A Randomized, Double-Blind Study of Continuation Treatment for Attention-Deficit/Hyperactivity Disorder After 1 Year

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Background: The efficacy of atomoxetine in maintaining symptom response following 1 year of treatment was assessed in children and adolescents ($n = 163$) with DSM-IV defined attention-deficit/hyperactivity disorder (ADHD).

Methods: Subjects had previously responded to atomoxetine acutely and had completed 1 year of double-blind atomoxetine treatment. They were then randomly assigned in double-blind fashion to continued atomoxetine or placebo substitution for 6 months.

Results: Atomoxetine was superior to placebo in preventing relapse (Wilcoxon test, $p = .008$) and in maintaining symptom response (ADHD Rating Scale IV score, $p < .001$). Among subjects assigned to discontinuation, the magnitude of symptom return was generally to a level of severity less than that observed at study entry.

Conclusions: Following 1 year of treatment with atomoxetine, continued treatment over the ensuing 6 months was associated with superior outcomes compared with placebo substitution. However, there was considerable variability between individuals in the magnitude of symptom return after drug discontinuation, suggesting that some subjects treated with atomoxetine for a year with good results may consolidate gains made during drug treatment and could benefit from a medication-free trial to assess the need for ongoing drug treatment.

Key Words: ADHD, atomoxetine, pediatric subjects, relapse prevention

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of childhood characterized by hyperactivity, impulsivity, and/or difficulty maintaining sustained attention. Attention-deficit/hyperactivity disorder occurs in 3% to 7% of school-aged children in the United States (American Psychiatric Association 2000), and similar figures have been reported elsewhere (Andres Carrasco et al 1995; Wang et al 1993). Attention-deficit/hyperactivity disorder is a chronic disorder, and pharmacotherapy is becoming increasingly accepted as a first-line intervention (American Academy of Pediatrics 2001).

Despite the fact that ADHD is a chronic disorder, systematic assessments of efficacy in ADHD have mainly taken place in trials limited to several weeks in duration. Few prospective studies have examined the value of continued treatment in subjects who have had a satisfactory initial response to treatment. Moreover, to our knowledge, no studies assessing the value of maintenance treatment following differing periods of initial treatment or, indeed, after an initial period of any length have been reported. The recent Multimodal Treatment Study of ADHD (MTA) (MTA Cooperative Group 1999) compared different interventions and provided data over 14 months of treatment, with further reports of longer term outcomes planned. However, that study did not include placebo control during long-term treatment, did not re-randomize acute treatment responders, and could not test the effect of medication in maintaining response and preventing relapse. The only placebo-controlled relapse prevention study of pharmacotherapy for ADHD of which we are aware was reported by Gillberg et al (1997) and demonstrated the superiority of amphetamine to placebo in maintaining response during the 12 months following an initial 3-month treatment period.

Atomoxetine, a highly selective norepinephrine reuptake inhibitor, is approved for the treatment of ADHD in the United States and elsewhere. We have previously reported that subjects who continued atomoxetine had superior outcomes during the 9 months following an initial 3-month treatment period (Michelson et al 2004). However, the need for continued pharmacotherapy could change over longer periods. Therefore, a second phase of the previous study was designed to assess the efficacy of continuing atomoxetine for 6 additional months in subjects who completed 1 year of treatment and to determine the value of differing lengths of continuation treatment following an initial response. We report results from this portion of the study here.

Methods and Materials

Participants

This study was conducted at academic investigative centers in Europe (24 centers), Israel (2 centers), South Africa (4 centers), and Australia (3 centers). Patients aged 6 to 15 years who met DSM-IV criteria for ADHD, as assessed by clinical history and confirmed by a structured interview (Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version [K-SADS-PL]) (Kaufman et al 1996), and whose symptom severity was at least 1.5 standard deviations above US age and sex norms on the ADHD Rating Scale IV (ADHD RS) were eligible to participate. Patients with bipolar disorder or psychotic illness were excluded, as were patients with unstable medical illness or conditions requiring ongoing administration of a psychoactive medication (other than atomoxetine). Comorbid psychiatric disorders were assessed clinically

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Received October 14, 2004; revised March 24, 2006; accepted March 28, 2006.

