

Atomoxetine in the Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Dose-Response Study

David Michelson, MD*‡; Douglas Faries, PhD*; Joachim Wernicke, MD, PhD*; Douglas Kelsey, MD, PhD*; Katherine Kendrick, BS*; F. Randy Saltee, MD, PhD§; Thomas Spencer, MD||; and the Atomoxetine ADHD Study Group

ABSTRACT. *Objective.* Atomoxetine is an investigational, nonstimulant pharmacotherapy being studied as potential treatment for attention-deficit/hyperactivity disorder (ADHD). It is thought to act via blockade of the presynaptic norepinephrine transporter in the brain. We assessed the efficacy of 3 doses of atomoxetine compared with placebo in children and adolescents with ADHD.

Methods. A total of 297 children and adolescents who were 8 to 18 years of age and had ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*, were randomized to placebo or atomoxetine dosed on a weight-adjusted basis at 0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day for an 8-week period. ADHD symptoms, affective symptoms, and social and family functioning were assessed using parent and investigator rating scales.

Results. Approximately 71% of children enrolled were male, approximately 67% met criteria for mixed subtype (both inattentive and hyperactive/impulsive symptoms), and the only common psychiatric comorbidity was oppositional defiant disorder (approximately 38% of the sample). At baseline, symptom severity was rated as moderate to severe for most children. At endpoint, atomoxetine 1.2 mg/kg/day and 1.8 mg/kg/day were consistently associated with superior outcomes in ADHD symptoms compared with placebo and were not different from each other. The dose of 0.5 mg/kg/day was associated with intermediate efficacy between placebo and the 2 higher doses, suggesting a graded dose-response. Social and family functioning also were improved in the atomoxetine groups compared with placebo with statistically significant improvements in measures of children's ability to meet psychosocial role expectations and parental impact. Discontinuations as a result of adverse events were <5% for all groups.

Conclusion. Among children and adolescents aged 8 to 18, atomoxetine was superior to placebo in reducing ADHD symptoms and in improving social and family functioning symptoms. Atomoxetine was associated with a graded dose-response, and 1.2 mg/kg/day seems to be as effective as 1.8 mg/kg/day and is likely to be the appropriate initial target dose for most patients. Treatment with atomoxetine was safe and well tolerated. *Pediatrics* 2001;108(5). URL: <http://www.pediatrics.org/cgi/content/>

full/108/5/e83; atomoxetine, ADHD, dose-response, children, adolescents.

ABBREVIATIONS. ADHD, attention-deficit/hyperactivity disorder; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children; SD, standard deviation; ADHD RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; CPRS-R, Conners' Parent Rating Scale-Revised; CGI-S, Clinical Global Impressions of Severity; CDRS-R, Children's Depression Rating Scale-Revised; CHQ, Child Health Questionnaire; ANOVA, analysis of variance.

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of childhood that affects 6% to 10% of school-aged children.¹ It is associated with impairment of academic and social functioning,² and a growing body of data suggests that it also is associated with considerable morbidity and poorer outcomes later in life.³⁻⁹

The recent National Institute of Mental Health-funded MTA study demonstrated that careful, standardized drug therapy is associated with superior symptom reduction for most children compared with psychosocial interventions alone.¹⁰ Evidence also suggests that stimulant therapy that includes treatment outside of school (thrice daily methylphenidate) is superior to therapy restricted to school hours (twice daily methylphenidate).^{11,12} Currently, stimulants such as methylphenidate and d-amphetamine are the standard drug therapies.

Stimulants are efficacious and safe. However, there is considerable interest in other classes of therapy, because some patients fail to respond to stimulants or are intolerant of them and also because stimulants are controlled substances. A number of compounds, such as desipramine and bupropion, that affect noradrenergic and/or dopaminergic pathways are efficacious in ADHD,¹³⁻¹⁵ but no nonstimulant is currently approved for use in children with ADHD.

Atomoxetine (originally called tomoxetine but changed to avoid any potential confusion with tamoxifen that might lead to errors in dispensing the drug) is a potent inhibitor of the presynaptic norepinephrine transporter (K_i 4.5 nM), with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. It is metabolized through the cytochrome P450 2D6 (CYP

From the *Lilly Research Laboratories and ‡Indiana University School of Medicine, Indianapolis, Indiana; §University of Cincinnati, Cincinnati, Ohio; and ||Massachusetts General Hospital, Boston, Massachusetts.

Received for publication Apr 12, 2001; accepted Jul 12, 2001.

Reprint requests to (D.M.) Lilly Corporate Center, DC 6026, Indianapolis, IN 46285. E-mail: dmicelson@lilly.com

PEDIATRICS (ISSN 0031 4005). Copyright © 2001 by the American Academy of Pediatrics.

2D6) pathway and has a plasma half-life of approximately 4 hours in CYP 2D6 extensive metabolizers and 19 hours in CYP 2D6 poor metabolizers. It has 1 known active metabolite, 4-hydroxyatomoxetine, which is glucuronidated and excreted in the urine. Atomoxetine's clinical profile seems to differ from that of stimulants,¹⁶ and it is being studied as a treatment for ADHD.

Several reports have provided evidence that atomoxetine is superior to placebo in reducing symptoms of ADHD in children and adults.^{17,18} However, the relative efficacy and the relative safety and tolerability of different doses have not been assessed. We hypothesized that atomoxetine would be superior to placebo for the treatment of ADHD and report results of a fixed-dose study of comparing 3 different doses of atomoxetine with placebo.

METHODS

This multicenter study was conducted at 13 outpatient investigative sites in the United States. Children and adolescents who were 8 to 18 years of age were eligible to participate if they met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*¹⁹ criteria for ADHD by clinical assessment, confirmed by a structured interview (the behavioral module of the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children—Present and Lifetime Versions (KSADS-PL)).²⁰ Patients also had to have a symptom severity score at least 1.5 standard deviations (SD) above age and gender norms on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV—Parent Version: Investigator Administered and Scored (ADHD RS) for the total score or either of the inattentive or the hyperactive/impulsive subscales.²¹

DNA from whole blood samples drawn at the initial visit were isolated and purified and analyzed for CYP 2D6 genotype using a validated polynucleotide chain reaction method (Quest Diagnostics Clinical Trials, Collegeville, PA, or PPGx, Morrisville, NC). CYP 2D6 genotype was evaluated by testing the *3, *4, *5, *6, *7, and *8 poor metabolizer alleles. Patients homozygous for any combination of these alleles were assigned a poor metabolizer genotype; otherwise, an extensive metabolizer genotype was assigned. Each patient's genotype was reported to the investigative sites in a sealed envelope for blinding purposes, not to be opened except in the case of emergency.

