Prospective, Naturalistic, Pilot Study of Open-Label Atomoxetine Treatment in Preschool Children with Attention-Deficit/Hyperactivity Disorder

Jaswinder K. Ghuman, M.D.,¹ Michael G. Aman, Ph.D.,² Harinder S. Ghuman, M.D.,¹
Thomas Reichenbacher, M.D.,¹ Alan Gelenberg, M.D.,^{1,3} Ron Wright, M.D., Ph.D.,¹
Sydney Rice, M.D.,⁴ and Carolyn Fort, M.S.¹

Abstract

Objective: The aim of this study was to report preliminary data regarding effectiveness and tolerability of atomoxetine in 3- to 5-year-old preschool children with attention-deficit/hyperactivity disorder (ADHD).

Methods: Nine boys and 3 girls (mean age = 5.0 ± 0.72 years) diagnosed with ADHD were treated with atomoxetine in an open-label pilot study. Atomoxetine was gradually titrated to a maximum dose of 1.8 mg/kg per day.

Results: There was a significant effect of time from baseline to end point on the parent-rated hyperactivity/impulsivity Swanson Nolan and Pelham (SNAP-IV-HI) subscale ratings ($F[9, 11] = 6.32, p < 0.0001$). The mean difference between the baseline and end-point parent SNAP-IV-HI scores was 10.2 ± 7.3 ($p = 0.0005$). The rate of positive response (defined as at least a 30% reduction in the end-point parent SNAP-IV-HI scores and a Clinical Global Impressions–Improvement [CGI-I] rating of Much Improved or Very Much Improved) was 75%. The Children's Global Assessment Scale scores improved significantly over time [$F(9, 11) = 6.24, p < 0.001$]. The mean end-point daily dose of atomoxetine was 1.59 ± 0.3 mg/kg. A high proportion (66.7%) of the preschoolers experienced side effects with atomoxetine. Side effects of defiance, tantrums, aggression, and irritability were most disconcerting to parents, and gastrointestinal complaints were the most commonly reported adverse effects. One child was terminated from the study due to "chest ache." There were no changes in weight, height, or cardiovascular measures.

Conclusion: This open-label pilot study provides preliminary evidence of effectiveness and tolerability of atomoxetine for treating ADHD in preschool children, although double-blind, randomized, placebo-controlled studies are needed to confirm this.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a common, chronic, and impairing disorder that frequently begins between 2 and 4 years of age (Wilens et al. 2002a; Connor 2002; Egger and Angold 2006). It is estimated that between 2% and 5.7% of preschool children in the United States have ADHD (Keenan et al. 1997; Lavigne et al. 1996; Gadow et al. 2001; Egger and Angold 2006). Clinically referred preschool children with ADHD are considerably impaired in

their daily functioning. They often exhibit aggressive and disruptive behaviors at home and at school, leading to expulsion from day-care or early education settings, and impulsive behaviors that may lead to accidental injuries and safety concerns (Rappley et al. 2002; Pelham et al. 2004; Egger and Angold 2006). Preschool-onset ADHD is a strong risk factor for persistent behavior problems, poor academic performance, poor peer social skills, substance abuse, and poor job performance, resulting in very substantial lifetime emotional turmoil and socioeconomic costs to families, schools,

¹Department of Psychiatry, University of Arizona, Tucson, Arizona.

²Ohio State University, Columbus, Ohio.

³Present address: Healthcare Technology Systems, Madison, Wisconsin.

⁴University of Arizona, Department of Pediatrics, Tucson, Arizona.

The statistical consultant for this study was Michael G. Aman, Ph.D.

This research was supported by National Institute of Mental Health grant number NIMH K23 MH01883 and Arizona Institute of Mental Health Research grants to J.K.G.

The paper is based in part on a poster presented at the May, 2006, Annual Meeting of the American Psychiatric Association held in Toronto, Canada.

and society at large (Richman et al. 1982; Campbell and Ewing 1990; Egeland et al. 1990; Campbell et al. 2000; Birnbaum et al. 2005; Kessler et al. 2005; Biederman et al. 2006b; Molina et al. 2007; Wilens 2007; Lee et al. 2008). Impairment from ADHD and persistence of problems at later ages suggest that early intervention may be helpful in preschool children with ADHD.