0006-3223/07/$32.00
doi:10.1016/j.biopsych.2006.03.066

and by the K-SADS-PL. All subjects had a medical evaluation including physical examination, routine chemistries, liver function tests, complete blood count, urinalysis, and electrocardiogram (ECG). After receiving a complete description of the study, a parent or guardian for each subject provided written informed consent to participate, and subjects provided written assent. The study was reviewed and approved by each site's ethical review board and was conducted in accordance with the ethical standards of the 1975 Declaration of Helsinki, as revised in 2000 (World Medical Association 2000).

Measures

The primary efficacy measure was the investigator-administered version of the ADHD RS, an 18-item scale with psychometric properties that have been described elsewhere (DuPaul et al 1998). Other measures included the Clinical Global Impression-Severity (CGI-S), Child Health Questionnaire (CHQ, an assessment of functional outcomes and quality of life) (Landgraf et al 1996), the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski and Mokros 1999), the revised Conners' Parent and Teacher Rating Scales: Short Form (CPRS-R:S and CTRS-R:S) (Conners 1997), and the Multidimensional Anxiety Scale for Children (MASC) (March and Sullivan 1999). Intelligence quotient (IQ) was estimated using four subscales of the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler 1991). Principal investigators at each site were child psychiatrists or pediatricians. A central meeting was held prior to the start of the study at which time all raters received training that included discussions of the rating procedures and conventions and how to conduct interviews and rate videotaped and observed interviews. Interrater reliability was not reassessed while the study was ongoing.

Safety was assessed at each visit by open-ended questioning for adverse events and by vital sign measurements and periodic retesting of blood chemistries, liver function tests, complete blood counts, urinalysis, and ECG.

Study Design

The study design is summarized in Figure 1. After an initial evaluation period, including a medication washout for a period lasting at least five times the plasma half-life of any psychoactive medication the subject was taking, treatment was initiated with open-label atomoxetine .5 mg/kg/d, increased to a target dose of 1.2 mg/kg/d, and administered as a divided twice-daily dose. Further increases were allowed based on clinical response to a maximum dose of 1.8 mg/kg/d. Investigators and subjects were told that randomization to drug or placebo could occur at week 10 or beyond; from week 10, treatment was administered in a double-blind fashion. Randomization into the initial 9-month, double-blind, relapse prevention phase, which has been reported previously (Michelson et al 2004), took place at week 12. A second randomization occurred after approximately 1 year of treatment, with subjects initially randomly assigned to atomoxetine being re-randomized to an additional 6 months of atomoxetine or placebo substitution. Patients and investigators were blind to the timing of both randomizations. Visits during the randomized portion of the study were monthly. Patients who discontinued because they met full relapse criteria (see below) were eligible to enter an open-label study that provided continued access to atomoxetine, which was not yet marketed at the time the study was conducted. Patients who discontinued for other reasons were referred for evaluation for usual care available in their area. Randomization sequences were generated by an outside vendor and stratified by investigational site.

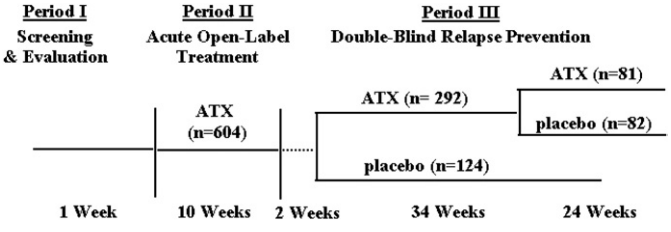

Figure 1. Study design.

Statistical Analyses

An initial positive response to treatment sufficient to enter the randomized, relapse prevention phase was defined as a decrease of at least 25% in symptom severity from baseline, as measured by the ADHD RS total score and a CGI-S score of 1 or 2 (no or minimal symptoms) after 10 weeks.