Patients were assessed for concurrent depression and anxiety with the KSADS present and lifetime depression and anxiety modules. Important exclusion criteria included IQ <80 as assessed by the Wechsler Intelligence Scale for Children—3rd Edition,²² serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug. Patients were recruited by referral and by advertisement. After description of the procedures and purpose of the study, written informed consent was obtained from each patient's parent or guardian and written assent was obtained from patients. Informed consent and assent were obtained before the administration of any study procedure or dispensing of study medication. This study was conducted in accordance with the ethical standards of each of the investigative sites' institutional review boards and with the Helsinki Declaration of 1975, as revised in 2000.

After an initial 12- to 18-day evaluation and medication wash-out period, patients were randomized to 1 of 3 doses of atomoxetine (0.5 mg/kg/day, 1.2 mg/kg/day, or 1.8 mg/kg/day) or placebo for approximately an 8-week treatment period. Visits were weekly for the first 4 weeks and biweekly thereafter. All patients in the atomoxetine arms began treatment at 0.5 mg/kg/day. In the higher dose arms, the drug was titrated with intermediate steps of 0.8 mg/kg/day and 1.2 mg/kg/day at 1-week intervals. The middle and upper doses were chosen to bracket the final mean atomoxetine dose (1.5 mg/kg/day) of 2 previous placebo-controlled trials that used dose titration based on clinical response (T. Spencer, unpublished data). In addition, the upper dose was lower than the highest doses studied in clinical pharmacology studies of healthy adult CYP 2D6 extensive and poor

metabolizers. The study drug was administered as equally divided doses in the morning and late afternoon. The study drug for all treatment groups was identical in appearance. Patients were randomized using computer-generated codes via an interactive voice response system. The study included a 1-year extension period that is ongoing; only acute results are presented in this report.

The protocol-specified primary outcome measure was the ADHD RS, an 18-item scale based on a semistructured interview with the patient's parent (or primary caregiver). Each item corresponds to 1 of the 18 *DSM-IV* diagnostic criteria. This scale has been studied and found to have satisfactory psychometric properties (Faries et al, unpublished observations). Other assessments included the hyperactivity/impulsivity and inattention subscales of the ADHD RS, the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R), and Clinical Global Impressions of Severity (CGI-S). Affective symptoms were assessed using the revised Children's Depression Rating Scale (CDRS-R). Broader social and family functioning was assessed using the Child Health Questionnaire (CHQ), a parent-rated health outcome scale that measures physical and psychosocial well-being. The psychometric properties of the CHQ have been studied, and normative data have been reported.²³ Safety and tolerability were assessed by open-ended questioning for adverse events, as well as by regular monitoring of vital signs and laboratory data.

Statistical Methods

Sample size was chosen on the basis of the treatment differences observed in an initial study of atomoxetine and placebo. For each continuous efficacy measure, change from baseline to endpoint was computed for all patients with a baseline and at least 1 postbaseline measurement using a last-observation-carried-forward approach. Treatment differences in mean change were assessed using an analysis of variance (ANOVA) model with terms for treatment group, CYP 2D6 genotype, and investigator. Pairwise comparisons between outcomes in each atomoxetine dose group and the placebo group were conducted using least squares means from the above model. The protocol-specified primary efficacy analyses were pairwise comparisons of mean change in ADHD RS total score between the high dose of atomoxetine and placebo and between the middle dose of atomoxetine and placebo. Dunnett's adjustment was used to control for the multiple comparisons to placebo for the primary efficacy variable; however, as outcomes were similar after adjustment, only unadjusted *P* values are reported. The consistency of the treatment effect across investigational sites was assessed by adding a treatment-by-investigator term to the ANOVA model. Ninety-five percent confidence intervals for treatment differences were computed on the basis of the least squares means from the ANOVA model. To assess dose-response relationships using continuous measures, we modified the above ANOVA model to include dose as a numeric variable with linear and quadratic terms.

For binary measures, such as the percentage of treatment-emergent adverse events, pairwise treatment comparisons were conducted using Fisher's exact test. Once again, unadjusted *P* values are reported. Dose-response relationships were assessed using the Cochran-Armitage trend test.

To assess symptom severity at endpoint relative to an unaffected population, we analyzed scores on the primary outcome measure as *t* scores. These are a transformation based on normative data adjusted for gender and age. For a normal population, 50 represents the mean score and 10 points represents 1 SD from the mean.

Analyses of efficacy measures included all randomized patients with both a baseline and a postbaseline measurement. Analyses of safety measures were restricted to randomized patients who took at least 1 dose of the study drug (either atomoxetine or placebo); 294 of 297 [98.9%] randomized patients). All statistical analyses were performed using SAS software (SAS Institute, Cary, NC).

RESULTS

Of the 381 patients screened, 297 (212 boys/85 girls) met entry criteria and were randomized to treatment. Details of patient characteristics and baseline symptom measures were similar for all treatment groups and are summarized in Tables 1 and 2,

respectively. The study cohort is summarized in the patient flow diagram (Fig 1).

Efficacy outcomes are summarized in Table 3. At endpoint, atomoxetine was superior to placebo on the primary outcome measure (mean change to endpoint in ADHD RS scale score) in both the 1.2 mg/kg/day and 1.8 mg/kg/day treatment groups, and there was evidence of a graded dose-response (Fig 2A). At endpoint, mean (SD) *t* scores for the 1.2 mg/kg/day and 1.8 mg/kg/day groups were 66.2 (14.8) and 66.9 (15.6), respectively, compared with 73.8 (15.6) for the placebo group ($P < .001$ for pairwise comparisons of each active treatment dose to placebo). Outcomes were similar for the inattentive and hyperactive/impulsive subscales, as were outcomes on secondary measures, including the CGI-S (Fig 2B) and CPRS-R. Symptom reduction as assessed by reduction in mean ADHD RS scores was similar for younger children compared with older children and adolescents on the basis of the median age split (10.8 years). However, among older children and adolescents, outcomes in the 0.5 mg/kg/day group were superior to placebo (mean [SD] reduction in ADHD RS: placebo [$n = 41$], -5.6 [11.3]; 0.5 mg/kg/day [$n = 19$], -14.11 [14.5]; 1.2 mg/kg/day [$n = 44$], -12.8 [13.7]; and 1.8 mg/kg/day [$n = 42$], -12.1 [11.8]; pairwise comparison for each atomoxetine dose versus placebo, $P < .05$). The assessment of treatment-by-investigator interaction indicated some variability in treatment effect across investigative sites for the primary efficacy variable (treatment-by-investigator interaction, $P = .05$). However, numerical treatment effects favoring atomoxetine 1.2 mg/kg/day over placebo were observed in 11 of the 13 sites and removal of 1 site with 13 patients eliminated the significant interaction effect ($P = .21$).

