A Double-Blind, Placebo-Controlled Study of Atomoxetine in Young Children With ADHD

WHAT'S KNOWN ON THIS SUBJECT: Atomoxetine has been demonstrated to be safe and efficacious for the treatment of attention-deficit/hyperactivity disorders in children 6 years of age and older.

WHAT THIS STUDY ADDS: This study provides the first randomized controlled data from children under the age of 6 years. In this trial of 101 5- to 6-year-old children, atomoxetine generally was well tolerated and reduced core attention-deficit/hyperactivity disorders symptoms, although significant impairment persisted.

abstract

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OBJECTIVE: To evaluate the efficacy and tolerability of atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in 5- and 6-year-old children.

METHODS: This was an 8-week, double-blind, placebo-controlled randomized clinical trial of atomoxetine in 101 children with ADHD. Atomoxetine or placebo was flexibly titrated to a maximum dose of 1.8 mg/kg per day. The pharmacotherapist reviewed psychoeducational material on ADHD and behavioral-management strategies with parents during each study visit.

RESULTS: Significant mean decreases in parent ($P = .009$) and teacher ($P = .02$) ADHD–IV Rating Scale scores were demonstrated with atomoxetine compared with placebo. A total of 40% of children treated with atomoxetine met response criteria (Clinical Global Impression–Improvement Scale indicating much or very much improved) compared with 22% of children on placebo, which was not significant ($P = .1$). Decreased appetite, gastrointestinal upset, and sedation were significantly more common with atomoxetine than placebo. Although some children demonstrated a robust response to atomoxetine, for others the response was more attenuated. Sixty-two percent of subjects who received atomoxetine were moderately, markedly, or severely ill according to the Clinical Global Impression–Severity Scale at study completion.

CONCLUSIONS: To our knowledge, this is the first randomized controlled trial of atomoxetine in children as young as 5 years. Atomoxetine generally was well tolerated and reduced core ADHD symptoms in the children on the basis of parent and teacher reports. Reductions in the ADHD-IV Rating Scale scores, however, did not necessarily translate to overall clinical and functional improvement, as demonstrated on the Clinical Global Impression–Severity Scale and the Clinical Global Impression–Improvement Scale. Despite benefits, the children in the atomoxetine group remained, on average, significantly impaired at the end of the study. *Pediatrics* 2011;127:e862–e868

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KEY WORDS

ADHD, atomoxetine, child, pharmacotherapy

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
CGI-S—Clinical Global Impression–Severity
CGI-I—Clinical Global Impression–Improvement
ADHD-RS—ADHD–IV Rating Scale

This trial has been registered at www.clinicaltrials.gov (identifier NCT00561340).

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, the symptoms of which often are evident as early as preschool age.[1] *Diagnostic and Statistical Manual of Mental Disorders–IV, Text Revision* diagnostic criteria, in fact, require ADHD symptom onset before 7 years of age.[2] Epidemiologic samples have identified as many as 5% of 3- to 5-year-olds with the disorder.[3] Even at this young age, ADHD creates significant impairments in behavior, peer interactions, family functioning, and early academic skills and, for some children, persists over time, predicting behavioral, academic, and social problems in later years.[4,5]

Despite limited data in children under the age of 7 years, practitioners commonly treat ADHD in preschoolers with stimulant and nonstimulant agents such as atomoxetine.[6] The Preschool ADHD Treatment Study provided data supporting the safety and efficacy of immediate-release methylphenidate in 3- to 5-year-old children[7,8]; however, these data also suggest that there may be developmental variability in the response and tolerability of methylphenidate. Moderate-to-severe adverse events were reported in 30% of Preschool ADHD Treatment Study subjects, and irritability, emotional outbursts, difficulty falling asleep, repetitive behaviors or thoughts, and decreased appetite were most commonly reported.[8] School-aged children, on the other hand, experience decreased appetite, delayed sleep onset, headaches, and stomachaches most frequently.[9] Effect sizes also varied between Preschool ADHD Treatment Study subjects (0.35 parent report; 0.43 teacher report)[7] and school-aged subjects in the Multimodal Treatment of ADHD Study (0.52 parent report; 0.75 teacher report).[10] With this in mind, data on young children treated with atomoxetine are needed to determine whether variation in efficacy and tolerability exist for it as well.