The protocol-specified primary outcome measure was a comparison of mean time to relapse, defined as an increase in ADHD RS total score to 90% of the score at study entry and an increase in CGI-S score of at least 2 points above the CGI-S score at the end of the initial 10-week treatment period. The distribution of days to relapse was estimated for each treatment group using the Kaplan-Meier product-limit estimator, and treatment differences were assessed using Wilcoxon test. To provide more sensitive assessments of symptom return, prospectively specified secondary analyses included relapse, defined as a 50% increase in ADHD RS total score and increase in CGI-S score of 2 or more points compared with scores at the time of second randomization, and a comparison of mean change in ADHD RS after randomization. All analyses are reported in the intent-to-treat sample.

Effects of subject characteristics on risk of relapse, including age ($\leq$12 or $>$12), sex, previous stimulant treatment, diagnostic subtype (combined or inattentive), and presence of oppositional defiant disorder (ODD), were examined by including baseline information as a covariate in a proportional hazards analysis of time to relapse. For each covariate, the model included treatment, the covariate, and the treatment-by-covariate interaction. Treatment differences in mean change from baseline to end point for secondary efficacy measures were assessed using an analysis of variance model with terms for treatment and investigator. All randomly assigned subjects with at least one postbaseline measurement were included, and change scores were computed using a last-observation-carried-forward approach. Baseline was defined as the last measurement prior to randomization after 1 year of atomoxetine treatment. Treatment differences for categorical variables were assessed using the Fisher exact test. Within-group analyses were performed using the Wilcoxon signed rank test. All tests used a two-sided significance level of .05. As the protocol prospectively declared, a primary outcome measure and all other comparisons were considered secondary; no correction for multiple comparisons was employed.

Growth chart data provided by the National Center for Health Statistics for the US population were used to assess height and weight relative to expected normative values. Raw height and weight were standardized relative to age and sex norms by computing the growth chart percentiles corresponding to each subject's weight or height. The use of US standards may yield normative values slightly different from those in the different study regions but are relevant for estimating change over time.

Table 1. Subject Characteristics and Symptom Ratings

Characteristic	Study Entry	First Randomization (3 Months)	Second Randomization (1 Year)	
	Atomoxetine (n = 604)	Atomoxetine (n = 292)	Atomoxetine (n = 81)	Placebo (n = 82)
Age, years, mean (SD)	10.2 (2.3)	10.6 (2.3)	10.7 (2.4)	11.0 (2.0)
Sex, *n* (%)				
Male	541 (89.6)	261 (89.4)	72 (88.9)	74 (90.2)
Female	63 (10.4)	31 (10.6)	9 (11.1)	8 (9.8)
ADHD Diagnostic Subtype, *n* (%)				
Combined	450 (74.5)	212 (72.6)	60 (74.1)	61 (74.4)
Hyperactive/Impulsive	30 (5.0)	13 (4.5)	4 (4.9)	4 (4.9)
Inattentive	124 (20.5)	67 (22.9)	17 (21.0)	17 (20.7)
Comorbid Psychiatric Conditions, *n* (%)				
Oppositional Defiant Disorder	275 (45.5)	123 (42.1)	40 (49.4)	32 (39.0)
Depression	9 (1.5)	6 (2.1)	1 (1.2)	3 (3.7)
Anxiety (Separation)	31 (5.1)	16 (5.5)	4 (4.9)	4 (4.9)
Anxiety (General)	14 (2.3)	8 (2.7)	2 (2.5)	0 (.0)
Symptom Severity Ratings, mean (SD)[a]				
ADHD RS Total	41.3 (7.8)	41.2 (8.0)	41.0 (8.2)	40.7 (7.3)
ADHD RS Total T-Score	80.3 (9.2)	80.3 (9.4)	80.4 (10.3)	79.7 (8.5)
ADHD RS Inattention Score	21.5 (4.1)	21.7 (4.2)	21.7 (4.4)	21.3 (3.8)
ADHD RS Hyperactivity/Impulsivity Score	19.9 (5.6)	19.5 (5.8)	19.4 (5.7)	19.4 (5.6)
CTRS-R:S ADHD Index	24.0 (8.0) (n = 458)	23.6 (8.0) (n = 250)	24.6 (7.0) (n = 71)	22.8 (7.7) (n = 73)
CPRS-R:S ADHD Index	28.4 (5.7) (n = 572)	28.3 (6.0) (n = 291)	28.6 (6.4) (n = 80)	28.2 (5.9)
CDRS Total Score	26.9 (7.7)	26.6 (7.6)	26.4 (7.2)	26.5 (6.9)
MASC Anxiety Disorder Index	11.3 (4.8) (n = 540)	11.1 (5.0) (n = 269)	11.2 (5.5) (n = 76)	10.7 (4.8) (n = 79)
CHQ Psychosocial Summary Score	30.1 (10.3) (n = 481)	30.1 (10.1) (n = 239)	30.6 (10.9) (n = 67)	30.4 (9.6) (n = 65)