At baseline, 1 patient met diagnostic criteria for major depression and 1 patient met criteria for generalized anxiety. Mean CDRS-R baseline scores for all groups were well below the conventional threshold of 36 associated with major depression. Nonetheless, reduction in affective symptoms, as measured by the CDRS-R, was greater among those in the 2 higher dose groups of atomoxetine compared with placebo (Table 3). Improvements in social and family functioning also were superior among atomoxetine-

treated patients compared with those in the placebo group (Table 3).

Atomoxetine was well tolerated at all doses. No adverse event was statistically significantly more frequent among either of the 1.2 mg/kg/day or 1.8 mg/kg/day atomoxetine dose groups compared with placebo. For 2 events (somnolence and anorexia), the data suggested a dose-response effect that approached but did not reach statistical significance. All events that occurred in at least 5% of any atomoxetine group are listed in Table 4. Increasing doses of atomoxetine were associated with small increases in diastolic blood pressure and pulse and decreases in weight (Table 5). No differences from placebo were observed in mean changes of systolic blood pressure or corrected QT interval (mean [SD] change in Fridericia corrected QT interval: placebo, -3.3 (13.2); atomoxetine 1.8 mg/kg/day, -5.5 (13.6) [$P = .211$]; mean [SD] change in systolic blood pressure: placebo, 2.1 (9.5); atomoxetine 1.8 mg/kg/day, 2.5 (8.8) [$P = .801$]). Table 5 provides details of changes in vital sign measurements.

Discontinuations as a result of adverse events were low and similar for all treatment groups (Table 6). A high percentage of patients who were randomized to atomoxetine completed the acute treatment period (83%).

Seventeen CYP 2D6 poor metabolizers were randomized to treatment (6 to placebo, 3 to 0.5 mg/kg/day, 4 to 1.2 mg/kg/day, and 4 to 1.8 mg/kg/day). Mean (SD) change from baseline on ADHD RS followed a pattern similar to that seen in extensive metabolizers, but the magnitude of the effect at 1.2 mg/kg/day and 1.8 mg/kg/day was greater among poor metabolizers than extensive metabolizers (mean [SD] reduction among poor metabolizers: placebo, -6.0 [6.3]; 0.5 mg/kg/day, -10.0 [11.8]; 1.2 mg/kg/day, -30.5 [10.3]; 1.8 mg/kg/day, -37.8 [5.6]; CYP 2D6 group by therapy, $P < .05$). Of the 17 poor metabolizers randomized, 16 (94.1%) completed the trial and none discontinued as a result of an adverse event (1 patient in the 0.5 mg/kg/day group discontinued early for personal reasons). Because the number of patients in each group was relatively small, formal comparisons of adverse events between extensive and poor metabolizers are difficult to interpret; however, the general pattern

TABLE 1. Patient Characteristics

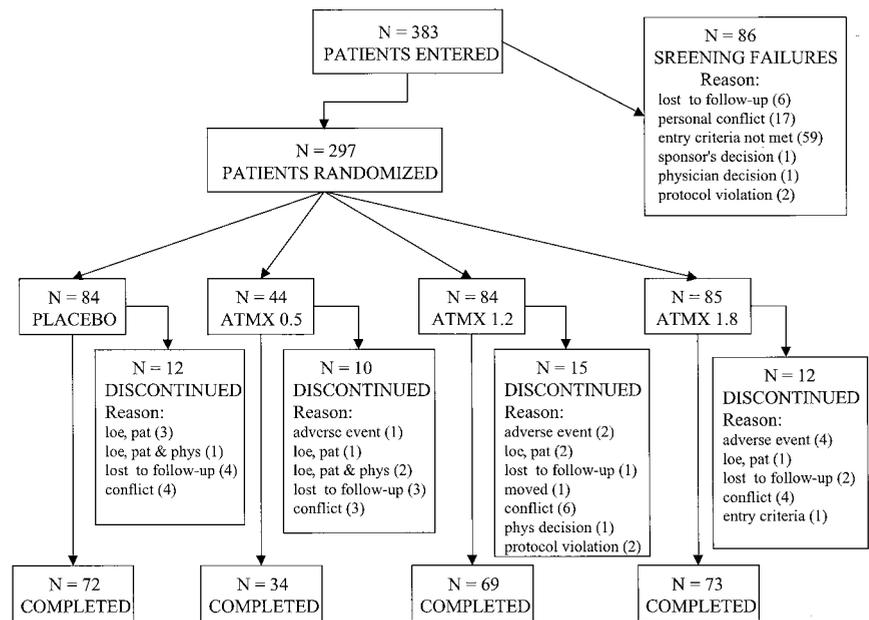
Characteristic	Placebo ($n = 84$)	Atomoxetine (mg/kg/day)		
		0.5 ($n = 44$)	1.2 ($n = 84$)	1.8 ($n = 85$)
Gender (M/F)	60/24	31/13	60/24	61/24
Age (mean [SD])	10.9 (2.1)	11.3 (2.5)	11.5 (2.4)	11.1 (2.1)
ADHD subtype (n [%])				
Mixed	53 (63.1)	30 (68.2)	60 (71.4)	56 (65.9)
Hyperactive/impulsive	2 (2.4)	1 (2.3)	1 (1.2)	1 (1.2)
Inattentive	28 (33.3)	13 (29.5)	23 (27.4)	28 (32.9)
Unspecified	1 (1.2)	0	0	0
Comorbid conditions (n [%])				
Oppositional/defiant disorder	31 (36.9)	21 (47.7)	25 (29.8)	36 (42.4)
Depression	0	0	0	1 (1.2)
Generalized anxiety disorder	1 (1.2)	0	0	0

TABLE 2. Baseline Symptom Severity

	Placebo (n = 84)	Atomoxetine (mg/kg/day)		
		0.5 (n = 44)	1.2 (n = 84)	1.8 (n = 85)
ADHD RS total score	38.3 (8.9)	40.2 (9.6)	39.2 (9.2)	39.7 (8.7)
ADHD RS inattentive	21.4 (4.0)	22.4 (3.6)	22.2 (4.0)	22.1 (4.2)
ADHD RS hyperactive/impulsive	16.9 (6.6)	17.8 (7.4)	16.9 (7.1)	17.6 (6.2)
CPRS-R ADHD	27.3 (6.3)	30.7 (4.4)	28.0 (5.6)	27.9 (6.7)
CPRS-R hyperactive	10.3 (4.9)	12.0 (4.8)	10.2 (5.1)	10.6 (4.6)
CPRS-R cognitive	14.0 (3.7)	16.0 (2.5)	14.4 (3.2)	14.4 (4.0)
CPRS-R oppositional	9.1 (5.0)	11.0 (4.4)	9.6 (4.6)	10.3 (4.8)
CGI-S	4.7 (0.8)	4.8 (0.9)	4.8 (0.9)	4.9 (0.7)
CDRS-R	24.8 (8.0)	26.3 (7.3)	25.3 (7.3)	27.1 (8.0)
CHQ				
Psychosocial summary				
Score	35.2 (11.4)	32.9 (9.6)	35.4 (10.4)	31.3 (10.6)
Behavior	47.2 (19.7)	43.2 (17.2)	44.8 (19.1)	41.0 (16.2)
Family activity	58.3 (23.9)	44.5 (22.1)	52.1 (24.9)	48.9 (26.0)
Parent impact–emotional	48.1 (22.6)	46.5 (17.6)	48.4 (17.0)	44.4 (19.3)
Parent impact–time	67.2 (23.2)	64.4 (23.5)	69.3 (22.2)	64.0 (23.5)
Mental health	72.5 (17.7)	68.1 (17.1)	72.9 (13.9)	66.6 (16.0)
Emotional role	67.6 (33.2)	60.8 (39.6)	67.6 (35.3)	61.0 (34.2)

All values are mean (SD) change from baseline to endpoint.

