

# Efficacy of Atomoxetine Versus Placebo in School-Age Girls With Attention-Deficit/Hyperactivity Disorder

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**ABSTRACT.** *Objective.* The efficacy of atomoxetine was assessed in school-age girls with attention-deficit/hyperactivity disorder (ADHD). Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

*Methods.* A total of 291 children who were 7 to 13 years of age and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for ADHD participated in 1 of 2 combined, double-blind, placebo-controlled, multisite, identical clinical trials. This intent-to-treat subset analysis examined the effects of atomoxetine versus placebo in 51 girls who were randomized to atomoxetine ( $n = 30$ ) or placebo ( $n = 21$ ) for 9 weeks. ADHD symptoms were assessed using parent- and investigator-rated scales.

*Results.* Atomoxetine was superior to placebo on the following measures: the Attention-Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored Total Score; the Inattentive and Hyperactive/Impulsive subscales of the Attention-Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored Total Score; the ADHD Index subscale of the Conners' Parent Rating Scale-Revised: Short Form; and the Clinical Global Impressions of Severity of ADHD. Statistically significant efficacy was seen 1 week after randomization and remained so for the duration of the study. One patient from each of the atomoxetine and placebo groups discontinued the study as a result of an adverse event.

*Conclusion.* Atomoxetine was found to be effective and well tolerated for the treatment of ADHD in school-age girls. *Pediatrics* 2002;110(6). URL: <http://www.pediatrics.org/cgi/content/full/110/6/e75>; atomoxetine, ADHD, school-age, girls, nonstimulant.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; ADHD RS, Attention-Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered

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Atomoxetine was originally called tomoxetine. The name was changed to avoid any potential confusion with tamoxifen that might lead to errors in dispensing the drugs.

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and Scored Total Score; SD, standard deviation; CPRS-R, Conners' Parent Rating Scale-Revised: Short Form; CGI-ADHD-S, Clinical Global Impressions of Severity of ADHD.

Attention-deficit/hyperactivity disorder (ADHD) is an early-onset childhood disorder that is estimated to occur in 3% to 7% of school-age children.<sup>1</sup> Its pathophysiology seems to involve the interaction of norepinephrine, epinephrine, and dopamine in modulation of attention and impulsivity.<sup>2</sup> ADHD is frequently associated with impaired academic and social functioning and persists into adulthood in a sizable number of affected youths.<sup>3</sup>

Literature on the efficacy of pharmacologic treatment in school-age children with ADHD has focused almost exclusively on boys. There is a paucity of data reporting findings of the pharmacologic treatment of ADHD in school-age girls, most likely because many more boys with ADHD are referred for treatment. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* estimated that boys with ADHD outnumber girls by as much as 9:1.<sup>1</sup> In contrast, community-based studies have found the ratio of boys to girls with ADHD to be as low as 2.5:1,<sup>4</sup> suggesting that school-age girls with ADHD are less likely to be diagnosed properly and receive adequate treatment.<sup>5</sup> Although the reasons for lack of studies in girls is not completely clear, Biederman et al,<sup>6</sup> Gaub and Carlson,<sup>7</sup> and Carlson et al<sup>8</sup> suggested that lower levels of psychiatric problems, aggression, and related behaviors in girls as compared with boys may contribute to fewer treatment referrals of girls. Consistent with this hypothesis, Newcorn et al<sup>9</sup> examined data from the National Institute of Mental Health Collaborative Multisite Multimodal Treatment Study of Children with ADHD<sup>10</sup> and found that girls were less impaired than boys on most ADHD symptom ratings and were less impulsive on a continuous performance test.