ADHD, attention-deficit/hyperactivity disorder; ADHD RS, ADHD Rating Scale IV; CTRS-R:S, revised Conners' Teacher Rating Scale: Short Form; CPRS-R:S, revised Conners' Parent Rating Scale: Short Form; CDRS, Children's Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children; CHQ, Child Health Questionnaire.

[a] *N*s for several scales vary due to missing data.

Results

Of 604 subjects who entered the study, 416 completed the 12-week, open-label atomoxetine treatment phase and entered the double-blind portion of the study. Of these 416 subjects, 292 were randomly assigned to continued treatment with atomoxetine, and 163 (26% of the original sample) completed 1 year of treatment with atomoxetine and were re-randomized to 6 additional months of treatment with atomoxetine (n = 81) or placebo (n = 82). Reasons for discontinuation during the 9 months between the first and second randomizations included relapse (75/292 [25.7%]), adverse events (9/292 [3.1%]), protocol violation (11/292 [3.8%]), loss to follow-up or moving (3/292 [1.0%]), physician decision (13/292 [4.5%]), subject decision or personal conflict (20/292 [6.8%]), and subject and physician perception that treatment was no longer required (1/292 [.3%]).

Subject characteristics and symptom ratings are summarized in Table 1. Two subjects assigned to atomoxetine and one to placebo discontinued at the randomization visit and were excluded from efficacy analyses. At end point, more subjects assigned to atomoxetine treatment completed the 6-month randomized phase of the study (atomoxetine, 65/79 [82.3%]; placebo, 54/81 [66.7%]; p = .030). Subjects who continued with atomoxetine treatment had lower relapse rates compared with those of subjects receiving placebo (days to relapse, mean [SD]: atomoxetine, 160.5 [.7]; placebo, 130.8 [3.1]; Wilcoxon p = .008) (Figure 2). Relapse rates were 2 (2.5%) of 81 subjects for atomoxetine and 10 (12.2%) of 82 subjects for placebo, and the relative risk ratio for relapse during placebo treatment was 5.6 (95% confidence interval [CI]: 1.2, 25.6). Survival curves for relapse are shown in Figure 2, and time course for mean symptom return is shown in Figure 3. After the first randomization at 12 weeks, 6-month relapse rates were also significantly different between treatment groups but had been markedly higher than those observed after the second (1-year) randomization (relapse during the 6 months after 3 months of initial treatment: atomoxetine, 61/292 [20.9%]; placebo, 46/124 [37.1%]; $p < .001$).