Fig 1. Patient flow diagram. LOE, lack of efficacy; ATMX, atomoxetine; PAT, patient.



did not suggest unexpected or serious safety or tolerability concerns. With respect to the adverse events that seemed to be related to atomoxetine in previous studies, 3 of 4 poor metabolizers in the 1.2 mg/kg/day group but none in the 1.8 mg/kg/day group reported decreased appetite as an adverse event. Mean change in heart rate (as assessed by electrocardiogram but not clinicians) was higher in the poor metabolizers (mean [SD] beats per minute increase on 1.8 mg/kg/day: poor metabolizers, 15.3 [4.4]; extensive metabolizers, 9.1 [14.0]).

DISCUSSION

A large body of data provides evidence for the efficacy and safety of stimulants in the treatment of ADHD. Several nonstimulants also have been shown to be efficacious,^{13–15,24–26} but dose-response, safety in children, and other relevant questions have not been well studied for these agents. Atomoxetine has

been reported to be efficacious in children with ADHD (T. Spencer, unpublished data). That report, however, did not assess dose-response, and it excluded adolescents as well as children who metabolize atomoxetine slowly. The results of our study provide additional strong evidence of the efficacy of atomoxetine in the treatment of ADHD and extend the findings of the previous report by providing evidence of dose-response and optimal dose, by including adolescents, and by providing additional information about safety and tolerability.

Several factors limit the interpretation of these data. It is not possible to determine the time to onset of the initial response, because at the 2 higher (and most efficacious) doses, the target dose was not reached until the third (1.2 mg/kg/day group) or fourth week (1.8 mg/kg/day group) of the study. It also is not possible to compare the degree or spectrum of symptom reduction associated with atomox-

TABLE 3. Efficacy Outcomes

	Placebo (n = 83)	Atomoxetine 0.5 mg/kg/day (n = 43)	95% CI for Difference From Placebo	Atomoxetine 1.2 mg/kg/day (n = 84)	95% CI for Difference From Placebo	Atomoxetine 1.8 mg/kg/day (n = 82)	95% CI for Difference From Placebo
ADHD RS							
Total	-5.8 (10.9)	-9.9 (14.6)	[-8.9, 0.9]	-13.6 (14.0)*	[-12.1, -4.0]	-13.5 (14.5)*	[-11.9, -3.7]†
Inattention Subscale	-2.5 (6.6)	-5.1 (7.5)	[-5.2, 0.3]	-7.0 (8.1)*	[-6.8, -2.2]	-6.8 (7.9)*	[-6.6, -2.0]†
Hyper/Imp Subscale	-3.2 (5.6)	-4.8 (7.9)	[-4.1, 1.0]	-6.6 (7.1)*	[-5.6, -1.4]	-6.7 (7.5)*	[-5.7, -1.4]†
CPRS-R							
ADHD Index	-1.5 (8.5)	-7.2 (8.9)*	[-9.2, -2.1]	-8.9 (9.7)*	[-10.3, -4.5]	-8.8 (9.7)*	[-10.0, -4.2]†
Hyperactive Subscale	-1.1 (3.9)	-4.1 (4.4)*	[-4.5, -1.2]	-4.1 (4.9)*	[-4.4, -1.6]	-4.3 (4.6)*	[-4.5, -1.8]†
Cognitive Subscale	-0.4 (5.2)	-3.2 (4.8)*	[-4.7, -0.6]	-4.8 (5.2)*	[-6.0, -2.6]	-4.6 (5.7)*	[-5.8, -2.4]†
Oppositional Subscale	-0.6 (3.6)	-2.4 (4.5)*	[-3.3, -0.2]	-2.4 (3.9)*	[-3.1, -0.5]	-2.7 (4.4)*	[-3.3, -0.7]†
CDRS-R							
CDRS-R	+1.1 (6.4)	-0.3 (8.8)	[-4.0, 1.6]	-1.5 (6.0)*	[-5.0, -0.5]	-2.0 (7.7)*	[-5.2, -0.7]†
CHQ							
Physical‡	0.4 (8.2)	-.6 (8.7)	[-4.1, 0.25]	-1.1 (8.0)	[-4.0, 1.4]	-2.0 (8.4)	[-4.9, 0.5]
Psychosocial Summary Score	-0.9 (11.8)	4.4 (10.3)*	[1.0, 9.4]	6.0 (9.0)*	[3.1, 10.0]	9.1 (11.1)*	[6.4, 13.1]†
Behavior	-0.4 (16.6)	8.2 (18.1)*	[1.7, 15.7]	13.0 (18.8)*	[7.9, 19.5]	16.3 (19.3)*	[10.9, 22.4]†
Family activity	0.7 (22.6)	8.7 (27.5)	[-0.6, 17.9]	14.6 (22.4)*	[6.3, 21.5]	15.2 (24.6)*	[7.3, 22.2]†
Parent impact-emotional	3.0 (22.4)	5.7 (21.3)	[-6.1, 11.1]	10.1 (19.4)	[-0.3, 14.0]	11.0 (24.3)*	[1.2, 15.2]†
Parent impact-time	0.2 (26.1)	1.8 (26.0)	[-8.3, 11.2]	6.3 (21.8)	[-2.3, 13.7]	8.8 (25.2)*	[0.6, 16.4]†
Child emotional	-4.4 (40.2)	7.6 (35.8)	[-3.2, 26.1]	7.9 (33.8)	[-0.4, 23.9]	15.9 (40.0)*	[7.7, 31.6]†
Child mental health	-1.9 (16.0)	7.7 (17.7)*	[3.7, 15.1]	4.5 (12.5)*	[1.6, 11.1]	8.9 (14.1)*	[5.6, 15.0]†
Child self-esteem	1.4 (18.7)	1.4 (18.6)	[-4.7, 9.3]	5.4 (16.8)*	[-3, 11.9]	8.4 (19.5)*	[4.2, 15.6]†

Mean (SD) change from baseline to endpoint. CI, confidence interval.

