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Christopher J. Kratochvil
University of Nebraska Medical Center, ckratoch@unmc.edu

Brigette S. Vaughan
University of Nebraska Medical Center, bvaughan@unmc.edu

Michelle L. Mayfield-Jorgensen
University of Nebraska Medical Center

John S. March
Duke University

Scott H. Kollins
Duke University

See next page for additional authors

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A Pilot Study of Atomoxetine in Young Children With Attention-Deficit/Hyperactivity Disorder

Christopher J. Kratochvil, M.D.,[1] Brigette S. Vaughan, M.S.N., A.P.R.N.,[1] Michelle L. Mayfield-Jorgensen, M.D.,[1] John S. March, M.D., M.P.H.,[2] Scott H. Kollins, Ph.D.,[2] Desiree W. Murray, Ph.D.,[2] Hima Ravi, M.D.,[2] Laurence L. Greenhill, M.D.,[3] Lisa A. Kotler, M.D.,[3] Natalya Paykina, M.A.,[3] Patricia Biggins, B.A.,[3] and Julie Stoner, Ph.D.[1]

ABSTRACT

Objective: **The purpose of this study was to assess the effectiveness and tolerability of atomoxetine during acute treatment of attention-deficit/hyperactivity disorder (ADHD) in 5 and 6 year olds.**

Method: **Twenty two children (male $n = 19$, 86%) with ADHD were treated with atomoxetine for 8 weeks in a three-site, open-label pilot study. Dosing was flexible, with titration to a maximum of 1.8 mg/kg per day. Parent education on behavior management was provided as part of each pharmacotherapy visit.**

Results: **Subjects demonstrated a mean decrease of 20.68 points (SD = 12.80, $p < 0.001$)) on the ADHD Rating Scale-IV (ADHD-IV-RS) total score, 10.18 (SD = 7.48, $p < 0.001$) on the inattentive subscale and 10.50 (SD = 7.04, $p < 0.001$) on the hyperactive/impulsive subscale. Clinical Global Impression–Severity (CGI-S) was improved in 82% of the children (95% CI, 66–98%) and Children's Global Assessment (CGAS) scores improved 18.91 points on average (SD = 12.20, $p < 0.001$). The mean final dose of atomoxetine was 1.25 mg/kg per day (SD = 0.35 mg/kg per day). Mood lability was the most commonly reported adverse event ($n = 12$, 54.5%). Eleven subjects (50%) reported decreased appetite and a mean weight loss of 1.04 kg (SD = 0.80 kg) ($p < 0.001$) was observed for the group. Vital sign changes were mild and not clinically significant. There were no discontinuations due to adverse events or lack of efficacy.**

Conclusion: **Atomoxetine was generally effective for reducing core ADHD symptoms in the 5 and 6 year olds in this open-label study.**

INTRODUCTION

Approximately 3–7% of school-aged children are affected by attention-deficit/hyperactivity disorder (ADHD), yet limited data are available regarding treatment of youngsters early in its course (American Psychiatric Association 2000). Symptoms of this neurodevelop-

[1]University of Nebraska Medical Center, Omaha, Nebraska.
[2]Duke University Medical Center, Durham, North Carolina.
[3]Columbia University/New York State Psychiatric Institute, New York, New York.
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mental disorder are often identifiable at an early age, with epidemiological data indicating that approximately 2% of children ages 3–5 years meet diagnostic criteria for ADHD (Lavigne et al. 1996). When compared to their unaffected counterparts, preschool children with ADHD are at significant risk for behavioral, social, familial, and school difficulties (DuPaul et al. 2001). In a study of 94 3- to 5-year-old children, DuPaul and colleagues showed that not only were children with ADHD demonstrating more behavioral problems than children without ADHD, but the difference in behavioral ratings between the groups was significant, greater than 2 SD. Additionally, skill deficits in basic math concepts, prereading, and fine motor abilities are more likely seen in children entering school with ADHD than in those without the disorder (Lahey et al. 1998; Mariani and Barkley 1997; Shelton et al. 1998). When these deficits are combined with the potential for significant social and behavioral difficulties, impairment may result and ultimately persist if appropriate interventions are not initiated. In addition, ADHD symptoms can tax parent and caregiver resources, resulting in a strained home environment for these young children. A study by Escobar and colleagues demonstrated that parents of children with ADHD perceived the level of interference in daily life to be greater than that reported by parents of normal controls, as well as parents of asthmatic children (Escobar et al. 2005).