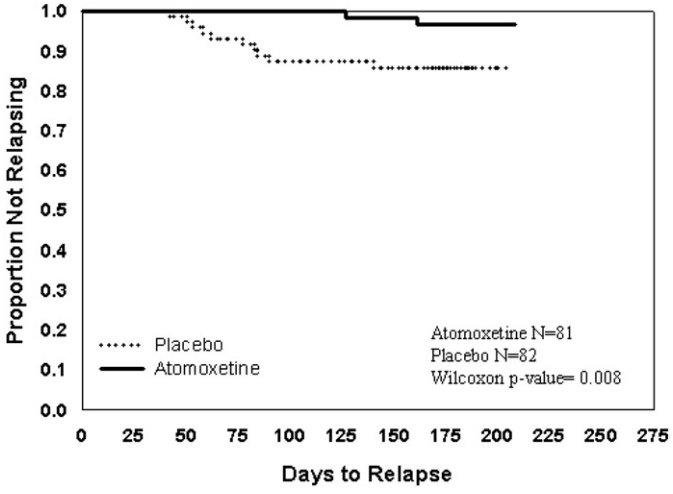

Figure 2. Proportion of patients remaining well after randomization.

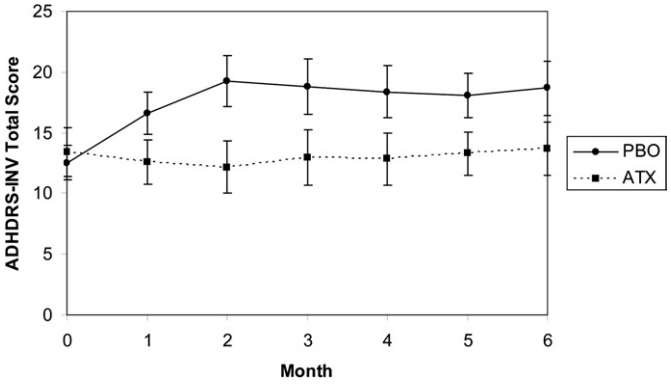

Figure 3. Change in ADHD symptom severity over time. ADHA, attention-deficit/hyperactivity disorder.

No treatment interaction was observed between relapse after the 1-year randomization and age (>12 or ≤12), sex, ADHD subtype, investigator, history of previous stimulant treatment, or comorbid ODD. Application of the secondary definition of relapse (≥50% worsening in ADHD RS severity score above the last prerandomization visit) resulted in similar relapse rates (atomoxetine, 6/81 [7.4%]; placebo, 16/82 [19.5%]; $p = .037$; relative risk ratio, 3.0 [95% CI: 1.2, 7.6]). The proportion of subjects whose symptom severity, as assessed by the ADHD RS, increased to at least 1.5 standard deviations above age and sex norms for their diagnostic subtype (the severity threshold required for study entry) was 17 (22.1%) of 77 subjects for atomoxetine and 34 (42.0%) of 81 subjects for placebo ($p = .010$).

Subjects assigned to placebo experienced greater symptom return, as assessed by increases in mean ADHD RS scores and other secondary measures, including teacher rating scales (Table 2). Compared with the mean worsening observed for subjects assigned to placebo during the 6-month period after the 3 months of acute treatment, treatment gains were better preserved in subjects treated for 1 year (mean [SD] baseline and change in ADHD RS total score: atomoxetine, 15.77 [9.59] and +6.48 [13.35]; placebo, 15.71 [9.96] and +11.54 [14.72]; $p < .001$). There was no evidence of significant anxiety or depressive symptoms for either group, as assessed by the MASC and CDRS-R, and no change in such scores following randomization in either group. Mean modal dose during the 1-year treatment period prior to randomization was similar in both groups (mean [SD] mg/kg/d: atomoxetine, 1.57 [.26]; placebo, 1.59 [.22]) and did not change significantly after randomization in the atomoxetine group (1.55 [.25]).

One subject in each treatment group discontinued after randomization because of an adverse event ($p > .99$). Two adverse events were reported in more than 5% of subjects in both treatment groups, headache (atomoxetine, 8 [10.1%]; placebo, 7 [8.6%]) and nasopharyngitis (atomoxetine, 6 [7.6%]; placebo, 7 [8.6%]). All other adverse events were reported by ≤5% of subjects, and none were reported significantly more often by those taking atomoxetine. There was no statistically significant difference in standardized height change between groups during the 6-month postrandomization period (mean [SD] baseline and change for height percentile: atomoxetine, 51.3 [27.7] and +.33 [9.31]; placebo, 56.3 [26.8] and −.11 [7.9], $p = .76$). Both placebo and atomoxetine were associated with an increase in weight percentile, but the increase was greater in the placebo group (mean [SD] baseline and change for weight percentile: atomoxetine, 48.2 [31.8] and +.72 [6.1]; placebo, 51.0 [28.2] and +9.9 [10.7]; $p < .001$). There were no clinically meaningful differences in routine chemistry, liver function tests, hematological measures, blood pressure, or cardiac QT intervals (corrected for heart rate) between the two groups.