* $P < .05$, pairwise comparison with placebo.

† $P < .05$, linear dose-response term.

‡ Not statistically significant.

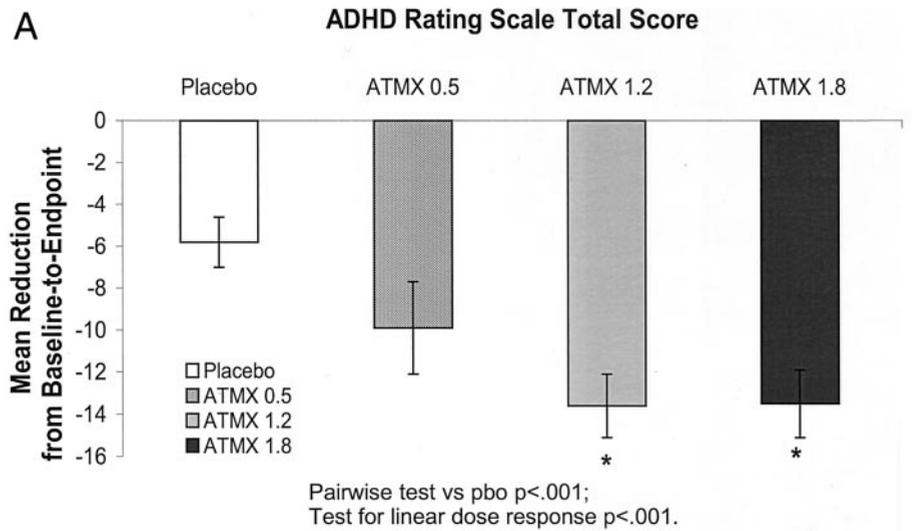


Fig 2. Change from baseline in ADHD RS score (A) and CGI-S score (B).

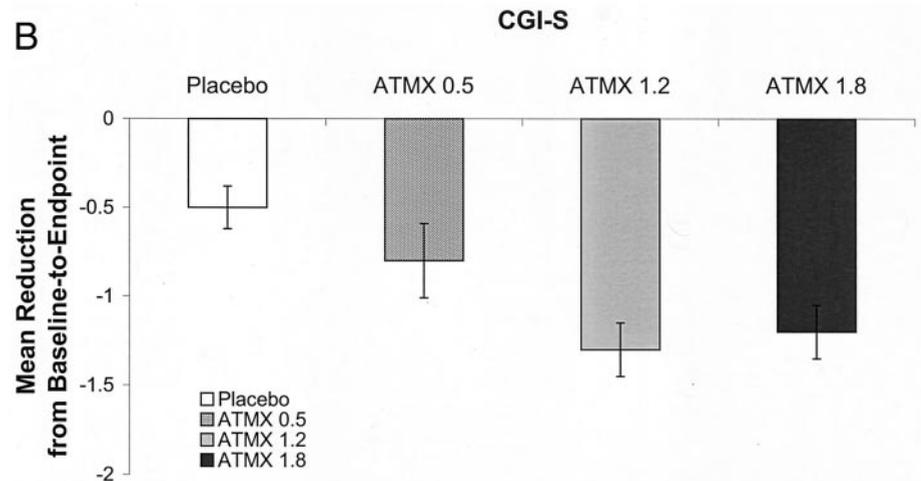


TABLE 4. Treatment-Emergent Adverse Events Reported by at Least 5% of Patients in Any Treatment Group (Arranged in Decreasing Frequency of the Total Population)

Event	Placebo (<i>n</i> = 83) <i>n</i> (%)	Atomoxetine (mg/kg/day)		
		0.5 (<i>n</i> = 44) <i>n</i> (%)	1.2 (<i>n</i> = 84) <i>n</i> (%)	1.8 (<i>n</i> = 83) <i>n</i> (%)
Headache	19 (22.9)	11 (25.0)	20 (23.8)	20 (24.1)
Rhinitis	18 (21.7)	7 (15.9)	10 (11.9)	12 (14.5)
Abdominal pain	9 (10.8)	5 (11.4)	12 (14.3)	12 (14.5)
Pharyngitis	12 (14.5)	4 (9.1)	9 (10.7)	9 (10.8)
Anorexia	4 (4.8)	3 (6.8)	10 (11.9)	10 (12.0)†
Vomiting	5 (6.0)	3 (6.8)	6 (7.1)	9 (10.8)
Cough increased	4 (4.8)	6 (13.6)	6 (7.1)	7 (8.4)
Somnolence	3 (3.6)	2 (4.5)	6 (7.1)	9 (10.8)†
Insomnia	5 (6.0)	4 (9.1)	5 (6.0)	4 (4.8)
Rash	3 (3.6)	3 (6.8)	5 (6.0)	7 (8.4)
Nausea	5 (6.0)	2 (4.5)	6 (7.1)	4 (4.8)
Nervousness	4 (4.8)	3 (6.8)	5 (6.0)	5 (6.0)
Fever	5 (6.0)	1 (2.3)	7 (8.3)	3 (3.6)
Pain	5 (6.0)	4 (9.1)	2 (2.4)	5 (6.0)
Accidental injury	7 (8.4)	1 (2.3)	3 (3.6)	3 (3.6)
Asthenia	4 (4.8)	3 (6.8)	2 (2.4)	4 (4.8)
Infection	1 (1.2)	0	5 (6.0)	6 (7.2)‡
Dizziness	1 (1.2)	4 (9.1)*	2 (2.4)	4 (4.8)
Diarrhea	5 (6.0)	0	4 (4.8)	0†
Depression	5 (6.0)	1 (2.3)	0 (0.0)*	2 (2.4)†
Pruritus	0	0	1 (1.2)	5 (6.0)‡

All patients who took at least 1 dose of the study medication are included.

* $P < .05$, pairwise versus placebo.

† $P < .10$ test for dose-response trend.

‡ $P < .05$ test for dose-response trend.

TABLE 5. Summary of Changes in Vital Sign Measurements

	Placebo (<i>n</i> = 83)	Atomoxetine (mg/kg/day)		
		0.5 <i>n</i> (%) [95% CI]‡ (<i>n</i> = 43)	1.2 <i>n</i> (%) [95% CI]‡ (<i>n</i> = 84)	1.8 <i>n</i> (%) [95% CI]‡ (<i>n</i> = 81)
Blood pressure				
Systolic	2.1 (9.5)	3.3 (10.4) [−2.3, 4.9]	4.3 (10.4) [−0.8, 5.2]	2.5 (8.8) [−2.6, 3.4]
Diastolic	−1.4 (9.8)	1.5 (9.5) [−0.7, 6.5]	2.8 (9.1)* [1.2, 7.2]	1.7 (10.5)*† [0.1, 6.1]
Pulse (bpm)	1.6 (10.5)	5.8 (9.6)* [0.1, 8.3]	6.3 (11.9)* [1.3, 8.1]	8.3 (11.6)*† [3.3, 10.1]
Weight (kg)	1.7 (1.6)	0.3 (1.1)* [−2.0, −0.9]	−0.4 (1.4)* [−2.6, −1.6]	−0.5 (1.7)*† [−2.6, −1.7]

BPM indicates beats per minute; *n*, number of patients with a baseline and at least 1 postbaseline vital sign measurement.