Psychopharmacological agents are used routinely to treat ADHD in school-aged children (Dulcan and Benson 1997; Wilens et al. 2002b; Biederman and Spencer 2008); specifically, the dopamine and the norepinephrine transporter blockers have been found to be helpful (Wilens 2006). The psychostimulant methylphenidate (MPH), a dopamine transporter blocker, is the most widely used and studied psychopharmacological agent in school-aged children with ADHD (Dulcan and Benson 1997). MPH was recently reported to improve ADHD symptoms in the Preschoolers with ADHD Treatment Study (PATs) of 165 preschool children between the ages of 3 and 5.5 years (Greenhill et al. 2006). However, a significant number (30%) of preschool children experienced adverse effects, including decreased appetite, stomachache, sleep difficulties, emotional outbursts, social withdrawal and lethargy, especially at higher doses. A discontinuation rate of 8.3% due to MPH side effects was reported (Wigal et al. 2006). Additionally, there was 20% less-than-expected annual height gain (-1.38 cm/year) and 55% less-than-expected annual weight gain (-1.32 kg/year) in the children who continued MPH for a year (Swanson et al. 2006). Given the concerns with MPH side effects, particularly decrements in growth, it is important to develop alternative treatment options for ADHD in preschool children.

Several nonstimulants have been reported to be efficacious in school-aged children and adults with ADHD (Higgins 1999; Silver 1999; Wilens 2001; Biederman et al. 2006a). Atomoxetine is the first nonstimulant to receive the Food and Drug Administration (FDA) approval for the treatment of ADHD in individuals over 6 years of age. It is a potent inhibitor of the presynaptic norepinephrine transporter with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Its efficacy in children over 6 years of age and adults with ADHD has been demonstrated in several double-blind, placebo-controlled trials (Michelson et al. 2001; Biederman et al. 2002; Michelson et al. 2002; Allen et al. 2003; Heiligenstein and Michelson 2003; Adler et al. 2005; Newcorn et al. 2005; Wilens et al. 2006a; Wilens et al. 2006b). Kratochvil et al. (2007) reported benefit from open-label atomoxetine treatment in a mixed-age (school- and preschool-aged) ADHD sample; 10 children were 5 years old and 12 were 6 years old (mean age = 6.06 ± 0.58 years). Adverse events (AEs) included mood lability, reduced appetite, and weight loss; there were no discontinuations due to adverse events or lack of efficacy. To the best of our knowledge, there have not been any atomoxetine treatment studies in ADHD children younger than 5 years; and it is not known whether children younger than 5 years will respond in a qualitatively different manner than children older than 5 years.

"Off-label" use of psychopharmacological agents in preschool children with ADHD is increasing despite limited empirical support or guidance (Rappley et al. 1999; 2002; Zito et al. 2007). Zito et al. (2007) reported that psychotropic use in Medicaid-insured preschoolers doubled from 1995 to 2001 and psychotropic prescription rates ranged from 0.96% to

2.3% for 2 year olds to 3.99% for 4 year olds. Atomoxetine prescription rates to treat ADHD in 0- to 5-year-old children from 75 managed-care organizations over a 9-month period in 2003 were reported to be 1.9%, despite the lack of empirical data on its use in children younger than 6 years old (Van Brunt et al. 2005).

Atomoxetine is gaining favor among some parents and practitioners because it is considered a noncontrolled substance (it does not have abusive potential); therefore, it is not subject to the control of the Drug Enforcement Administration. However, no empirical information is available to guide practitioners regarding: (1) appropriate atomoxetine dosage ranges, (2) efficacy, and (3) safety of atomoxetine in 3- to 5-year-old children with ADHD. We explored the potential utility of atomoxetine to treat ADHD in 3- to 5-year-old children in a prospective, naturalistic, open-label pilot study. We specifically included the wider age range because pharmacological agents are being prescribed for very young children including 3-, 4-, and 5-year-old children (Rappley et al. 1999; Zito et al. 2007) without empirical support or guidance. The primary objective of this pilot study was to conduct a systematic assessment of the effectiveness and tolerability and to collect preliminary information regarding safe dosage ranges for a randomized, placebo-controlled trial of atomoxetine in 3- to 5-year-old children with ADHD.

