demonstrated statistically significant reductions in the ADHD RS total and inattentive and hyperactive/impulsive subscale scores, as well as the CGI-ADHD-S score and CPRS-ADHD Index in both studies. Atomoxetine was found to be effective in children with the primarily inattentive subtype as well as the combined subtype of ADHD. Too few patients (1%) met DSM-IV criteria for the hyperactive/impulsive subtype to allow for a meaningful interpretation of the data in this patient subset.

The findings from these studies support the hypothesis that noradrenergic agents are effective for the treatment of ADHD and expand upon the earlier work of Biederman and colleagues who demonstrated the efficacy of desipramine in children and atomoxetine in adults.[17,30] However, unlike desipramine, atomoxetine has little activity at other receptors, resulting in a more favorable adverse event profile, particularly as this relates to its electrocardiographic profile, most notably changes in the QTc interval (Lilly Research Laboratories, data on file).

Acute treatment with atomoxetine was well tolerated in this study population. The majority of atomoxetine-treated patients completed treatment; no serious adverse events occurred in the atomoxetine group. Of 129 atomoxetine-treated patients who began the study, 6 (4.7%) discontinued the study due to an adverse event. A greater percentage of patients treated with atomoxetine compared with those treated with placebo experienced weight loss, most of which was regained within 1 week of drug discontinuation. The mean weight loss for the atomoxetine group during active treatment was 0.5 kg. In previous studies of atomoxetine in adults with depression, weight loss was seen acutely but did not persist during longer-term atomoxetine treatment.[19] In addition, atomoxetine treatment was associated with statistically significant, although not clinically important, increases in heart rate and diastolic blood pressure, consistent with increased noradrenergic tone. No significant changes in laboratory values or ECG intervals were observed.

Interpretation of these results is subject to limitations. The studies reported here were conducted early in the atomoxetine clinical program and were intended to test the noradrenergic hypothesis by comparing the efficacy and safety of atomoxetine with placebo, thus providing essential information regarding further development of atomoxetine for ADHD. Because of the wide range of weights expected among participating children, the studies utilized a weight-based dosing schedule in an effort to detect a signal as to an efficacious mg/kg dose. As such, dose increases were less aggressive than in subsequent studies.[31] In spite of the cautious dose titration, atomoxetine separated early and consistently from placebo throughout the 9 weeks of active treatment. Nonetheless, a more vigorous earlier dose titration could have provided even greater efficacy than was seen during those early weeks. It is important to note that the studies did provide important information regarding weight-based dosing, an important consideration given the wide weight range of children and adolescents.

These studies did not include the systematic collection of teacher ratings. Although this was intentional, the lack of teacher ratings should be viewed as a limitation. The lack of a direct assessment of the effects of atomoxetine on teacher reports of school performance and behavior, as compared with parent reports that synthesized teacher reports when the children were in school with parental observations in the home and other settings, does not allow for direct conclusions to be made regarding the effects of atomoxetine in the school environment. Future studies are planned that will include teacher rating instruments as primary efficacy outcome measures.

These studies were not designed to provide a comparison of the effects of atomoxetine versus methylphenidate. Methylphenidate was included as a treatment for stratum of patients who had never been treated with any psycho-

stimulant to validate the study design in the event that atomoxetine failed to separate from placebo. Randomization was unbalanced, with fewer patients randomized to methylphenidate; hence, the studies were not powered to detect a difference in the efficacy of atomoxetine versus methylphenidate. Comparative studies with psychostimulants were not deemed appropriate until the efficacy of atomoxetine in children had been established and additional information regarding optimal dosing was available. Thus, these studies would not provide useful information concerning the comparative efficacy of atomoxetine versus methylphenidate. As treatment with psychostimulants is currently considered the primary pharmacotherapy for ADHD, well-designed and appropriately powered double-blind studies of psychostimulants and atomoxetine are needed to make inferences about the differential effects of each of these drug classes. Another limitation was the brief duration of these studies, which hampers the ability to make assumptions regarding the long-term safety or efficacy of atomoxetine in pediatric patients with ADHD. Studies are underway to assess long-term efficacy and safety of atomoxetine in children.

In summary, 2 studies comparing atomoxetine with placebo provide conclusive evidence to support the hypothesis that a selective and specific noradrenergic uptake inhibitor is effective for the treatment of ADHD in children. In addition, atomoxetine was shown to be well tolerated and safe in patients treated for 9 weeks.

Drug names: atomoxetine (Strattera), desipramine (Norpramin and others), methylphenidate (Ritalin, Concerta, and others).

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