* $P < .05$, pairwise comparison with placebo.

† $P < .05$, linear dose-response term.

‡ Values reported are mean (SD) change from baseline to endpoint and 95% confidence intervals on treatment difference in mean change scores (atomoxetine-placebo).

etine with that of stimulants, because no active comparator was included in the study. These data provide evidence of acute efficacy but not about the value of longer-term therapy once patients have achieved a satisfactory initial response. In this context, it is not yet possible to determine the place of atomoxetine relative to stimulants as a therapeutic option. A teacher assessment was not part of this study, for reasons detailed below, and no direct conclusions about effects on classroom behavior can be drawn from these data. Finally, the study population had very few comorbid psychiatric conditions other than oppositional defiant disorder compared with some previous studies. We cannot definitively account for this difference but suspect that it is related

to the requirement that comorbid psychiatric diagnoses be confirmed by the KSADS, which is highly specific but also highly stringent.

Outcomes in the 1.2 and 1.8 mg/kg/day groups were superior to placebo on almost all measures. The number of patients in the 0.5 mg/kg/day group was (by design) approximately half that of the other treatment arms, because the intent in that arm was to provide evidence for a dose-response and a threshold dose for drug effect rather than definitive evidence of efficacy. In this context, outcomes among patients in the 0.5 mg/kg/day group on the ADHD RS scale and CGI-S scale were not statistically significantly different from those of the placebo group. There was, however, consistent evidence of a dose

TABLE 6. Patient Disposition

Reason	Placebo <i>n</i> (%)	Atomoxetine (mg/kg/day)		
		0.5 <i>n</i> (%) [95% CI]*	1.2 <i>n</i> (%) [95% CI]*	1.8 <i>n</i> (%) [95% CI]*
Completed	72 (85.7)	34 (77.3) [-22.9, 6.0]	69 (82.1) [-14.7, 7.5]	73 (85.9) [-10.4, 10.7]
Adverse event	0 (0.0)	1 (2.3)	2 (2.4)	4 (4.7)
Personal conflict	4 (4.8)	3 (6.8)	6 (7.1)	4 (4.7)
Lack of efficacy	4 (4.8)	3 (6.8)	2 (2.4)	1 (1.2)
Lost to follow-up	4 (4.8)	3 (6.8)	1 (1.2)	2 (2.4)
Protocol violation/entry criteria not met	0 (0.0)	0 (0.0)	2 (2.4)	1 (1.2)
Patient moved	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)

P = .054 Cochran-Armitage test for a dose-response trend.

* 95% confidence intervals (CI) on pairwise differences (atomoxetine-placebo) are reported when the overall event incidence is at least 5%.

effect, as well as statistically significant differences between each atomoxetine group and placebo on the CPRS-R. These data suggest that 0.5 mg/kg/day was associated with some drug-specific effect on symptoms and also that there was a graded dose-response. The 1.8 mg/kg/day did not seem to be associated with any overall gain in efficacy beyond that observed with 1.2 mg/kg/day, but there also was no “fall-off” and the higher dose was well tolerated.

There may have been some selection bias toward difficult-to-treat or medication-nonresponsive illness in our sample, given that approximately 70% of patients had previously been treated with stimulants, which presumably reflects some dissatisfaction with those therapies. Despite this, changes associated with atomoxetine seem to have been clinically, as well as statistically, significant. Mean *t* scores at endpoint were approximately 1.5 SDs above age and gender norms for the 2 higher dose groups. Similarly, the final mean CGI-S scores were slightly above 3 for both of the higher dose groups, suggesting that after treatment approximately half of patients had no, minimal, or mild symptoms. These data, together with the outcomes on the quality of life measures (discussed below), suggest that atomoxetine’s effects on ADHD symptoms were clinically important and associated with a meaningful functional improvement. However, we cannot determine how these outcomes would compare with currently available agents in a similar population because there was no active comparator.

The dosing regimen used in this and other studies was chosen on the basis of pharmacokinetic and pharmacodynamic factors. Body size varies greatly from early childhood into adolescence; we therefore used weight-adjusted dosing. Atomoxetine is not a psychostimulant, and rather than directly release norepinephrine from neurons, it seems to induce a regulatory change in cellular homeostasis through blockade of the norepinephrine transporter. This effect presumably depends on a consistent drug presence at the transporter and based on the plasma half-life of atomoxetine should be achieved during the waking hours with twice daily dosing in most individuals.

We envision that in clinical practice, atomoxetine will continue to be dosed by weight in children and many adolescents on a twice daily (early morning/late afternoon) basis, although the efficacy of once-daily dosing is being assessed as part of the clinical development program. The results presented here suggest a potential algorithm for dosing that would facilitate achieving an optimal dose early in treatment. Dosing would be initiated at approximately 0.5 mg/kg/day and increased quickly to a target dose at or about 1.2 mg/kg/day. The results of this study did not test whether nonresponders or partial responders, after a period of weeks at 1.2 mg/kg/day, would benefit from an additional dose increase. However, there is interindividual variability in plasma concentrations associated with any particular dose, and some patients with low drug exposures at 1.2 mg/kg/day might fail to achieve a satisfactory response at 1.2 mg/kg/day but benefit from an increase to 1.8 mg/kg/day.

The results of this study also provide additional support for the safety and tolerability of atomoxetine. All doses were well tolerated. Discontinuations as a result of adverse events were very low for all groups, and overall completion rates were high. No single adverse event was statistically significantly more frequent in either of the 2 higher atomoxetine dose groups as compared with placebo (although the data did suggest that decreased appetite and somnolence increased with dose, a finding consistent with previous studies). Changes in vital signs consistent with a noradrenergically mediated increase in autonomic tone were observed, but for most patients these changes were modest and asymptomatic. In a study that included both methylphenidate and atomoxetine, changes in vital signs were comparable for both drugs (C. Kratochvil et al, data submitted for publication). A dose-related loss of weight also was observed and is of potential importance. This finding is being investigated further in other, longer-term atomoxetine studies. As with the changes in pulse and blood pressure, the magnitude of the effect seems to be similar to that seen with methylphenidate (C. Kratochvil et al, data submitted for publication). It also is possible that the difference from placebo

cebo may have been magnified by a “rebound” weight gain in children who had previously experienced appetite suppression during stimulant treatments that were discontinued to enter this study.