Despite evidence suggesting that the initial symptoms of ADHD often present by 3 years of age, systematic study of the use of medications in 3- to 6-year-old children with ADHD has been quite limited (Food and Drug Administration 1997; Food and Drug Administration 1997; National Institutes of Health 1998). The need for additional research on the safety and efficacy of psychotropic medication use in preschoolers has been emphasized, especially in light of the rates of prescriptions for this age group (Greenhill 1998). Zito and colleagues found a three-fold increase in the use of psychotropic agents in 2- to 5-year-old children from 1991 to 1995 (Zito et al. 2000). Zuvekas et al. analyzed data from the Medical Expenditure Panel Survey (MEPS) and found that an estimated 0.3% of children under age 6 were treated with psychostimulants from 1997 to 2002 (Zuvekas et al. 2006). While stimulant use in children under age 18 increased from 2.7% to 2.9% during those 5 years, the rate of use in the preschool age group remained stable, indicating that prescription of ADHD medications in young children may be leveling off in this group. Another database, however, indicated that use of stimulants in this population may be increasing, as a 2004 report by Medco Health Solutions showed a 49% increase in the number of stimulant prescriptions written for preschoolers from 2000 to 2003 (Greenhill et al. 2006).

Unfortunately, until recently, only 10 of over 160 controlled trials of psychostimulants for school-aged children included preschoolers ages 4–6, and all 10 assessed the use of methylphenidate (MPH) (Conners 1975; Schleifer et al. 1975; Cohen et al. 1981; Barkley et al. 1984; Barkley 1988; Mayes et al. 1994; Musten et al. 1997; Firestone et al. 1998; Handen et al. 1999; Chacko et al. 2005). Even in these few trials, not all of the samples were made up entirely of young children. By merging samples of younger and older children, limitations present, in that the studies are not necessarily specifically designed to evaluate and monitor symptoms in younger children. Scales may not be normed for both groups, appropriateness of diagnostic assessments may vary, and the studies may be underpowered solely to examine the younger children in the sample. The recently completed Preschool ADHD Treatment Study (PATS), a multisite trial of 303 preschoolers with ADHD added significantly to this literature base in that it was designed solely for young children and adequately powered, but again this study examined MPH (Greenhill et al. 2006).

Although stimulants have been shown to be safe and effective in the treatment of ADHD in children, adolescents, and adults, a range of factors have led parents and clinicians to seek alternative medication treatments, especially for younger children. As such, there has been considerable interest in developing additional treatments, including nonstimulant options, for ADHD.

Although information on the use of stimulants in preschoolers is limited, data on the use

of nonstimulants in young children with ADHD is virtually nonexistent. A review of the PharMetrics database shows that a significant number of prescriptions of atomoxetine are written for children under 5 years of age, despite the lack of data on its use in children younger than 6 years old (Van Brunt et al. 2005). Thus, the management of preschool ADHD with nonstimulant pharmacotherapy currently requires clinicians to extrapolate from the data available on use of these medications in older children and adolescents to guide their clinical practice.

Atomoxetine is a nonstimulant medication that received Food and Drug Administration (FDA) approval for the treatment of ADHD in children 6 years and older, adolescents, and adults in November, 2002. Atomoxetine acts by selectively blocking the presynaptic norepinephrine transporter, increasing noradrenergic tone. It is highly specific, with minimal affinity for other receptors or other neuronal transporters (Spencer et al. 1998). To date, approximately 5,500 children and adolescents have been treated with atomoxetine in clinical trials.

As the only nonstimulant medication FDA approved for the treatment of ADHD, and one clinically used off-label in the treatment of ADHD in young children, atomoxetine was selected as the medication to be examined in this clinical trial. The goal of this pilot study was to evaluate systematically the effectiveness and tolerability of atomoxetine for the treatment of ADHD in children 5 and 6 years of age, and to collect pilot data for a larger double-blind, placebo-controlled trial.