Methods

Study population

Preschool children were recruited through referrals from pediatricians and preschool teachers and self-referrals by interested parents in response to study flyers, media advertising, and word of mouth. Participants were preschool children, between the ages of 3 and 5 years, who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) criteria for ADHD, combined or predominantly hyperactive impulsive subtype as determined via a semistructured diagnostic interview with the caregiver. In addition to the categorical diagnosis, the preschool study participants had to meet dimensional and impairment criteria to be eligible to participate in the study. The preschoolers had to meet the dimensional threshold based on a Hyperactive-Impulsive subscale average score of 1.7 or above on the parent-rated Swanson, Nolan, and Pelham IV Rating Scale (SNAP-IV) (Swanson 1992). If the child was in a preschool or day-care setting, the teacher-rated Hyperactive-Impulsive subscale average score of the SNAP-IV also had to be 1.7 or above. The preschool children were included in the study only if they were significantly impaired in their everyday functioning as indicated by a Children's Global Assessment Scale (C-GAS) (Shaffer et al. 1983) score of 60 or below and a Clinical Global Impressions-Severity (CGI-S) (Guy 1976) score of moderate or above. Exclusion criteria included the following: (1) history of prior failed treatment with an adequate trial of atomoxetine; (2) taking monoamine oxidase inhibitors currently or within the previous 2 weeks; (3) concurrent treatment with other medications that have central nervous system (CNS) effects or that affect performance; (4) narrow-angle glaucoma; (5) significant hepatic disease, or major medical condition that could be affected negatively by atomoxetine; and (6) diagnosis of pervasive developmental disorders, bipolar disorder, psychosis, signifi-

cant suicidality, or other psychiatric disorders that required treatment with additional/alternative medication.

The University of Arizona Institutional Review Board approved the study; caregivers/legal guardians provided written informed consent prior to study participation. Because the FDA has not approved the use of atomoxetine for the treatment of ADHD in children younger than 6 years, we submitted an Investigational New Drug (IND) application to the FDA and were granted an exemption for its off-label use in preschool children with ADHD.

Twelve children were started on atomoxetine and had at least one medication follow-up visit. Mean age of the 12 children was 5.0 ± 0.72 years (range 3.5–5.8 years) at initial screening; 1 child was $3\frac{1}{2}$ years old, 5 children were 4 years old, and 6 children were 5 years old. There were 9 boys (75%) and 3 girls; 8 children (66.7%) were Caucasian and 4 were Hispanic. Six children lived with both biological parents; 5 children lived with a single parent, and 1 child lived with adoptive parents. The mean age of the mothers was 34.6 ± 9.74 years (range = 25–58 years). Two families received public assistance; mean socioeconomic status (SES) (Hollingshead 1975) of the sample was 39.2 ± 7.5 (range = 29–52.5). Nine children were either in family day care or attended preschool or kindergarten. Three children had a history of environmental allergies; 3 children had bronchial asthma and had received treatment with an albuterol inhaler in the past. One child had sickle cell trait, and 1 child had a seizure disorder and continued taking carbamazepine during his study participation. Three children were born prematurely between 27 and 36 weeks. One child had been hospitalized twice, once for breaking her arm by flipping backwards from a chair at age $2\frac{1}{2}$ and another time for drug poisoning when she got into the medicine cabinet and ingested an unknown quantity of clonidine that had been prescribed for her.

Co-morbidity was common. Oppositional defiant disorder was the most common co-morbid psychiatric disorder ($n = 8$, 66.7%). Communication disorders were present in 5 children (41.7%), elimination disorders in 5 children (41.7%), and anxiety disorders in 2 children (16.7%); conduct disorder, adjustment disorder, reactive attachment disorder, and pica were present in one child each (8.3% each). Two children (16.7%) had no co-morbid disorder. Three children had received brief pharmacological treatment trials for ADHD in the past with stimulants, α -agonists, and/or atomoxetine. Dosage and duration of the trials had been inadequate; parents had discontinued treatment due to adverse effects or lack of response. None of the children took any concurrent psychotropic medicines during the treatment trial. Concomitant treatments received by the children included behavior therapy ($n = 4$), speech therapy ($n = 4$), special education services ($n = 2$), and other services (sensory integration, occupational therapy, music therapy; $n = 3$). These were continued unaltered while the children took part in this trial.