Atomoxetine is metabolized through the genetically polymorphic CYP 2D6 pathway, which has 2 clinically important phenotypes relative to atomoxetine (extensive and poor metabolizers). At a given dose, poor metabolizers have higher exposures to atomoxetine compared with extensive metabolizers, and it is possible that poor metabolizers would tend to achieve a satisfactory therapeutic response at somewhat lower doses of drug than extensive metabolizers. However, because of the infrequency of the phenotype (approximately 7% of the US population), an adequately sized, poor metabolizer-only dose-response study would be extremely difficult to conduct successfully. Results in the subgroup of poor metabolizers in our study did suggest, subject to the limitations of a small sample, that the pattern of dose-response was similar to that seen in extensive metabolizers. The maximum response was attained at the 2 higher doses, and both of these (1.2 mg/kg/day and 1.8 mg/kg/day) seemed to be relatively similar. Of interest, symptom reduction at the 2 higher doses in the poor metabolizers was extremely robust, with mean endpoint ADHD RS scores in both groups of <10 (no or minimal symptoms on most items). Although the small sample size makes comparisons to extensive metabolizers problematic, it is intriguing to speculate on the possibility that poor metabolizers obtain better efficacy on the basis of either longer plasma half-life (more constant and consistent receptor blockade) or higher drug exposures. However, it also is important to assess whether these higher exposures led to differential safety or tolerability.

In this regard, only 1 poor metabolizer discontinued the study early, and that patient was in the 0.5 mg/kg/day group and did not discontinue because of an adverse event. There were no differences between atomoxetine and placebo in the percentages of poor metabolizers who reported new or worsened adverse events relative to extensive metabolizers. The only area of apparent difference was in heart rate (as assessed by electrocardiogram but not by clinicians). Heart rate increased more among the poor metabolizers than the extensive metabolizers but was not symptomatic. This observation, however, may not reflect a true difference among groups, because extensive metabolizers do not reach steady-state atomoxetine plasma concentrations. Therefore, unlike poor metabolizers, who have relatively constant plasma drug concentrations, many of the assessments of heart rate in extensive metabolizers are likely to have occurred during periods of little or no plasma drug exposure. Overall, because the number of poor metabolizers in each treatment group was relatively small, judgments based on comparisons with extensive metabolizers must be made cautiously. These data are, however, encouraging and provide initial support for the tolerability and safety of atomoxetine in poor metabolizers, although definitive conclusions must await the results of an ongoing

study with larger numbers of extensive and poor metabolizers treated at comparable doses of atomoxetine.

Another subgroup of interest is that of adolescents and older children. The body of data concerning adolescents with ADHD and treatment responses is more limited than that in children, and no previous placebo-controlled studies had been conducted with atomoxetine in this group. The results of our study demonstrated that adolescents with ADHD responded well to atomoxetine. Among adolescents and older children, the 0.5 mg/kg/day dose was efficacious and to a degree that was similar to that seen in the higher doses. The pharmacokinetics of atomoxetine are similar across the age range when dose is adjusted for weight, so differences in drug exposure between younger and older individuals do not explain this outcome. Although it is possible that these results indicate that adolescents have a different dose-response pattern compared with younger children based on some other factor, we believe that it is more likely an artifact of the smaller number of adolescents and older children, resulting in less precise measurement.

As noted above, this study did not include teacher evaluations. The ADHD RS and CPRS-R query about symptoms at school and suggest drug-associated improvement in behaviors relevant to school performance as based on parental reports. Although some large studies have had success in getting teacher ratings,¹⁰ our experience in multicenter trials has been unsatisfactory. In 2 previous studies, we had extreme difficulty getting baseline and endpoint teacher evaluations returned consistently. This probably was because these large multisite studies involved several hundred different schools and teachers, as well as a variety of attitudes toward participation. We believed that this problem would have been compounded in the study reported here, because it was a year-round study and included adolescents in junior high and high school with multiple teachers seeing students for limited periods. As our main objective in this study was to define the dose-response and optimal dose for atomoxetine in the context of overall symptom reduction in all spheres of functioning, and as we thought it unlikely that we would be more successful in obtaining teacher reports than previously without making this the primary objective of the study and altering its design accordingly, we did not include a teacher rating scale. However, we believe that academic performance is a central aspect of children’s lives and is crucially affected by ADHD, and a study that directly assesses atomoxetine effects on school performance is in development.

Atomoxetine, by virtue of its blockade of the norepinephrine transporter, could potentially have efficacy in affective syndromes as well as in ADHD. Only 1 patient in this study met *DSM-IV* criteria for depression, and mean scores on the CDRS-R were below the threshold of 36 that is generally associated with depressive disorders.²⁷ However, atomoxetine did show some specific effects in reducing CDRS-R scores compared with placebo and was superior to

placebo in outcomes on the self-esteem subscale of the CHQ. These data suggest that atomoxetine may have specific benefit in the population of patients whose ADHD is comorbid with affective disorders.

Results on the functional and quality-of-life measures, including the CHQ, as well as oppositional behavior as assessed by the CPRS-R in this study suggested a marked benefit for both patients and families of patients who were taking atomoxetine compared with placebo in these domains. Previous studies have demonstrated that ADHD is not a benign disorder^{28–30} and has an impact on functioning in social and family spheres as well as at school. However, data demonstrating that successful pharmacotherapy and reduction of ADHD symptoms leads to concurrent, drug-specific improvement in functional outcomes are limited. Outcomes on the CHQ provide important evidence that the improvements in ADHD symptoms associated with atomoxetine also are associated with better family and social functioning during acute therapy and that the statistically significant findings of differences from placebo in ADHD symptom reduction are clinically important as well. That differences were observed on the psychosocial but not the physical subscales suggests that the measured changes represent specific effects rather than indiscriminate reports of improvement related to halo or other nonspecific effects. If these improvements persist over time, then treatment could have longer-term benefits for children and families well beyond immediate symptom reduction.

CONCLUSION

The data reported here provide additional evidence of the efficacy and safety of atomoxetine in older children and adolescents with ADHD and that successful treatment with atomoxetine is associated with both symptomatic and functional improvement. The data suggest that there is a graded dose-response, and for most patients, 1.2 mg/kg/day is likely to be the appropriate dose.

ACKNOWLEDGMENTS

This research was funded by Eli Lilly and Company.

The Atomoxetine Study Group includes Peter Ahmann, MD; Stan L. Block, MD; Charles Casat, MD; David Dunn, MD; Chris Kratochvil, MD; Jeffrey Newcorn, MD; Humberto Quintana, MD; R. Bart Sangal, MD; Keith Saylor, PhD; Mark Stein, PhD; and Scott West, MD. Drs. Ahmann, Block, Casat, Dunn, Kratochvil, Newcorn, Quintana, Sangal, Saylor, Stein, West, Sallee, and Spencer have acted as paid consultants and/or investigators for studies sponsored by Eli Lilly and Company. Drs. Michelson, Faries, Wernicke, and Kelsey and Ms. Kendrick are employees and shareholders of Eli Lilly and Company.