Other studies have not found significant gender differences for overall impairment, behavioral ratings, or psychological measures. Sharp et al,<sup>11</sup> in a study that compared boys and girls with ADHD, found few differences in ratings of symptomatology, comorbid diagnoses, and psychological function. Likewise, in a study that compared 140 girls with ADHD and 122 normal girls, Biederman et al<sup>5</sup> found that the core ADHD symptoms observed in girls with ADHD are similar to those seen in boys with

ADHD. However, the prevalence of both conduct disorder and oppositional defiant disorder in the girls with ADHD was half of those previously reported in boys with ADHD.<sup>12</sup> Thus, lower rates of disruptive behaviors in girls may result in fewer clinic referrals, contributing to the lack of recognition of the disorder and hence a lower reported prevalence of ADHD in girls.<sup>5</sup>

Currently, psychostimulants such as methylphenidate and amphetamines are the standard pharmacotherapies for the treatment of ADHD. However, there are significant limitations to treatment with psychostimulants, which are not effective or well tolerated in approximately 30% of school-age children with ADHD. Adverse effects such as insomnia, decreased appetite, and irritability may lead to discontinuation or dosage limitations. The lack of adequate full-day treatment often results in recurrence of impairing symptoms at home and in the community. In addition, psychostimulants bear the additional burden of being controlled substances, resulting in concerns about abuse and diversion. For these reasons, there remains a need for safe, effective, and nonstimulant alternatives for the treatment of ADHD in children and adults.

Studies have shown that several nonstimulant compounds that affect noradrenergic and/or dopaminergic pathways (eg, desipramine, bupropion) are somewhat effective in ADHD.<sup>13,14</sup> However, no nonstimulant is currently approved for use in children or adults with ADHD. Atomoxetine is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. It is being investigated for the treatment of pediatric and adult ADHD. Several recent reports have provided evidence that atomoxetine is superior to placebo in reducing symptoms of ADHD in children and adults.<sup>15,16</sup>

There is a paucity of data regarding the efficacy of medications for the treatment of ADHD in girls. The limited published literature suggests that psychostimulant treatment is equally effective in boys and girls with ADHD. Two studies found no gender differences in response to methylphenidate.<sup>17,18</sup> Sharp et al<sup>11</sup> compared the efficacy of methylphenidate and d-amphetamine in boys and girls with ADHD and found no differences in efficacy. The lack of adequately controlled, double-blind, placebo-controlled clinical trials in school-age girls represents a significant absence in information available for patients, parents, and physicians. In an effort to address this void, we conducted a subset analysis from 2 identical, randomized, double-blind, placebo-controlled clinical trials, examining the effects of the nonstimulant atomoxetine versus placebo in school-age girls who received a diagnosis of ADHD. To our knowledge, this is 1 of the largest studies of treatment effects of medication in this population.

## METHODS

Two identical, double-blind, placebo-controlled clinical trials were conducted simultaneously in the United States. Study 1 had 7 sites; study 2 had 10 sites. Patients, boys and girls, met diagnostic

criteria for ADHD based on the *DSM-IV* and as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia.<sup>19</sup> Patients had a score on the Attention-Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHD RS)<sup>20</sup> at least 1.5 standard deviations (SDs) 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 had normal intelligence based on the Wechsler Intelligence Scale for Children, Third Edition.<sup>21</sup> After the study was explained, written informed consent was obtained from the child's parent or legal guardian. These studies were approved by each of the investigative sites' institutional review boards and were conducted in accordance with the Declaration of Helsinki 1975, as revised in 1983.

Physical examinations, routine laboratory tests of blood and urine (including urine toxicology), and electrocardiograms were obtained from all patients during baseline. The following were exclusionary criteria: poor metabolism of the cytochrome P450 2D6 isoenzyme; weight <25 kg at the initial visit; a documented history of bipolar I or II disorder or history of psychosis; history of an organic brain disease or a seizure disorder; currently taking psychotropic medication; history of alcohol or drug abuse within the past 3 months; positive screening for drugs of abuse; or significant previous or current medical conditions (eg, human immunodeficiency virus positive, surgically corrected congenital heart defects, leukemia in remission).