Discussion

Attention-deficit/hyperactivity disorder is generally thought of as a persistent disorder requiring chronic treatment. However, little has been reported of placebo-controlled data evaluating long-term pharmacologic treatment, and few studies have used a treatment discontinuation design that tests the efficacy of maintenance therapy. We have previously reported data from an analysis of the initial phase of this study that demonstrate the efficacy of atomoxetine in maintaining response after a 3-month treatment (Michelson et al 2004), and Gillberg et al (1997) demonstrated the value of continued amphetamine therapy after

Table 2. Efficacy Results

	Treatment Group						
	Atomoxetine ($n = 77$)		Placebo ($n = 81$)		Analysis of Variance (LOCF)		
Efficacy Measure	Baseline[a] Mean (SD)	Change from Baseline Mean (SD)	Baseline[a] Mean (SD)	Change from Baseline Mean (SD)	*F*	*df*	*p* Value
ADHD RS Total Score	13.4 (9.0)	1.7 (9.1)	12.5 (6.5)	7.8 (12.4)	13.4	1,125	<.001
ADHD RS Total T Score	52.3 (9.0)	1.7 (9.2)	51.3 (7.1)	8.0 (13.1)	13.8	1,125	<.001
ADHD RS Inattention Score	7.2 (4.7)	1.2 (5.4)	7.3 (4.2)	4.1 (6.1)	10.1	1,125	.002
ADHD RS Hyperactivity/Impulsivity Score	6.2 (5.7)	.5 (4.7)	5.2 (4.0)	3.6 (6.8)	12.5	1,125	<.001
CTRS-R:S ADHD Index	15.8 (9.0) ($n = 64$)	−1.8 (9.0)	16.1 (8.4) ($n = 67$)	3.3 (9.0)	14.0	1,98	<.001
CPRS-R:S ADHD Index	11.4 (7.0)	1.2 (6.0)	12.2 (6.9)	3.5 (7.6)	3.8	1,125	.054
CDRS	21.4 (4.5) ($n = 73$)	.9 (4.4)	21.2 (5.1) ($n = 77$)	1.1 (5.5)	.04	1,117	.84
MASC Total Score	31.9 (15.4) ($n = 68$)	−.5 (10.3)	31.8 (15.3) ($n = 74$)	.5 (10.0)	.3	1,109	.56
CHQ Psychosocial Summary Score[b]	45.6 (8.9) ($n = 59$)	−.9 (10.1)	44.3 (10.0) ($n = 62$)	−2.9 (10.9)	.9	1,92	.35

LOCF, last observation carried forward; ADHD RS, ADHD Rating Scale IV; ADHD, attention-deficit/hyperactivity disorder; CTRS-R:S, revised Conners' Teacher Rating Scale: Short Form; CPRS-R:S, revised Conners' Parent Rating Scale: Short Form; CDRS, Children's Depression Rating Scale; MASC, Multidimensional Anxiety Scale for Children; CHQ, Child Health Questionnaire; IQ, intelligence quotient.

[a]Baseline refers to rating at randomization after 1 year of atomoxetine treatment; note that the *n* differs slightly from the survival (relapse) analysis and also between measures because of subjects without postrandomization observations for particular measures.

[b]Decrease in CHQ score indicates worsened symptoms; for all other measures except IQ, increased score indicates worsening symptoms.

3 months. Our study extends these results by examining the value of continued atomoxetine after a 1-year treatment period.