A majority of the caregivers indicated that their child was not experienced with swallowing pills. Because atomoxetine is an eye irritant and opening of the capsules is not advised, we provided brief behavioral instruction to teach the children to swallow pills by practicing swallowing increasing sizes of cake decorations (Ghuman et al. 2004; Beck et al. 2005). Eight children (67%) were able to swallow atomoxetine during the study. Nevertheless, parents of 4 children poured the contents of the capsules into small amounts of liquid. None of the

parents reported any problem with eye irritation or refusal on their child's part to take atomoxetine due to unpleasant taste.

Study design

This study was a prospective, naturalistic, open-label, pilot study of atomoxetine conducted in an outpatient setting. Potentially eligible preschool children were screened for categorical diagnosis, dimensional rating scale threshold, and functional impairment threshold to determine eligibility. The dimensional and clinician ratings were repeated 1 week later at the baseline visit; children still meeting inclusion criteria were considered eligible to continue. Each eligible child first participated in a flexible, step-wise, open-label titration of atomoxetine. Children were seen weekly during the titration phase to monitor treatment response and AEs. Atomoxetine dose was initiated at 10 mg at bedtime for 1 week. The schedule for subsequent dose adjustments included increasing atomoxetine dose to 18 mg/day at week 2, 25 mg/day at week 3, 30 mg/day at week 4, 35 mg/day at week 5, and 40 mg/day at week 6. The dose adjustments were made at the discretion of the psychiatrist at the weekly clinic visits. Dose adjustments were based on clinical response and tolerability. The dose was increased until an optimal dose that produced the maximal effect with minimal side effects was reached. The maximum allowed dose in the study was 1.8 mg/kg per day. The maximum allowed absolute dose in the study was 40 mg/day. For moderate AEs, the child's atomoxetine dose was reduced to the last tolerated dose. After resolution of the AE, the dosage titration procedure was resumed as described above or at a slower pace based on tolerability and clinical response. Atomoxetine was administered as a single dose at bedtime or in the morning based on caregiver preference and child response. Atomoxetine could be administered twice/day if clinically indicated (e.g., due to excessive side effects with a single dose).

After the open-label titration, each child entered a 4-week open-label dosage maintenance and observation phase on the child's "optimal" dose. During the maintenance and observation phase, children were seen every other week to monitor for treatment response and AEs. Pretreatment efficacy assessments were conducted at baseline and repeated weekly during the titration phase and every other week during dosage maintenance and observation phase.

Measures

Baseline diagnoses of ADHD and associated co-morbidities were established via a semistructured psychiatric interview with the caregiver and with child observation conducted by a child and adolescent psychiatrist experienced in assessing and treating preschool children (J.K.G.). The semistructured psychiatric interview with the caregiver followed the same format as established for the PATS Diagnostic Interview (PDI) (Posner et al. 2007). The PDI includes age-appropriate probes to assess systematically the presence of DSM-IV-TR symptoms of ADHD and associated co-morbid disorders. The ADHD symptoms were rated on a scale of 0 (never) to 5 (always) by the clinician; a score of "3 (often)" or above was considered a symptom. All areas of ADHD impairment, including home, school, peer relations, other settings, and physical risk and injury, were assessed systematically. The primary efficacy measure was the Hyperactive-Impulsive

subscale of the SNAP-IV completed by the parents. Parent ratings on the SNAP-IV were obtained at screen, baseline, and at every subsequent medication monitoring visit. If the child attended preschool or was in a day-care setting, teacher ratings of the SNAP-IV were also obtained. The SNAP-IV items are based on the DSM-IV diagnostic criteria. We used the SNAP-IV hyperactive/impulsive (9 items), inattentive (9 items), and oppositional defiant disorder (8 items) subscales to monitor treatment response. The SNAP-IV items are rated 0 (not at all) to 3 (very much).