## Study Design

Figure 1 displays the design for each study. Visits 1 through 3 (study period 1) was a 2-week medication washout, screening, and assessment period; visits 3 through 12 (study period 2) was a 9-week, double-blind, acute treatment period; and visits 12 through 13 (study period 3) was a 1-week, single-blind study drug discontinuation period.

Before randomization, patients were divided into 2 groups on the basis of their previous psychostimulant treatment. Patients with no history of psychostimulant treatment (stimulant-naïve stratum) were randomized to double-blind treatment with atomoxetine, placebo, or methylphenidate. (The methylphenidate treatment arm was included in the stimulant-naïve stratum to validate the study design in the event that atomoxetine failed to separate from placebo.) Patients who had received psychostimulant treatment (previous stimulant exposure stratum) were randomized to double-blind treatment with atomoxetine or placebo. Randomization was also stratified by investigational site. The randomization schedules were generated by validated software and implemented in a blinded manner by using an interactive voice-response telephone system to dispense study medication.

The present report describes a subset intent-to-treat analysis that examined the effects of atomoxetine versus placebo in female patients. A total of 52 girls were randomized to either atomoxetine ( $n = 31$ ) or placebo ( $n = 21$ ). In the stimulant-naïve stratum, patients who were assigned to atomoxetine treatment received active drug before school and in the late afternoon/early evening, as well as a midday dose of placebo to preserve the blinding with the use of methylphenidate (the medication used to validate the study design). (Note: because of the small sample size of girls randomized to the methylphenidate treatment arm in the stimulant-naïve stratum, we did not include them in the subset analysis reported in this article.) Patients in this stratum who were assigned to placebo received study medication 3 times daily to maintain blinding. Patients in the previous stimulant exposure stratum were randomized to double-blind treatment with either atomoxetine or placebo, each administered before school and in the late afternoon/early evening. Study drug materials for all treatment groups were identical in appearance. The atomoxetine dose was titrated on the basis of clinical response on a milligram/kilogram/day basis to a maximum daily dose of 2.0 mg/kg/d for atomoxetine (maximum allowable daily dose: 90 mg).

The primary efficacy measure for this study was the ADHD RS, 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 during the previous week and was administered and scored by qualified and trained personnel at the investigative site at every visit, based