Over a dozen double-blind placebo-controlled studies have given evidence of the safety and efficacy of atomoxetine for the treatment of children 6 years of age and older, adolescents, and adults.[11] No controlled data are available on its use in children younger than 6 years. In an 8-week, open-label, proof-of-principle study of atomoxetine that was conducted by the authors in 22 5- and 6-year-old children with ADHD, atomoxetine demonstrated significant improvement on the ADHD–IV Rating Scale (ADHD-RS) total and subscale scores ($P < .001$), the Children's Global Assessment Scale ($P < .001$), and the Clinical Global Impression–Severity (CGI-S) ($P < .001$). The present study describes a larger, randomized, double-blind placebo-controlled efficacy trial in the same patient population.

PATIENTS AND METHODS

The objective of this study was to evaluate the efficacy and tolerability of atomoxetine for the treatment of ADHD in 5- and 6-year-old children. This age group was selected because at the time of the study design, atomoxetine was relatively new to the market and few data were available with young children (under 7 years of age). The use of atomoxetine in children under 6 years of age is off-label.

The hypothesis was that atomoxetine would be well tolerated and more efficacious than placebo for reducing core symptoms of ADHD, as measured by the investigator-administered ADHD-RS. An 8-week, double-blind placebo-controlled randomized trial was conducted at 3 academic research sites and was approved by each site's institutional review board, and oversight was provided by an independent data safety-monitoring committee. Recruitment began in October 2005 and ended in June 2008. The last patient visit was September 2008.

Inclusion criteria were written informed consent by a legal guardian and verbal assent from the child; age 5 to 6 years at the time of consent; criteria met for any subtype of ADHD on the Diagnostic Interview Schedule for Children, clinical interview, and on review by a clinical consensus conference of all 3 sites; ADHD is the primary disorder with symptoms present for ≥9 months; a *T* score of ≥65 on the ADHD-RS; a Children's Global Assessment Scale score of ≤55; a CGI-S score of ≥4 (at least moderate severity); a Peabody Picture Vocabulary Test-IIIA SS score of ≥70; attending day care, preschool, kindergarten, or elementary school for ≥2 half-days per week with a peer group of 8 or more; living with the same parent or guardian for ≥6 months; and having a teacher who is able to provide assessments. Exclusion criteria included concurrent use of psychotropic or other medications with significant central nervous system effects; current effective treatment with atomoxetine; medical contraindication to atomoxetine; current diagnosis of adjustment disorder, autism, psychosis, bipolar disorder, or significant suicidality; history of abuse that may confound symptoms of ADHD; and failure to respond to an adequate previous trial of atomoxetine.

The Diagnostic Interview Schedule for Children–IV[12] and a clinical diagnostic interview were completed with the parent or guardian by a child and adolescent psychiatrist, advanced-practice registered nurse, or licensed clinical psychologist. The Peabody Picture Vocabulary Test-IIIA,[13] an assessment of receptive language skills, was completed as a proxy for general cognitive ability. The Childhood Autism Rating Scale[14] was used to screen for autism spectrum disorders.

Subjects were randomly assigned 1:1 to atomoxetine or placebo. The study drug was initiated at 0.5 mg/kg per day. Four weekly and 1 biweekly visit allowed for flexible titration to 0.8, 1.2, 1.4, and a maximum of 1.8 mg/kg per day on the basis of patient response, tolerability, and clinical judgment of the pharmacotherapist. Atomoxetine was administered in a single daily dose; however, divided doses were permitted at the investigator's discretion for effectiveness and tolerability. Each study visit lasted 30 to 40 minutes; half of that time was spent providing psychoeducation about ADHD and behavioral management strategies using handouts adapted from McMahon and Forehand's *Helping the Noncompliant Child: Family-Based Treatment for Oppositional Behavior*.[15] Although parents were encouraged to implement the strategies, and pharmacotherapists inquired about their success in doing so, no skills training was provided. Parent satisfaction and the perceived efficacy of this approach is described elsewhere.[16]

Outcome Measures

The primary efficacy measure for the study was the ADHD-RS[17] total score, completed by investigator interview with the parent present at each visit. The CGI-S and the Children's Global Assessment Scale also were completed at each visit and the ADHD-specific Clinical Global Impression–Improvement (CGI-I) at each visit after baseline. The primary efficacy raters/pharmacotherapists were child and adolescent psychiatrists or advanced-practice registered nurses. These raters completed standardized training on the ADHD-RS, CGI-S, and CGI-I using videotaped, ADHD symptom–specific interviews. A scoring guide with specific anchor points was used by raters to facilitate consistent completion of these measures. Scores on the training tapes were individually reviewed by the principal investigator with each rater to enhance consistency of ratings. Weekly teleconferences were used to discuss scoring of the ADHD-RS as well as reporting of adverse events. The teacher version of the ADHD-RS was completed before randomization and again at weeks 3 and 8.