METHODS

This study was a 22-subject feasibility trial that included children aged 5 and 6 years old who met Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) criteria for ADHD, any subtype, as confirmed by the Diagnostic Interview Schedule for Children-IV (DISC-IV) (Shaffer et al. 2000) and clinical interview. Symptom severity as measured by the ADHD Rating Scale-IV, by parent interview (ADHD-IV-RS) (DuPaul et al. 1998) at entry was required to be at least 1.5 SD above age and gender norms. Impairment as measured by the Clinical Global Impression–ADHD–Severity scale (CGI-S) (Guy 1976) had to be at least 4 (moderate severity), with a Children's Global Assessment Scale (CGAS) $\leq$55. Subjects were required to have estimated IQ's of $\geq$70. Patients who previously failed a trial of atomoxetine or who were already being effectively treated with atomoxetine were not included in the study. Diagnoses of an adjustment disorder, autism, psychosis, bipolar disorder, significant suicidality, or any other psychiatric disorder requiring treatment with additional medications were exclusionary, as was the presence of current or previous clinically significant hepatic disease, or any significant medical condition that would interfere with the study medication. Each case was discussed on a conference call, which included study personnel from each of the three sites, and a consensus decision regarding appropriateness for enrollment was required prior to initiation of study treatment. Several of these inclusion criteria were chosen to be consistent with the PATS, and also to provide a relatively conservative approach to inclusion.

The study was conducted at three sites in the United States: University of Nebraska Medical Center in Omaha, NE; Duke University Medical Center in Durham, NC; and Columbia University/New York State Psychiatric Institute in New York, NY. Prior to entering the study, there was a review of the consent document, oral description and discussion of the study, and written informed consent was obtained from a parent or guardian for each patient. 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 Declarations of Helsinki as revised in 2000 (World Medical Association 2000).

Measures

An initial assessment using the DISC-IV was completed interview style with the parent/guardian, followed by a clinical diagnostic assessment with a psychiatrist, psychologist or advanced practice registered nurse (APRN) trained and experienced in the assessment and

treatment of pediatric mental health disorders. The clinical diagnostic assessment confirmed or refuted any co-morbid psychiatric diagnoses reported on the DISC-IV, and also evaluated the child for co-morbid diagnoses potentially missed by the computerized interview. The DISC-IV was used in PATS in a similar manner, despite lacking norms for children under the age of 6. The primary efficacy measure for the study was the ADHD-IV-RS, completed by investigator interview with the parent at study entry and at all subsequent visits, along with the CGI-S and CGAS. The Clinical Global Impression–Improvement (CGI-I) was completed at each visit following baseline. All of these measures were completed by the pharmacotherapist, a physician, or APRN with extensive experience using pharmacotherapy to treat young children with ADHD. An effort was made to have the same pharmacotherapist follow each child throughout his or her study participation.

Additional measures completed at the study screening visit included the Multidimensional Anxiety Scale for Children (MASC) (March et al. 1997), Children's Depression Inventory (CDI) (Kovacs 2001), and Childhood Autism Rating Scale (CARS) (Garfin et al. 1988). The Peabody Picture Vocabulary Test (PPVT-IIIA) (Dunn and Dunn 1997), an assessment of receptive language abilities, was completed at the initial evaluation visit as a proxy for intelligence quotient (IQ), given the correlation of receptive language with general cognitive ability. Scales completed by the parent included the Conners' Parent Rating Scale-Revised (L) (CPRS) (Conners et al. 1998a) and Parent Stress Index (PSI) (Abidin 1995). The child's teacher, or structured day-care provider in the case of those children not yet enrolled in school, completed the Conners' Teacher Rating Scale–Revised (L) (CTRS) (Conners et al. 1998b) and the teacher version of the ADHD-IV rating scale. The teacher scales, as well as MASC, CDI, CPRS, and PSI, were repeated at visit 5 and again at study completion (visit 8 or early discontinuation).

Safety analyses

Baseline height, weight, and vital signs, including heart rate and blood pressure, were obtained at study entry. Weight and vital signs were assessed at each subsequent visit, and height was measured again at the final study visit. Laboratory tests [complete blood count (CBC), liver function tests (LFT's), electrolytes, blood urea nitrogen (BUN), creatinine, and lead level], an electrocardiogram (EKG), and physical examination were performed at the screening visit. Hematology, chemistry, EKG, and physical examination were repeated at the final study visit. Preexisting conditions were reviewed at the screening visit and monitored for changes during study participation. Adverse events and concomitant medications were assessed by the physician or APRN prescribing and monitoring the study medication at each visit via open-ended discussion with the parent/guardian. The prescribing clinician evaluated the relatedness to the study drug for each event. Clinically significant laboratory and EKG results were documented as adverse events.