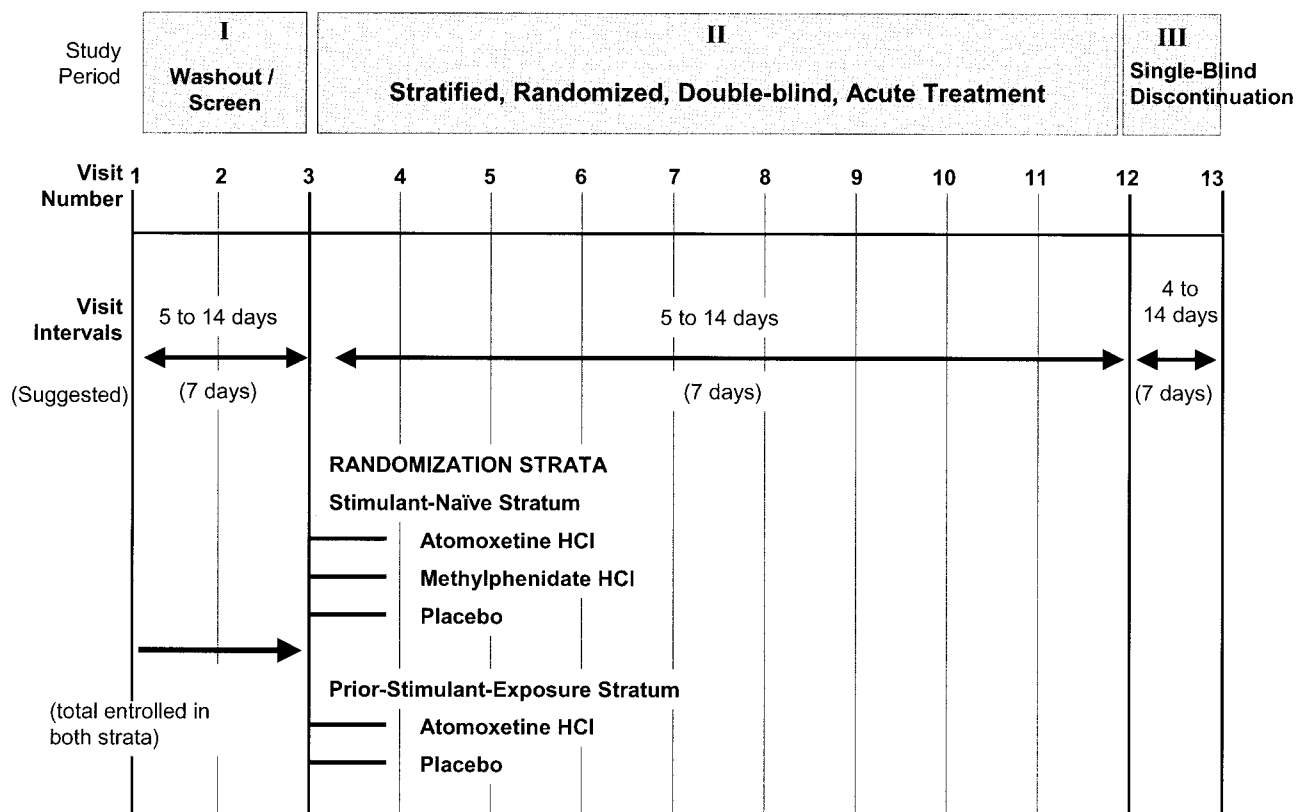


Fig 1. Study design for each of the 2 identical placebo-controlled, double-blind, randomized, clinical trials.

on an interview with the parent. The total score, which was the primary efficacy measure, 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.

Secondary efficacy measures included the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R),<sup>22</sup> which is a parent-rated scale that assesses behaviors symptomatic of ADHD. It includes Oppositional, Cognitive Problems, Hyperactivity, and ADHD Index subscales. Another secondary efficacy measure was the Clinical Global Impressions of ADHD Severity (CGI-ADHD-S),<sup>23</sup> which 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).

### Statistical Analysis

All statistical tests were performed using a 2-tailed, .05 significance level using an intent-to-treat principle. Treatment differences in baseline patient characteristics were assessed using an analysis of variance model or Fisher exact test. For continuous measures, such as the ADHD RS, the CPRS-R, and the CGI-ADHD-S scale 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 between atomoxetine and placebo in mean change from baseline to endpoint scores were assessed using an analysis of variance model with terms for baseline, gender, investigator, treatment, treatment-by-gender, and previous stimulant exposure strata. The primary efficacy analysis was the treatment comparison in mean change from baseline to endpoint ADHD RS total scores for atomoxetine and placebo.

The ADHD RS scores over time were also assessed using a repeated measures mixed model. The model included terms for treatment, investigator, strata, visit, and treatment-by-visit interaction, whereas the covariance matrix selection was based on Akaike's Information Criteria. Treatment differences in percent-

ages of unsolicited treatment-emergent adverse events were assessed using the Fisher exact test.

### RESULTS

A total of 52 girls were randomized for treatment (atomoxetine:  $n = 31$ ; placebo:  $n = 21$ ) across the 2 studies. A total of 51 patients who had a baseline and at least 1 postbaseline measurement using a last observation carried forward were included in the statistical analyses. Efficacy data were not available for 1 girl in the atomoxetine group, who discontinued the study because of a personal conflict. There were no significant differences between the treatment groups with respect to baseline demographics and severity of illness scores (Table 1). The most common comorbid diagnoses were oppositional defiant disorder (38.5%) and phobias (13.5%). At baseline (combined treatment groups), female mean ADHD RS Total T-score was 88.9, which was 3.9 SD above the age/gender norm. (For comparison, the mean T-score in boys was 77.2, or 2.7 SD, above the age/gender norm.) Of interest, 201 boys were randomized to treatment with atomoxetine ( $n = 98$ ) or placebo ( $n = 103$ ) in the 2 studies.