Adverse events and concomitant medications were assessed at each visit by the pharmacotherapist via open-ended discussion with the parent or guardian. Baseline height, weight, pulse, and blood pressure were obtained at study entry. Weight, blood pressure, and pulse were assessed at each subsequent visit, and height was measured again at the final study visit. Laboratory tests (complete blood count, liver function tests, electrolytes, serum urea nitrogen, creatinine, and lead level), an electrocardiogram, and physical examination were performed at the screening visit. Hematology, chemistries, electrocardiogram, and physical examination were repeated at the final study visit.

Statistical Analyses

A target sample size of 76 subjects (38 per group) provided 80% power to detect a true difference of 8 points in the average change in the ADHD-RS over the 8-week treatment period between atomoxetine and placebo (12-point versus 4-point reduction), assuming an SD of 12 and a 2-sided α level of .05.[18] Given that the sample size was increased to 96 subjects (48 per group) to account for a 20% drop-out rate, the trial was powered to identify a moderate standardized effect size of $d = 0.67$.

Analyses were performed by using SAS.[19] Distributions of baseline characteristics for each group were compared using a 2-sample t test and a χ^2 or Fisher's exact test. Generalized estimating equations were used to fit linear or logistic regression models to compare the mean changes in ADHD-RS measures from baseline or log odds for the CGI-I and CGI-S categorical measures.[20] Changes in continuous outcomes were calculated as the follow-up minus the baseline value. Primary analysis focused on 8-week changes. Regression models were adjusted for randomization stratification factors (age and study center) and baseline outcome scores (except for CGI-I, for which a baseline score was not available). A similar modeling approach was used for the analysis of blood pressure, weight, and pulse. A 2-sided α level of .05 was used, unless otherwise specified.

As a secondary analysis, weekly changes relative to baseline were compared between treatment groups. Covariates in the regression models included time, treatment, and their interaction, as well as age, center, and baseline outcome. An autoregressive working correlation structure was used. If the time-by-treatment interaction was statistically significant, time-specific comparisons between treatment groups were made. A Pocock group-sequential 2-sided α level of .014 was used when making time-specific comparisons between treatment groups at weeks 1 through 8, and a level of .03 was used when making comparisons at weeks 3 and 8.[21,22]

Data from all subjects who were dispensed medication and had at least 1 postrandomization visit were analyzed. A multiple imputation approach, based on predictive mean matching, was used to impute the missing measures. Results presented are based on imputed data, which were similar to the results using only observed data (not presented).

Adverse events were defined, and a patient-level adverse-event indicator was coded for each type of event if the event occurred any time during the treatment period and was either not

present at baseline or progressed in severity from baseline. A χ^2 test, or Fisher's exact test, was used to compare the distribution of adverse events between treatment groups.

RESULTS

A total of 147 children were screened and 101 were randomly assigned to treatment. Of 101 randomly assigned subjects, 8 did not take at least 1 dose of the study medication (6 atomoxetine and 2 placebo) and withdrew before completing a postrandomization visit. Per protocol, the intention-to-treat analyses were based on the remaining 93 subjects. Eighteen of 93 randomly assigned subjects withdrew before study completion (8 atomoxetine and 10 placebo) because of adverse events (severe irritability, moderate rash, mood lability, and severe impulsivity; 0 atomoxetine and 3 placebo), withdrawal of consent (4 atomoxetine and 3 placebo), were lost to follow-up (3 atomoxetine and 0 placebo), or had a lack of efficacy (1 atomoxetine and 4 placebo). A mean (±SD) final total daily dose of 1.4 mg/kg (±0.4) was reached in the atomoxetine group, whereas the placebo group had a mean final total daily dose of 1.5 mg/kg (±0.3).