Study design

Once approved to enter the trial, study treatment with open-label atomoxetine was initiated. Atomoxetine was dosed by weight and increased at the discretion of the investigator on the basis of tolerability and response. The initial dose of atomoxetine was 0.5 mg/kg per day, with titration to a maximum of 0.8 mg/kg per day at week 1, 1.2 mg/kg per day at week 2, 1.4 mg/kg per day at week 3, and 1.8 mg/kg per day at week 5. Patients could be dosed once or twice daily. The parent/guardian also participated in an 8-week parent education protocol administered by the pharmacotherapist during the course of each pharmacotherapy visit to be consistent with practice guidelines recommending nonpharmacological interventions for this age group. Approximately 10–15 minutes of each pharmacotherapy visit were spent in parent education using an eight-session protocol adapted in part from McMahon and Forehand's "Helping the Noncompliant Child: Family-Based Treatment for Oppositional Behavior" (McMahon and Forehand 2003). Education on ADHD and identification of target behaviors for improvement comprised the first session, with two subsequent sessions

on rewarding positive and ignoring negative behavior, and giving clear instructions. Optional sessions at visits 5–7 included effective utilization of time out, challenges to time out, standing rules, and implementation of a token-reinforcement program or daily report card for home and school use. The optional modules were selected at the discretion of the pharmacotherapist to tailor the parent education to the needs of the child.

Data analysis

Descriptive statistics were used to describe the baseline patient characteristics and outcome variables. The Wilcoxon signed-rank test was used to determine whether the median change in the outcome variables was statistically significant (tested the null hypothesis that the median change over the treatment period was 0). Data analyses were conducted on the 22 patients who took study drug.

RESULTS

A total of 30 subjects completed the screening visit, with 22 of these meeting all entry criteria and initiating study treatment at visit two. Six of the 8 subjects who did not proceed to the treatment phase of the study were excluded due to a failure to meet criteria for a diagnosis of ADHD. One subject withdrew consent prior to beginning atomoxetine and 1 subject refused the required blood draw. Two subjects (6.7%) withdrew from the study after completion of visit 3 due to inability to consistently swallow the capsules containing study medication. Twenty of the 22 patients who began treatment (90.9%) completed the study.

Nineteen males and 3 females met all inclusion and no exclusion criteria and were eligible to begin study treatment (Table 1). These subjects had a mean age at baseline 6.06 years (SD 0.58 years). The majority of subjects met criteria for the combined subtype of ADHD ($n = 18$, 82%), with the remaining 4 subjects meeting criteria for the hyperactive/impulsive subtype. The mean baseline ADHD-IV-RS total score was 38.23 (SD 8.05), with a mean inattentive subscale of 18.23 (SD 4.21) and mean hyperactive impulsive subscale of 20.0 (SD = 5.43). Nearly three fourths of subjects ($n = 16$, 73%) had a baseline CGI-S of 5 (markedly ill), with a mean baseline CGAS for the group of 53.23 (SD 3.85). There were no significant differences in ADHD severity between the 5 year olds and the 6 year olds at baseline, as measured by the ADHD-IV-RS total score, subscales, CGI-S, or CGAS. Twelve subjects (55%) were identified as having co-morbid oppositional defiant disorder, 5 (23%) had enuresis, and 2 (9%) met criteria for simple phobia. The mean CARS score for the group was 17.07 (SD = 1.83), with a range of 15–21, which is in the nonautistic range. The mean standard score for the PPVT-IIIA was 106.50 (SD = 13.07). All subjects who participated in the treatment portion of the study were treatment naïve.

The final total daily dose of atomoxetine ranged from 10 to 45 mg/day, with a mean total daily dose of 30.23 mg/day (SD = 9.70). By weight, the final mean total daily dose was 1.25 mg/kg per day, SD = 0.35, with a range of 0.47–1.88 mg/kg per day. The atomoxetine was given in either a single morning dose ($n = 20$) or in divided doses given morning and afternoon ($n = 2$). Though slightly higher than the final mean doses of older children in prior atomoxetine studies, it was below the FDA-approved maximum dose of 1.4 mg/kg per day.