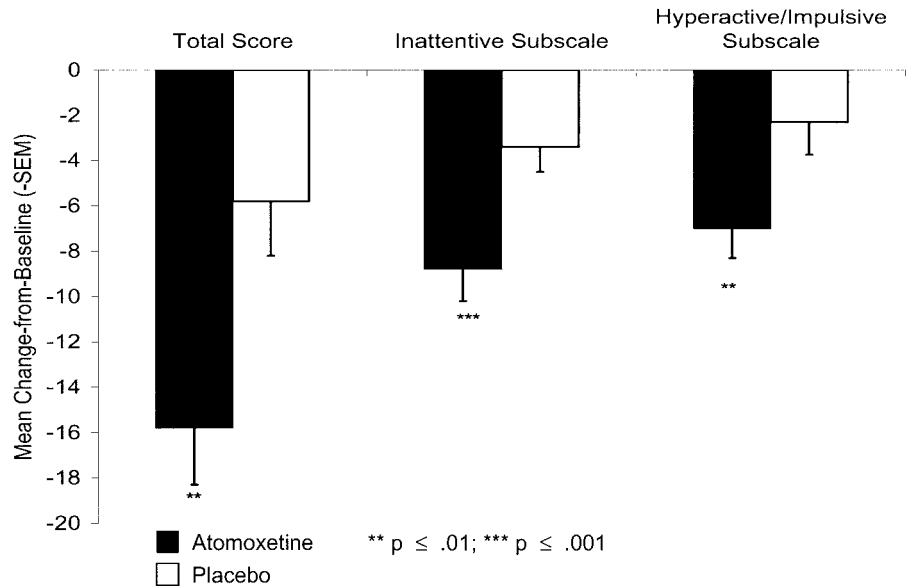
Atomoxetine was superior to placebo on the primary outcome measure (mean change from baseline to endpoint on the ADHD RS Total score; Fig 2). Atomoxetine-treated school-age girls experienced a statistically significantly greater decrease in their ADHD RS Total Score compared with placebo-treated school-age girls (15.8 vs 5.8, respectively;  $P = .002$ ). Significant differences were also found on the



**TABLE 1.** Baseline Demographics and Illness Characteristics

Demographic	Atomoxetine (n = 31)	Placebo (n = 21)	P Value
Age (mean in y [SD])	9.7 (1.6)	9.6 (1.5)	.970
Weight (mean in kg [SD])	38.3 (11.4)	39.7 (12.1)	.450
Height (mean in cm [SD])	138.6 (10.7)	138.6 (9.9)	.635
Diagnostic subtypes (n [%])			
Inattentive	6 (19.4%)	5 (23.8%)	.739
Hyperactive/impulsive	0 (0.0%)	0 (0.0%)	1.000
Combined	25 (80.6%)	16 (76.2%)	.739
WISC full-scale IQ (mean [SD])	104.1 (15.7)	106.9 (16.5)	.373
ADHD RS Total score (mean [SD])	37.6 (9.5)	39.0 (8.1)	.292
ADHD RS Inattentive subscale (mean [SD])	20.8 (4.2)	22.4 (3.6)	.069
ADHD RS Hyperactive/Impulsive subscale (mean [SD])	16.8 (7.3)	16.5 (6.7)	.820
CPRS-R ADHD index (mean [SD])	27.4 (5.6)	26.2 (6.6)	.889
CGI-ADHD-S (mean [SD])	4.7 (0.8)	5.0 (0.8)	.467

WISC indicates Wechsler Intelligence Scale for Children—Third Edition.