The data presented here provide evidence that after 1 year of atomoxetine treatment, subjects who continue atomoxetine for 6 additional months are less likely to relapse or experience partial symptom return compared with those who discontinue treatment. Of interest, the severity of recurrent symptoms after drug discontinuation in the group randomly assigned to placebo was generally less than that observed at the time of entry into the study, and the proportion of subjects who met full relapse criteria was small, even using the less stringent criterion.

After randomization, relapse rates (defined as persistent return of symptoms at a severity similar to that observed at study entry) were low not only for subjects who continued atomoxetine but also for subjects randomly assigned to placebo. Compared with 6-month relapse rates for subjects who discontinued treatment after 3 months, 6-month relapse rates for subjects discontinuing treatment after 1 year were lower, and they experienced less mean worsening in symptom severity. However, these data do not demonstrate that most subjects who discontinue atomoxetine after 1 year remain minimally symptomatic. The primary definition of relapse in this study was very stringent, requiring a return to near study entry severity. Other less stringent definitions are likely to be more sensitive to less pronounced but still clinically relevant symptom return. For this reason, the study specified alternative definitions of relapse as secondary measures, and using the criterion of an increase in ADHD RS total score to at least 1.5 standard deviations above age and sex norms for their diagnostic ADHD subtype (the degree of symptom severity required to be eligible to enter the study), 42% of those in the placebo group would be classified as relapsers compared with 22.1% of atomoxetine-treated subjects ($p = .010$). Additionally, the placebo group showed an overall mean worsening in symptom severity after randomization, while there was minimal mean change in the atomoxetine group. This pattern was replicated on secondary measures and was observed by clinicians, parents, and teachers and is also consistent with observation that the number of discontinuations following randomization for any reason in the atomoxetine group was statistically significantly lower than the placebo group.

It is of interest that symptoms seen after drug discontinuation did not return to the severity observed at study entry and could be accounted for by several factors. It has been reported that as children mature, diagnostic criteria for ADHD may continue to be met, but core ADHD symptom severity (especially hyperactivity) tends to decline, as demonstrated by the association of ADHD RS normative scores at a given value with lower raw scores over time (DuPaul et al 1998). Over the year of active treatment prior to drug discontinuation, cognitive and emotional development would be expected to continue. As a result, some subjects may have been better able to cope with their symptoms at the end of the study than at baseline, perhaps as a result of persistent beneficial effects of treatment (for example, more positive feedback and learning related to improved functioning), or perhaps related to the natural history of the disorder, or a combination of both. This hypothesis is consistent with the finding that using age-adjusted normative scores (T-scores) rather than raw severity scores, the proportion of subjects whose symptoms increased to the threshold required for study entry, was higher than the proportion of subjects who met stringent criteria for relapse (return to 90% of study entry ADHD RS total raw score).

Another factor that could have contributed to the low absolute relapse rates is the possibility that many subjects presented for evaluation at study entry because their disorder was particularly troublesome or impairing at that point. After 1 year, the severity of recurrent symptoms following drug discontinuation would likely be less than that observed at the time of study entry. The observed outcomes could also have been influenced by the fact that the subjects randomly assigned to treatment in this study had all achieved near-complete symptomatic remission during acute treatment. Relapse rates might well have been higher if subjects with good responses but with some persistent symptoms had been included. Finally, it is possible that medication treatment itself had a positive effect on outcomes, though we do not know the mechanism that would account for this.

No serious safety concerns were observed during the study, and atomoxetine was well tolerated. During the 6-month period following the initial year of treatment, growth was normal in the atomoxetine group, as assessed by minimally changed normative height and weight, which implies normal growth velocity. These data are consistent with previous observations in long-term atomoxetine studies (Spencer et al 2005) demonstrating a modest decrease in growth rates early in treatment but normal growth rates during long-term treatment. In the placebo group, there was no significant change in normative height, but normative weight did increase significantly, most likely related to increased appetite following the discontinuation of atomoxetine.