TABLE 1. DEMOGRAPHICS[a]

Characteristic	*Count*
Age at visit 1 (years)	
Mean (SD)	6.06 (0.58)
5 year old	10 (45%)
6 year old	12 (55%)
Gender	
Male	19 (86%)
Female	3 (14%)
Race	
Black or African American	4 (18%)
White	18 (82%)
ADHD Subtype	
Hyperactive/Impulsive	4 (18%)
Combined	18 (82%)
Co-morbidities	
ODD	12 (55%)
Enuresis	5 (23%)
Simple phobia	2 (9%)
Phonological disorder	1 (5%)

ADHD = Attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; SD = standard deviation

[a]$N = 22$.

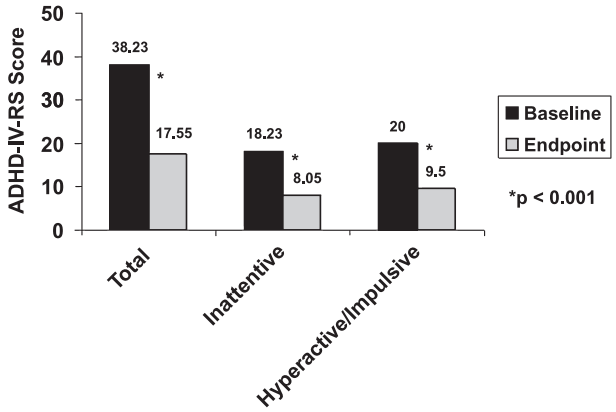

FIG. 1. ADHD-IV-RS. ADHD-IV-RS-Attention-Deficit/Hyperactivity–Rating Scale-IV.

The subjects demonstrated a mean decrease in the ADHD-IV-RS total score of 20.68 points (SD = 12.80, $p < 0.001$), with mean improvements in the inattentive subscale of 10.18 points (SD = 7.48, $p < 0.001$) and 10.50 points in the hyperactive/impulsive subscale (SD = 7.04, $p < 0.001$) (Fig. 1). At the end point, CGI-S was improved in 82% (95% CI, 66–98%) (Table 2) and mean improvement in CGAS score was 18.91 points (SD = 12.20, $p < 0.001$). Clinical improvement was reflected by the final CGI-I ratings, where 86% showed at least some improvement (95% CI, 72–100%). Sixteen of the 22 subjects who started study drug (72.7%) achieved the generally accepted criteria for response, a CGI-I score of 1 (very much improved) or 2 (much improved) by study end point (Fig. 2). The mean final total daily dose of atomoxetine (1.25 mg/kg per day, SD = 0.35) was below the FDA-approved maximum dose of 1.4 mg/kg per day, but near the approved target dose of 1.2 mg/kg per day.

Table 3 compares changes in outcome measures based upon age. Descriptively, the 5-year-old group appears to demonstrate greater improvement over time compared with the 6-year-old group, although with limited power, only the ADHD-IV inattentive subscale was statistically significant.

The most frequent spontaneously reported adverse event was mood lability, experienced by 12 of the 22 children (54.5%) at some point during the study, ranging from 13.6% to 31.8% at individual visits over 8 weeks (Fig. 3). Spontaneous mood-related adverse events classified as "mood lability" included: Angry/hostile, brittle mood, emotionally labile, fussy, mopey, rapid mood swings, tearful, and irritability. Half of the children (11 of 22) experienced decreased appetite (ranging from 9% to 45% at individual visits over 8 weeks). Additionally, a statistically significant mean decrease in weight of 1.04 kg (SD = 0.80, $p < 0.001$) was observed for the group. Parents/guardians were encouraged to use caloric supplementation to limit the effect of diminished appetite, and to give the medication after the child had eaten to minimize stomach upset. Five year olds did not differ significantly from 6 year olds in frequency or severity of adverse events reported.

Changes in vital signs were limited; with a mean change of systolic blood pressure of 2.98 mmHg (SD = 5.68) the only statistically significant change ($p = 0.03$) (Table 4). There were no clinically significant changes in heart rate, blood pressure, or on EKGs. No subjects discontinued due to adverse events or lack of efficacy.