**Fig 2.** Mean change from baseline to endpoint scores (–standard error of the mean [SEM]) for the ADHD RS Total Score and Inattentive and Hyperactive/Impulsive subscales for the atomoxetine and placebo treatment groups.

Inattentive and Hyperactive/Impulsive subscales of the ADHD RS. Atomoxetine-treated patients reported a decrease on the Inattentive subscale relative to placebo-treated patients (8.8 vs 3.4, respectively;  $P = .001$ ) and on the Hyperactive/Impulsive subscale (7.0 vs 2.3, respectively;  $P = .006$ ; Fig 2). A visit-wise analysis of the ADHD RS Total Score comparing atomoxetine with placebo found that atomoxetine-treated patients experienced significant efficacy that was evident at the first assessment 1 week after randomization ( $P < .05$ ) and persisted for the duration of the study (Fig 3).

Atomoxetine was also superior to placebo on the parent-rated CPRS-R ADHD Index. Parents of atomoxetine-treated patients reported a greater decrease in CPRS-R ADHD Index scores compared with parents of placebo-treated patients (10.3 vs 1.0, respectively;  $P < .001$ ; Fig 4). In addition, a statistically significant decrease was observed on the CGI-ADHD-S for the atomoxetine group compared with the placebo group (1.5 vs 0.6, respectively;  $P < .001$ ; Fig 4).

Atomoxetine was well tolerated in this population of school-age girls. The most frequently reported adverse events reported by atomoxetine-treated pa-

tients were abdominal pain (29%), rhinitis (26%), and headache (26%). However, there were no statistically significant differences between the treatment groups in the percentage of adverse events reported (Table 2). Furthermore, only 1 patient from each of the atomoxetine and placebo groups discontinued as a result of an adverse event (chest pain and somnolence, respectively).

## DISCUSSION

The results reported here represent 1 of the largest studies of medication effects in school-age girls with ADHD. An efficacy analysis of 51 school-age girls who met *DSM-IV* diagnostic criteria for ADHD enrolled in 2 identical, randomized, double-blind, placebo-controlled studies demonstrated that atomoxetine ( $n = 30$ ) was superior to placebo ( $n = 21$ ) in reducing the severity of ADHD symptoms. Compared with placebo, atomoxetine significantly reduced the ADHD RS Total Score, the Inattentive and Hyperactive/Impulsive subscales of the ADHD RS, the ADHD Index score of the CPRS-R, and the CGI-ADHD-S. When the data from the ADHD RS Total Score were examined using a visit-wise analysis, atomoxetine produced statistically significant efficacy at

Fig 3. Least squares mean ( $\pm$ SEM) by weeks of therapy for the ADHD RS Total Scores.