Participants (Table 1) were predominantly male (68%) and white (86%) and met criteria for the ADHD combined subtype (82%). Mean age was 6.1 years. Eleven subjects (12%) were previously treated with psychotropic medication, including 9 who were treated with stimulants. Mean baseline ADHD-RS parent total and subscale scores were above the 97th percentile for age and gender, and mean baseline ADHD-RS teacher total and subscale scores were above the 85th percentile for age and gender (Table 2).

The mean change (±SEM) on the parent ADHD-RS total score for the patients who received atomoxetine was −13.2 (±1.7), compared with −5.8 (±1.2) for placebo ($P = .009$) (Table 2). Significant improvement was observed with atomoxetine compared with placebo on both the hyperactive-impulsive ($P = .005$) and inattentive ($P = .002$) subscales. A significant difference between groups on the parent ADHD-RS total score was reached by week 6 ($P = .002$) (Fig 1) and remained significant at week 8 (mean change [±SEM]: −7.3 [±2.6] [95% confidence interval: −13.7 to −0.9]; $P = .009$).

TABLE 1 Baseline Characteristics

Characteristics	Study Drug		*P*
	Placebo ($N = 49$)	Atomoxetine ($N = 44$)	
Age, mean (SD), y	6.1 (0.5)	6.1 (0.6)	.9
Childhood Autism Rating Scale, SD	17.3 (2.2)	17.0 (1.9)	.4
Gender, *n* (%)			.3
Male	31 (63)	32 (73)	
Female	18 (37)	12 (27)	
Ethnicity, *n* (%)			.07
Hispanic or Latino	6 (12)	12 (27)	
Not Hispanic or Latino	43 (88)	32 (73)	
Race, *n* (%)			.06[a]
White	39 (80)	41 (93)	
Black or African American	7 (14)	3 (7)	
American Indian	3 (6)		
Grade in school, *n* (%)			.6
Daycare	1 (2)	0 (0)	
Preschool	5 (10)	5 (11)	
Kindergarten	23 (47)	18 (41)	
First grade	20 (41)	19 (43)	
Second grade	0 (0)	2 (5)	
ADHD subtype, *n* (%)			.9
Inattentive	4 (8)	4 (9)	
Hyperactive/impulsive	4 (8)	5 (11)	
Combined	41 (84)	35 (80)	
Comorbidities, *n* (%)			
Oppositional defiant disorder	17 (35)	15 (34)	.9
Enuresis	9 (18)	7 (16)	.8
Separation anxiety	0 (0)	1 (2)	.5
Phobia	5 (10)	3 (7)	.7
Tics	1 (2)	0 (0)	.9
Other	2 (4)	3 (7)	.7

[a] The *P* value compares the proportion of subjects whose race was white between treatment groups.

The mean change (±SEM) on the ADHD-RS teacher total score also was significant (−12.5 [±1.7] for atomoxetine compared with −5.0 [±1.4] for placebo; $P = .02$), as was the inattentive subscale ($P = .04$). At week 8, 40% of subjects who received atomoxetine and 22% of subjects who received placebo had CGI-I scores of 1 (very much improved) or 2 (much improved) relative to baseline, which was not a significant difference after adjustment for age and study center ($P = .1$). A total of 62% of subjects who received atomoxetine had CGI-S scores of moderately, markedly, or severely ill at study completion compared with 77% of subjects who received placebo ($P = .1$).

There were no clinically significant changes in laboratory tests and electrocardiograms. There were no significant differences in the mean change (±SEM) in systolic blood pressure with atomoxetine treatment (3.9 [±0.8]) compared with placebo (0.7 [± 0.9]) ($P = .09$) or in the change in diastolic blood pressure ($P = .8$) or heart rate ($P = .07$) with atomoxetine. There was a significant difference in change in weight (−0.2 kg [±0.1] in atomoxetine and 0.6 kg [±0.2] in the placebo group ($P = .0006$); however, this was not clinically significant. Subjects who received atomoxetine were significantly more likely to experience decreased appetite ($P = .008$), gastrointestinal upset ($P = .02$), and sedation ($P = .02$) (Table 3). These effects were mild or moderate in severity.

Atomoxetine was more effective than placebo for decreasing parent ADHD-RS scores with an effect size of 0.7 and teacher ADHD-RS scores with an effect size of 0.6. Although not statistically significant, the number needed to treat for response, as defined by a CGI-I end point of 1 or 2, with atomoxetine relative to placebo, was 6.