The most important factors limiting interpretation of this study relate to potential differences between research and clinical populations and to changes in the sample over the course of the study. All subjects in this trial had excellent responses after an initial trial of atomoxetine. Outcomes might have differed for patients with incomplete responses. The conclusions of this study are also applicable only to patients who have maintained an initial response to atomoxetine for 1 year and cannot be generalized to those who have periods of significant symptom return during ongoing treatment or who use atomoxetine in an episodic fashion. Subjects who discontinued after 3 months had higher relapse rates than those who discontinued after 1 year. The fact that some subjects relapsed after the initial (3-month) randomization, despite being assigned to continued atomoxetine treatment, suggests that factors other than drug discontinuation contributed to risk of relapse after the initial treatment period. Because these subjects had already relapsed and were discontinued from the study prior to the second (1-year) randomization, the sample at the second randomization may have been less likely to relapse in the sense that subjects at highest risk for symptom return due to nonspecific factors had already been excluded.

One other factor limiting the interpretation of the data relates to the preponderance of male subjects (approximately 9:1). While most ADHD studies enroll greater numbers of male subjects than female subjects, the ratio in this study is higher than that typically observed in North American studies and most likely is related to patterns of practice and diagnosis in non-North American countries. Therefore, though there was not an interaction between gender and outcomes, we cannot rule out the possibility that results would be different in a sample made up of female subjects.

A number of subjects discontinued treatment for reasons other than relapse, including adverse events, symptom return not meeting the threshold for relapse, protocol violations, and various other reasons, including some subjects who probably simply tired of the demands and uncertainties of a long, demanding,

double-blind study. These discontinuations could have created selection bias at the second randomization, limiting our ability to generalize these results. While we cannot rule out this possibility, we note that attrition rates during long-term treatment are high in naturalistic settings and that there were no important differences in subject characteristics or symptom severity between the subjects entering the 1-year randomization and the subjects at study entry or the first randomization. For these reasons, we believe that the outcomes presented here are clinically relevant to patients who obtain a good initial response to treatment and maintain that response for an extended period.

In summary, this study supports the value of long-term treatment for patients who respond well to atomoxetine initially and maintain that response for 1 year by providing evidence that continued treatment with atomoxetine after 1 year is associated with better symptom control in children and adolescents with ADHD compared with those who discontinue atomoxetine. The number of relapses during placebo treatment after 1 year of atomoxetine treatment was low, and while outcomes may differ in patients with improvement that is less robust or less sustained, this result also suggests that many patients successfully treated for a year or more can discontinue drug treatment and maintain their gains. For such patients, a medication-free trial to assess the need for continued drug treatment may be an appropriate option.

The research was funded by Eli Lilly and Company.

The authors were paid consultants and/or investigators for studies sponsored by or employees and shareholders of Eli Lilly and Company. The authors collaboratively designed the study protocol. Eli Lilly and Company monitored the data collected by the investigators according to the US Food and Drug Administration and International Clinical Harmonization guidelines for good clinical practice. Statistical analysis was planned and performed at Eli Lilly and Company according to the protocol and a detailed prespecified statistical analysis plan. The authors collaboratively interpreted the data and wrote the report. The decision to submit the paper for publication was agreed between the sponsor and investigators prior to starting the study.

We gratefully acknowledge Philip Hazell, John Wray, Michael McDowell, Richard Jarman, Dirk Deboutte, Hans Hellemans, Olivier Revol, Paul Messerschmitt, Marie-Christine Mouren-Simeoni, Manuel Bouvard, Martin Schmidt, Gotz-Erik Trott, Agnes Vetro, Julia Gadoros, Ilona Herczeg, T. Lerman-Sagie, Roni Yoran-Hegesh, Gabriele Masi, A. den Hertog, Rudolph Minderaa, L. Kalverdijk, C. Ketelaars, Pal Zeiner, Jadwiga Komender, Adrzej Rajewski, Marzena Zaboklicka, Androula Ladikos, Adriana van der Walt, Susan Hawkridge, David Benn, Javier San Sebastian, Cesar Soutullo, Mats Johnsson, Valerie Harpin, Nevyne Chalhoub, and Joanne Barton for their contributions.

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