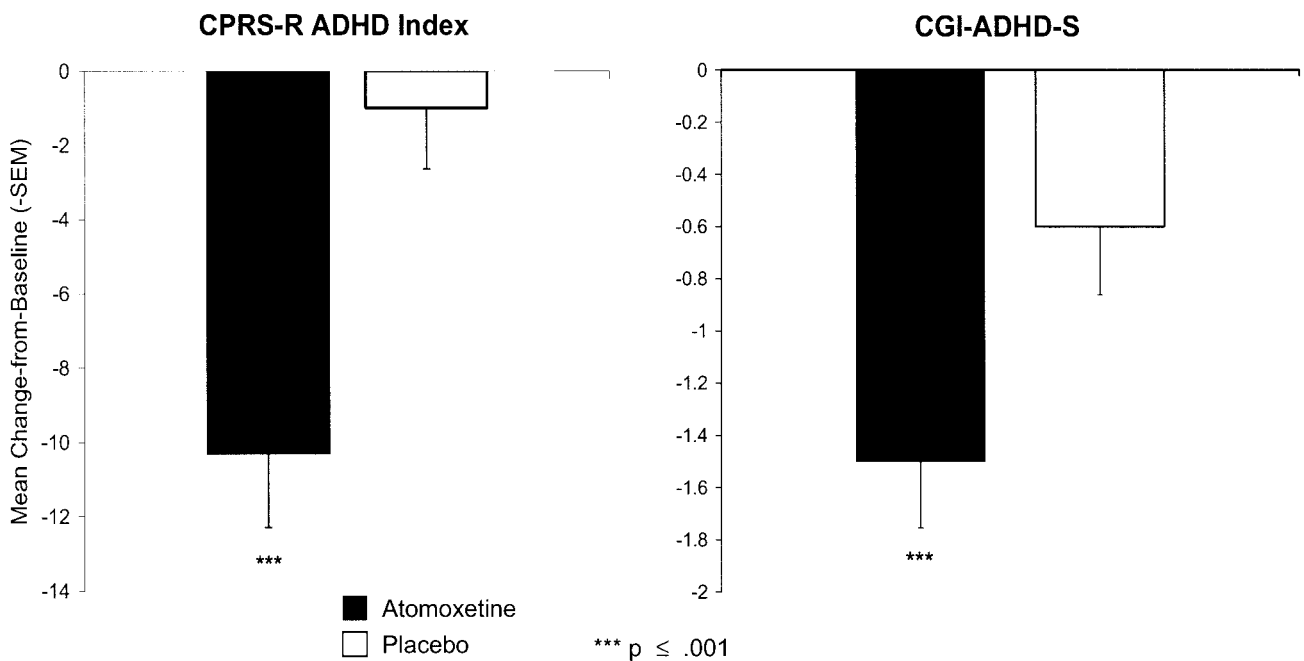
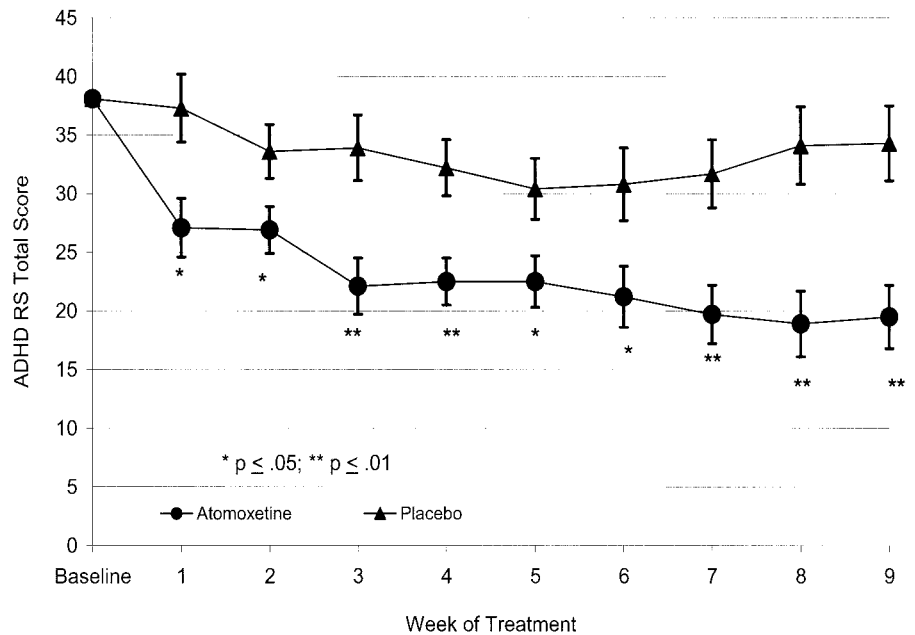


Fig 4. Mean change from baseline to endpoint scores ( $-$ SEM) for the CPRS-R ADHD Index and CGI-ADHD-S for the atomoxetine and placebo treatment groups.

the first week after randomization that continued for the remainder of the study. These data demonstrating significant efficacy for atomoxetine in school-age girls with ADHD extend data from studies that have shown that atomoxetine is efficacious in boys and girls as well as in men and women with ADHD<sup>15,16,24</sup>(Spencer et al, unpublished data). In addition to demonstrating significant differences on investigator-scored measures, atomoxetine resulted in a significant decrease on a well-validated parent-age rating scale, the CPRS-R. The finding of efficacy on separate parent- and clinician-scored measures strengthens the significance of these results.