DISCUSSION

The purpose of this open-label pilot study was to evaluate the general efficacy and tolerability of atomoxetine in 5 and 6 year olds with ADHD, prior to the initiation of a planned double-blind, placebo-controlled trial in this same population. Statistically and clinically significant improvement in symptoms of inattention and hyperactivity/impulsivity were observed in this open-label study, as evidenced by

TABLE 2. CLINICAL GLOBAL IMPRESSION–SEVERITY SCORES WERE DECREASED FROM BASELINE TO ENDPOINT ($p < 0.001$)

CGI-Severity	*Baseline* n *(%)*	*End point* n *(%)*
(1) Normal, not mentally ill	0 (0)	0 (0)
(2) Borderline mentally ill	0 (0)	8 (36)
(3) Mildly mentally ill	0 (0)	8 (36)
(4) Moderately mentally ill	3 (14)	3 (14)
(5) Markedly mentally ill	16 (73)	3 (14)
(6) Severely mentally ill	3 (14)	0 (0)
(7) Among the most extremely mentally ill	0 (0)	0 (0)

CGI-S = Clinical Global Impression–Severity.
Overall decrease in CGI-S was statistically significant ($p < 0.001$).

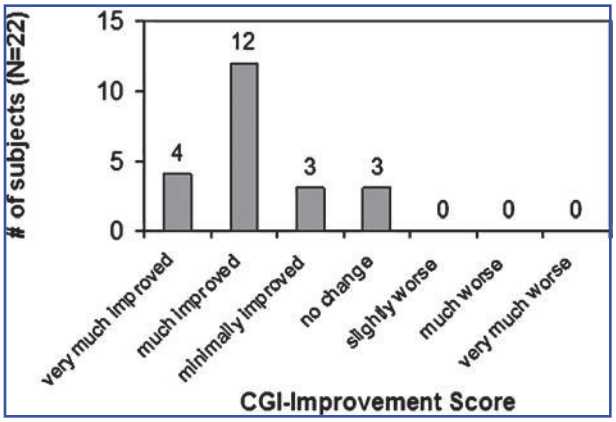

FIG. 2. CGI-I at end point. CGI-I = Clinical Global Impressions–Improvement.

decreases in the total and subscale scores of the investigator-scored ADHD-IV-RS. An improvement in functional status was also observed, evidenced by the changes in clinician-rated CGAS, CGI-S, and CGI-I scores. Because the MASC and CDI are not normed for use in this age group, they were not used to detect any significant changes in patient-reported anxiety or mood symptoms. Rather these scales were employed to support or rule out the presence of co-morbid disorders, particularly at the baseline visit as a part of the psychiatric assessment.

Atomoxetine is approved for use in children as young as 6 years old; however, it is being used in younger children in clinical practice. Because children are being identified and treated with pharmacotherapy at younger ages, it is worthwhile to examine the efficacy and safety of atomoxetine in a systematic fashion. This was the first study to assess atomoxetine use systematically in children younger than age 6 with ADHD. The authors' interest in identification and treatment of early-childhood ADHD, and well as their familiarity with atomoxetine from prior clinical trial experience, led to this study. Inclusion of children who were at least 5 years old allowed the investigators to collect data on younger children who were still likely to be in a structured setting such as a school or preschool. This provided investigators with an additional reporter of symptoms and impairment. Data obtained in this trial and its follow-up double-blind placebo-controlled study may lead to future studies that extend to younger children.

Despite the majority of children reporting at least one side effect, and at least half of the children reporting mood lability and half reporting diminished appetite, the medication was tolerated well enough so that no one discontinued the medication due to adverse effects. This is possibly due in part to the gradual and flexible titration schedule used over the course of treatment. There were no serious adverse events during the study, and the 2 chil-

TABLE 3. OUTCOME MEASURES COMPARING 5 YEAR OLDS TO 6 YEAR OLDS

	5 year old		*6 year old*		*Wilcoxon rank sum test* p *value comparing age groups*
Outcome measure	n	*Mean (SD)*	n	*Mean (SD)*	
Parent ADHD-IV Total	10	−27.00 (9.19)	12	−15.42 (13.32)	0.06
Parent ADHD-IV Inattentive	10	−14.40 (4.22)	12	−6.67 (7.91)	0.04
Parent ADHD-IV Hyperactive	10	−12.60 (6.45)	12	−8.87 (7.30)	0.2
CGAS	10	22.40 (9.92)	12	16.00 (13.54)	0.2
	n	*Count (%) improved*	n	*Count (%) improved*	*Fisher's exact test* p *value comparing age groups*
CGI-S	10	10 (100%)	12	8 (67%)	0.1
CGI-I	10	10 (100%)	12	9 (75%)	0.2

ADHD = Attention-Deficit/Hyperactivity Disorder Rating Scale-IV; CGAS = Children's Global Assessment Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impression–Severity; SD = standard deviation.