TABLE 2 Baseline, 8-Week, and Change-in-Outcome Measures

Scores	Baseline		Week 8		8-wk Change From Baseline		*P*[a]
	Placebo (*N* = 49)	Atomoxetine (*N* = 44)	Placebo (*N* = 49)	Atomoxetine (*N* = 44)	Placebo (*N* = 49)	Atomoxetine (*N* = 44)	
ADHD-RS parent total, mean (SEM)	37.6 (1.0)	38.9 (1.0)	31.8 (1.4)	25.8 (2.0)	−5.8 (1.2)	−13.2 (1.7)	.009
ADHD-RS parent hyperactivity, mean (SEM)	19.5 (0.7)	19.3 (0.7)	16.7 (0.9)	13.0 (1.1)	−2.8 (0.8)	−6.2 (1.0)	.005
ADHD-RS parent inattentive, mean (SEM)	18.1 (0.7)	19.7 (0.7)	15.6 (0.8)	12.3 (1.0)	−2.5 (0.8)	−7.3 (0.8)	.002
ADHD-RS teacher total, mean (SEM)	35.4 (1.5)	37.3 (1.4)	30.4 (1.5)	24.8 (1.9)	−5.0 (1.4)	−12.5 (1.7)	.02
ADHD-RS teacher hyperactivity, mean (SEM)	18.0 (1.0)	17.2 (1.0)	14.8 (0.9)	11.8 (1.1)	−3.2 (0.9)	−5.4 (1.0)	.08
ADHD-RS teacher inattentive, mean (SEM)	17.4 (0.9)	20.1 (0.8)	15.1 (1.0)	13.4 (1.2)	−2.3 (0.8)	−6.6 (1.0)	.04

[a] The *P* value was calculated from a linear regression model adjusted for baseline outcome score, study center, and age group.

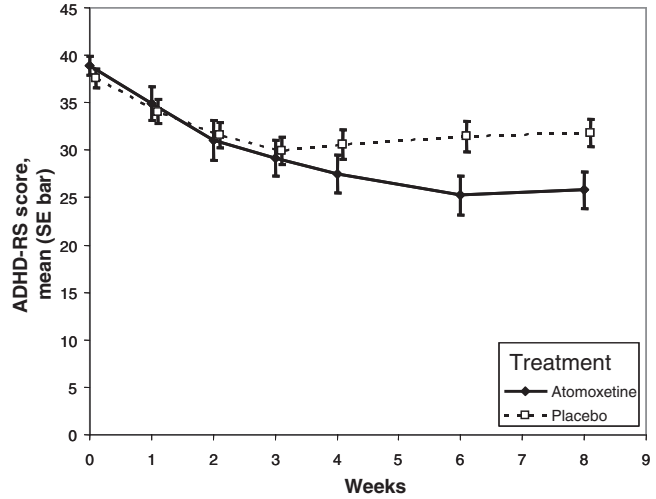

FIGURE 1
Mean ADHD-RS parent total score according to treatment group and study visit.

TABLE 3 Percentage of Subjects Who Reported Adverse Events, According to Event Type and Treatment Assignment

	Placebo (*N* = 49)	Atomoxetine (*N* = 44)	*P*
Adverse event, *n* (%)[a]			
Aches/pains	7 (14)	6 (14)	.9
Affective flattening/ blunting	2 (5)	2 (4)	>.9
Allergy	1 (2)	1 (2)	>.9
Anxiety	1 (2)	1 (2)	>.9
Attention/ hyperactivity[b]	6 (12)	3 (7)	.5
Auditory[c]	2 (4)	2 (5)	>.9
Constipation	1 (2)	0 (0)	>.9
Decreased appetite	4 (8)	13 (30)	.008
Dermatological	5 (10)	6 (14)	.6
Disruptive behaviors	4 (9)	3 (7)	>.9
Gastrointestinal upset	8 (16)	17 (39)	.02
Insomnia	3 (6)	1 (2)	.6
Mood lability	11 (22)	18 (41)	.06
Respiratory	4 (8)	5 (11)	.7
Sedation	5 (10)	13 (30)	.02
Self-harm	1 (2)	1 (2)	>.9
Weight loss	2 (4)	2 (5)	>.9
Other	10 (20)	6 (14)	.4

[a] Patients were coded as experiencing an event of a particular type if the event occurred any time during the treatment period and was either not present at baseline or progressed in severity from baseline.
[b] Attention/hyperactivity events include restlessness, inattention, hyperactivity, and impulsivity.
[c] Auditory events include otitis media and ear pain.