Overall, these data provide evidence that atomox-

etine can significantly reduce the severity of symptoms in school-age girls with ADHD. Our findings clearly indicate that school-age girls with ADHD responded robustly to treatment with atomoxetine. Pediatricians, child psychiatrists, primary care physicians, and other health care professionals should be mindful of the possible diagnosis of ADHD in girls who present with symptoms of inattentiveness, disorganization, distractibility, and failure to finish tasks. Because girls are less likely to have comorbid externalizing disorders (oppositional defiant disorder and conduct disorder) than their male counterparts, they are less likely to be identified and referred. Studies have suggested that many boys who

**TABLE 2.** Treatment-Emergent Adverse Events Reported by Patients Receiving Atomoxetine or Placebo\*

Event	Atomoxetine (n = 31) (%)	Placebo (n = 21) (%)
Rhinitis	25.8	38.1
Abdominal pain	29.0	14.3
Headache	25.8	14.3
Pharyngitis	19.4	19.0
Decreased appetite	19.4	19.0
Vomiting	19.4	0.0
Cough increased	16.1	4.8
Nervousness	6.5	14.3
Somnolence	6.5	14.3
Nausea	6.5	14.3
Emotional lability	3.2	14.3
Fever	9.7	4.8
Insomnia	3.2	9.5
Diarrhea	3.2	4.8
Dizziness	3.2	4.8

\* There were no statistically significant differences between treatment groups.

receive a diagnosis of ADHD are referred for evaluation because of disruptive disorders.<sup>7</sup> Others have noted that gender differences seen with children with ADHD are not as pronounced among adults with ADHD, most likely because adults can self-refer.<sup>25</sup> The present study indicates that atomoxetine can be used to treat girls with ADHD successfully. Early diagnosis and treatment of both boys and girls with ADHD is important to reduce the burden of illness in all patients.

The analysis reported here also provides additional information about the tolerability of atomoxetine by reporting the adverse events and reasons for discontinuation in these school-age girls. There were no significant differences in treatment-emergent adverse events between girls who were treated with atomoxetine and those on placebo. The largest difference was with vomiting. Among the atomoxetine-treated patients 19% (6 of the 31 patients) reported vomiting, whereas none of the girls on placebo reported this adverse event. However, this difference was not statistically significant, and no atomoxetine-treated patients discontinued treatment as a result of vomiting. Only 1 patient from each of the atomoxetine and placebo groups discontinued treatment as a result of an adverse event (chest pain and somnolence, respectively). The small sample size of school-age girls in this analysis limits the interpretability of the adverse event analysis.

A limitation of these studies was the lack of teacher-rated assessments of efficacy as a study objective. Although data were collected from teachers when available, an analysis of teacher data was neither a primary nor a secondary objective of this study. A study requiring data from teachers would have limited the conduct of the study to the middle months of a school year and the populations to be studied to those children with 1 teacher. Considering that atomoxetine treatment provides day-long coverage beyond school hours, carefully conducted interviews with parents by trained clinicians can provide adequate information regarding school-related behavior

and performance observable in the evening and during weekends. Future studies, however, should assess the impact of atomoxetine on teacher ratings of school behavior and performance.

Despite these considerations, the data presented here provide additional evidence of the efficacy, safety, and tolerability of atomoxetine, a promising nonstimulant treatment for ADHD. Atomoxetine significantly decreased ADHD signs and symptoms in girls with ADHD and may offer an alternative to stimulants in the treatment of this disorder. The data reported from this subset analysis of 2 identical placebo-controlled clinical trials address an important void in what is known about the treatment of school-age girls with ADHD.

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