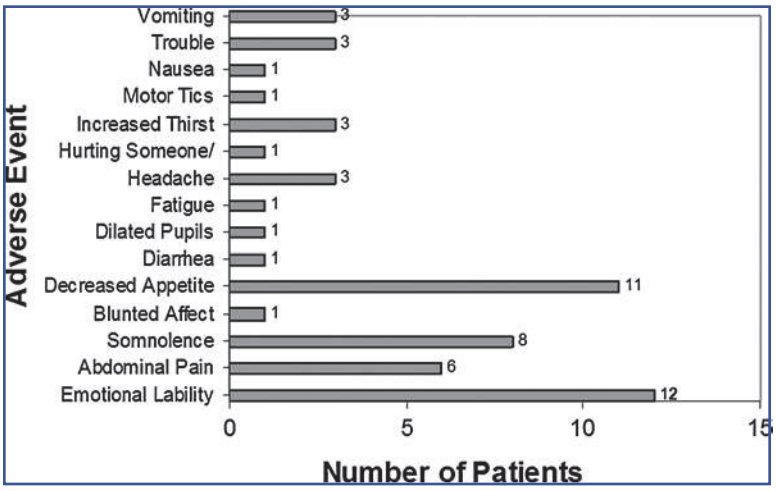

FIG. 3. Adverse events N = 22.

dren who discontinued the study after initiation of treatment were those who were unable to consistently swallow capsules. The most commonly reported adverse events, were mood lability ($n = 12$, 54.5%) and decreased appetite ($n = 11$, 50%), with a statistically significant decrease in weight of 1.04 kg (SD = 0.80, $p < 0.001$) observed for the group. The acute nature of the study, however, limits the ability to assess potential long-term effects on growth. Changes in vital signs were mild and not clinically significant. This is congruent with PATS, which demonstrated no significant changes in vital signs for subjects on MPH compared to those on placebo (Wigal et al. 2006). No clinically significant changes were observed in any of the laboratory tests or EKGs.

Mood lability was reported 1 week into treatment by 7 subjects, and was present for an average of $2\frac{1}{2}$ weeks. This side effect persisted until the end of the 8-week treatment period for 2 of the 12 subjects. Many of the adverse effects categorized as "mood lability" have been demonstrated in other trials of psychotropic medications in young children. In PATS, for example, 9 of the 14 children who discontinued due to adverse events did so because of emotionality or irritability (Greenhill et al. 2006). Also, Safer and Zito (2006) described a review of placebo-controlled clinical trials of serotonselective reuptake inhibitors (SSRIs) demonstrating that activation was consistently more prevalent in children than in adolescents (Safer and Zito 2006). All of these results indicate that younger children may be more prone to mood-related side effects than older children and adolescents. Decreased appetite appeared between the second and fourth weeks of treatment for the majority of the 11 subjects who reported it, and it was an ongoing adverse event at the end of the study for 8 subjects.

The frequency of adverse effects seen in this study, particularly the diminished appetite and mood lability, highlights the need for close monitoring of young children treated with pharmacotherapy for ADHD. Adjusting the rate of titration, total dose given, timing of doses, as well as caloric supplementation, can

TABLE 4. VITAL SIGNS

Measure	*Baseline mean (SD)*	*End point mean (SD)*	*Change mean (SD)*	
Weight (kg)	25.0 (38.1)	23.96 (3.45)	−1.04 (0.80)	$p < 0.001$
Systolic BP (mmHg)	94.25 (4.79)	100.10 (5.15)	2.89 (5.65)	$p = 0.03$
Diastolic BP (mmHg)	53.55 (5.25)	55.95 (6.58)	2.41 (6.80)	$p = 0.1$
Pulse (bpm)	93.36 (9.66)	92.05 (15.11)	−1.32 (14.37)	$p = 0.9$

BP = Blood pressure; bpm = beats per minute; kg = kilogram; mmHg = millimeters of mercury; SD = standard deviation.