DISCUSSION

An earlier meta-analysis of acute atomoxetine treatment in 280 children aged 6 to 7 years and 860 children aged 8 to 12 years showed that atomoxetine was superior to placebo in both age groups, as measured by the ADHD-RS. An effect size of 0.77 in the younger children and 0.65 in the older children fell in the moderate range. Atomoxetine generally was well tolerated in both age groups; there were only 2 adverse events (abdominal pain and cough) that demonstrated significant treatment-by-age-group interactions (younger $P = .044$ and .007, respectively).[23] The present study is the first to systematically assess the use of atomoxetine in children under the age of 6 years and is unique in that it incorporated a parent-education module along with each pharmacotherapy appointment.

ADHD symptoms based on parent and teacher reports improved with atomoxetine treatment, and the effect size of 0.7 (parent ADHD-RS) is comparable to that seen in clinical trials with older children treated with atomoxetine (0.65),[23] as well as the Preschool ADHD Treatment Study, which had effect sizes ranging from 0.4 to 0.89 for methylphenidate.[7] However, only a minority of atomoxetine-treated subjects in this study achieved response criteria defined by clinician improvement ratings, and this proportion did not differ significantly from subjects who received placebo. Furthermore, 62% of subjects who received atomoxetine had CGI-S scores of moderately, markedly, or severely ill at study completion. Some children in this study demonstrated a robust response to atomoxetine, whereas for others, the response was more attenuated. Decreases in ADHD symptom frequency and intensity for many did not necessarily result in overall functional improvement.

The actual time to response to atomoxetine is difficult to assess because titration was flexible and gradual. Dosing was guided by the pharmacotherapist's assessment of the patient's response and tolerability. The 5- and 6-year-old children tolerated the stepwise titration of atomoxetine to an average dose of 1.4 mg/kg per day, the Food and Drug Administration–approved maximum dose, with relatively few clinically significant adverse events. Weight loss, decreased appetite, sedation, and gastrointestinal discomfort occurred in approximately one-fourth to one-third of subjects who received atomoxetine; however, no children discontinued atomoxetine because of adverse events. In addition, there were no clinically significant changes in laboratory tests or electrocardiogram findings, and only a small increase in systolic blood pressure was observed.

Strengths of this study include its double-blind, placebo-controlled, randomized design with an understudied age group. Despite significant treatment gains on the ADHD-RS, fewer subjects benefited on response (CGI-I) and severity (CGI-S) criteria. The poorer performance on the CGI end points may reflect a broader range of behavioral–symptomatic indicators than just ADHD. Given the difference in adverse event profiles, it is possible that the pharmacotherapist raters "peeked through the blind." However, the fact that the teacher effect size paralleled the pharmacotherapist effect size mitigates this potential source of bias. Consistent with recommendations from the Preschool Psychopharmacology Working Group,[24] the addition of parent education in behavior management was a strength of this study. Unfortunately, the study design does not allow us to differentiate a placebo response from a psychoeducational treatment effect. The 8-week protocol also does not allow for examination of long-term effectiveness for core ADHD symptoms or assessment of adverse events over time, such as possible effects on growth. Because ADHD-RS change scores did not separate from placebo until week 6, longer treatment may have possibly led to additional gains as has been noted in an older population.[25]

CONCLUSIONS

The efficacy and tolerability of atomoxetine for 5- and 6-year-old children seems similar to that seen in older children. Even with doses of atomoxetine averaging 1.4 mg/kg per day (the Food and Drug Administration maximum approved dose), combined with a psychoeducational intervention, only 40% of atomoxetine-treated subjects were rated as "much" or "very much" improved at study end. Although a statistically significant change in ADHD-RS score was noted, the mean final ADHD-RS total score was still more than 1 SD above norms. Thus, although effective, clinically significant symptoms remained for the majority of children treated with atomoxetine. It also is difficult to separate oppositional defiant disorder symptoms from ADHD in this age group, a factor that may influence the CGI rating. Future research should include longer treatment studies and follow-up to help elucidate whether benefits of atomoxetine treatment may increase and/or be sustained over time and to assess for long-term adverse effects. Comparator trials also would help to clarify the role of atomoxetine in the treatment of young children with ADHD.

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