We thank Rosalinda Tepner, Nancy J. Raute, and Michele Y. Hill for assistance in the preparation of this manuscript.

REFERENCES

- American Academy of Pediatrics, Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics*. 2000;105:1158–1170
- Hechtman L. Assessment and diagnosis of attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin North Am*. 2000;9:481–498
- Brown RT, Borden KA. Hyperactivity at adolescence: some misconceptions and new directions. *J Clin Child Psychol*. 1986;15:194–209
- Hechtman L. Attention-deficit hyperactivity disorder. In: Hechtman L, ed. *Do They Grow Out of It? Long-Term Outcomes of Childhood Disorders*. Washington, DC: American Psychiatric Press; 1996:17–38
- Klein RG, Mannuzza S. The long-term outcome of the attention-deficit disorder/hyperkinetic syndrome. In: Sagvolden T, Archer T, eds. *Attention Deficit Disorder: Clinical and Basic Research*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1989:71–91
- Klein RG, Mannuzza S. Long-term outcome of hyperactive children: a review. *J Am Acad Child Adolesc Psychiatry*. 1991;30:383–387
- Thorley G. Review of follow-up and follow-back studies of childhood hyperactivity. *Psychol Bull*. 1984;96:116–132
- Weiss G. Research issues in longitudinal studies. In: Hechtman L, ed. *Do They Grow Out of It? Long-Term Outcomes of Childhood Disorders*. Washington, DC: American Psychiatric Press; 1996:1–16
- Weiss G, Hechtman LT. *Hyperactive Children Grown Up*. 2nd ed. New York, NY: Guilford Press; 1993
- MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry*. 1999;56:1073–1086
- Greenhill LL, Swanson JM, Vitiello B, et al. Impairment and department responses to different methylphenidate doses in children with ADHD: the MTA titration trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40:180–187
- Stein MA. Methylphenidate dosing: twice daily versus three times daily. *Pediatrics*. 1996;98:748–756
- Wilens TE, Biederman J, Abrantes AM, Spencer TJ. A naturalistic assessment of protriptyline for attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1996;35:1485–1490
- Wender PH, Reimherr FW. Bupropion treatment of attention-deficit hyperactivity disorder in adults. *Am J Psychiatry*. 1990;147:1018–1020
- Higgins ES. A comparative analysis of antidepressants and stimulants for the treatment of adults with attention-deficit hyperactivity disorder. *J Fam Pract*. 1999;48:15–20
- Laws HF, Heil SH, Bickel WK, Higgins ST, Faries DE. Subjective responses to LY139603 (Atomoxetine) and Methylphenidate [abstract 70]. *Biological Psychiatry*. 2001;49(8S):205
- Heiligenstein J, Spencer T, Faries DE, et al. Efficacy of atomoxetine vs. placebo in pediatric outpatients with ADHD. Poster presented at The American Academy of Child and Adolescent Psychiatry; New York, NY; October 2000
- Spencer TJ, Biederman J, Wilens TE, et al. Effectiveness and tolerability of tomoxetine in adults with attention deficit hyperactivity disorder. *Am J Psychiatry*. 1998;155:693–695
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994
- Kaufman J, Birmaher B, Brent D, Rao U, Ryan N. *Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)*. Version 1.0 of October 1996 ed. Pittsburgh, PA: Department of Psychiatry, University of Pittsburgh School of Medicine; 1996
- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretations*. New York, NY: The Guilford Press; 1998
- Wechsler D. *Wechsler Intelligence Scale for Children*. 3rd ed. San Antonio, TX: The Psychological Corporation; 1991
- Landgraf JM, Maunsell E, Speechley KN, et al. Canadian-French, German and UK versions of the Child Health Questionnaire: methodology and preliminary item scaling results. *Qual Life Res*. 1998;7:433–445
- Spencer T, Biederman J, Wilens T, Steingard R, Geist D. Nortriptyline treatment of children with attention-deficit hyperactivity disorder and tic disorder or Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1993;32:205–210
- Wilens TE, Biederman J, Geist DE, Steingard R, Spencer T. Nortriptyline in the treatment of ADHD: a chart review of 58 cases. *J Am Acad Child Adolesc Psychiatry*. 1993;32:343–349
- Wilens TE, Biederman J, Spencer T, Geist DE. A retrospective study of serum levels and electrocardiographic effects of nortriptyline in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1993;32:270–277
- Poznanski EO, Mokros HB. *Children's Depression Rating Scale (CDRS-R) Revised*. 2nd ed. Los Angeles, CA: Western Psychological Services; 1999
- Stubbe DE, Weiss G. Psychosocial interventions: individual psychotherapy with the child, and family interventions. *Child Adolesc Psychiatr Clin North Am*. 2000;9:663–670
- Dulcan M, Benson RS. Practice parameters for the assessment and treatment of children, adolescents and adults with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1997;35:85S–121S
- Diagnosis and treatment of attention deficit hyperactivity disorder. *NIH Consens Statements*. 1998;16:1–37

Atomoxetine in the Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Dose-Response Study

David Michelson, Douglas Faries, Joachim Wernicke, Douglas Kelsey, Katherine Kendrick, F. Randy Sallee, Thomas Spencer and the Atomoxetine ADHD Study Group

Pediatrics 2001;108;e83
DOI: 10.1542/peds.108.5.e83

Updated Information & Services

including high resolution figures, can be found at:
<http://pediatrics.aappublications.org/content/108/5/e83>

References

This article cites 18 articles, 2 of which you can access for free at:
<http://pediatrics.aappublications.org/content/108/5/e83#BIBL>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):
Developmental/Behavioral Pediatrics
http://www.aappublications.org/cgi/collection/development:behavioral_issues_sub
Attention-Deficit/Hyperactivity Disorder (ADHD)
http://www.aappublications.org/cgi/collection/attention-deficit:hyperactivity_disorder_adhd_sub
Pharmacology
http://www.aappublications.org/cgi/collection/pharmacology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
<http://www.aappublications.org/site/misc/Permissions.xhtml>

Reprints

Information about ordering reprints can be found online:
<http://www.aappublications.org/site/misc/reprints.xhtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Atomoxetine in the Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Dose-Response Study

David Michelson, Douglas Faries, Joachim Wernicke, Douglas Kelsey, Katherine Kendrick, F. Randy Sallee, Thomas Spencer and the Atomoxetine ADHD Study Group

Pediatrics 2001;108:e83
DOI: 10.1542/peds.108.5.e83

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/108/5/e83>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2001 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