Changes from baseline to end point were not statistically or clinically significant.

all potentially improve the tolerability when difficulties are identified.

Limitations

The results of this study are limited by its small sample size, predominantly Caucasian male population, and open-label design. Whereas boys constitute a higher proportion of preschoolers with ADHD, the ratio of males to females in this study was greater than that reported in clinical preschool samples. Additionally, it is difficult to identify the specific role of the atomoxetine, because the frequency of contact with the pharmacotherapist and the concomitant psychoeducational intervention may have also contributed to the overall robust response in this group. The parent education provided, while based on an evidence-based psychosocial treatment (McMahon and Forehand 2003), was very abbreviated and limited to eight 10- to 15-minute sessions (maximum of 2 hours). Parent training interventions demonstrating efficacy in this age group are much more intensive, averaging 8–12 hours duration, typically with significant behavioral rehearsal, modeling, and feedback components that the present intervention did not include (Pisterman et al. 1989; Strayhorn and Weidman 1989; Sonuga-Barke et al. 2001; Bor et al. 2002). Thus, although anecdotally many parents seemed to find the weekly discussions about behavior management strategies useful, it seems unlikely that this intervention alone provided significant direct benefits in reducing core ADHD symptoms. Nonetheless, it is certainly possible that the combination of psychoeducation with pharmacotherapy provided by the same physician contributed in some indirect ways to efficacy results. For example, psychoeducation may have enhanced the physician–patient relationship, which is believed to increase medication compliance.

Pharmacotherapists in this study had access to capsule strengths of atomoxetine that are not commercially available (2.5 mg, 5 mg, 20 mg), making smaller increases in study drug dose during titration possible. This allowed for dosing closer to the actual mg/kg dosing schedule, and a more gradual titration not possible or practical for clinicians in practice. Also, atomoxetine is only available in capsule form and sprinkling of the capsule contents is discouraged. Therefore, participation in this study was limited to those children able to swallow the atomoxetine capsule whole. For young children, this may not always be possible, as evidenced by the two discontinuations in this study. This may be a limiting factor for clinicians in the use of atomoxetine in younger children.

Another limitation of this study is that it only provides data on the short-term treatment of a disorder that generally lasts years. Longer-term follow up with young children taking atomoxetine to determine safety and effectiveness over time will be important. The potential long-term effects on growth in this population would be of particular interest. An additional limitation was the monitoring of adverse events by spontaneous report from the parent/guardian. Despite the high rates of adverse events, this method of adverse event collection may have resulted in a lower reporting rate compared to use of a systematic collection measure.

CONCLUSIONS

This open-label study demonstrated atomoxetine to be effective in the treatment of 5 and 6 year olds with ADHD. Although a significant number of children experienced adverse events, they were often transient, and no subjects discontinued due to side effects. There were no unanticipated adverse events, although the rates of decreased appetite and mood lability were higher than expected. Close monitoring is clearly warranted when using atomoxetine in young children with ADHD.

The study demonstrated the feasibility of the diagnostic assessments and the atomoxetine dosing strategy used, and anecdotal comments from parents reinforced the utility of the parent education protocol. These data supported the initiation of a 120-subject randomized double-blind placebo-controlled clinical trial currently underway at the three clinical sites.

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Dr. March is a consultant or scientific advisor to Pfizer, Lilly, Wyeth, GSK, Jazz, and MedAvante and holds stock in MedAvante; he receives research support from Lilly and study drug for an NIMH-funded study from Lilly and Pfizer; he is the author of the MASC.

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Dr. Greenhill is a consultant for Pfizer, Janssen, Lilly, & Novartis. He is on the advisory Board for Lilly and the Data & Safety Monitoring Board for Pfizer and Janssen. He has research contracts with McNeil, New River Pharmaceuticals, and Novartis.

Ms. Vaughan, Dr. Jorgensen, Dr. Ravi, Dr. Kotler, Ms. Paykina, Ms. Biggins, and Dr. Stoner have no conflicts of interest to report.

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Address reprint requests to:
Christopher J. Kratochvil, M.D.
985581 Nebraska Medical Center
Omaha, NE 68198-5581

E-mail: ckratoch@unmc.edu

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