The C-GAS (Shaffer et al. 1983) and the CGI-S (Guy 1976; National Institute of Mental Health 1985) ratings were completed by the psychiatrist at screen, baseline, and every medication monitoring visit. A CGI-Improvement (CGI-I) rating was completed at every titration and dose maintenance visit. The C-GAS is a clinician-rated instrument based on information obtained from the parents and other informants about the child's overall functioning across settings. The scale is rated from 1 to 100, with lower scores reflecting poorer adjustment. The scale was developed for use in school-aged children and adolescents and has been shown to discriminate between levels of functioning in children and adolescents (Bird et al. 1990; Weissman et al. 1990). The C-GAS has not been widely studied in preschoolers; however, recent pharmacological studies in preschool children with ADHD have employed the C-GAS as a measure of a preschool child's overall functioning (Greenhill et al. 2006). The CGI-S is rated on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The CGI-I is rated relative to the child's condition at baseline and is also assessed on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Parents also completed CGI ratings at screen, baseline, and every medication monitoring visit.

The Early Childhood Inventory-4 (ECI-4) (Gadow et al. 2001; Sprafkin et al. 2002) was completed by the parents at baseline and at every subsequent medication monitoring visit. The ECI-4 items are rated 0 (never) to 3 (very often). We used the ECI-4 to supplement the diagnostic information obtained from the semistructured diagnostic interview.

Assessing treatment response in psychopharmacological trials via standardized scales has many advantages, but may fail to capture change in behaviors most concerning to an individual family. As suggested by Arnold et al. (2003), we addressed parents' specific concerns regarding their child's behavior by including an individualized target symptom assessment. At baseline, caregivers identified two problems of greatest concern to them; behavioral description and quantification of the two target symptoms were recorded at baseline and end point. After all data were collected, the end-point target symptom descriptions were coded in reference to the baseline visit by 3 raters (2 of the 3 were independent raters) on a 9-point scale: 1 = normal behavior, 2 = markedly improved, 3 = definitely improved, 4 = equivocally improved, 5 = no change, 6 = equivocally worse, 7 = definitely worse, 8 = markedly worse, and 9 = disastrously worse (e.g., had to be hospitalized (Arnold et al. 2003). The ratings were averaged across the 3 raters for each target symptom.

Safety assessments

Each child had a general physical examination, baseline blood work-up (complete blood count [CBC], liver function

tests [LFTs], electrolytes, blood urea nitrogen [BUN], creatinine, and serum lead level) and a 12-lead electrocardiogram (ECG) before initiating atomoxetine. Physical examinations and ECGs were repeated at the end of the study. Height, weight, blood pressure, and pulse rate measurements, AE review, and concomitant medications and treatments review were conducted by the psychiatrist at baseline and at each subsequent monitoring visit via open-ended interview with the caregiver. Additionally, as recommended by Greenhill et al. (2003), parents completed a Side Effects Rating Scale (SERS) addressing potential atomoxetine specific adverse effects. The SERS is a 4-point scale with higher scores reflecting higher severity of the side effect (none = 0, mild = 1, moderate = 2, severe = 3).

Data analysis

Descriptive statistics were used to characterize the baseline subject features and outcome and safety variables. Effectiveness and tolerability analyses were conducted on the intent-to-treat sample and included all preschool children who had a baseline visit and at least one post-treatment visit. The data from all medication follow-up visits were used to analyze the effect of medication over time. On the basis of the intent-to-treat principle, the last observation was carried forward (LOCF) if a child dropped out before completing the study because of side effects, lack of response, premature withdrawal from the study, or if data were missing for a particular visit. Repeated-measures one-way analysis of variance (ANOVA) was used to determine whether there was a significant change with treatment over time in the SNAP-IV hyperactive/impulsive (HI), inattentive (IA), ADHD composite (HI and IA combined), and oppositional (ODD) subscales, CGI-S, and C-GAS ratings for the weekly titration and 2-weekly dose maintenance and observation visits. *Post hoc* planned comparisons with two-tailed paired *t*-tests were performed to compare the baseline ratings with the ratings at each subsequent medication monitoring visit. Because the CGI-S is an ordinal scale, nonparametric (Wilcoxon signed rank test) analysis was also performed to examine whether there was significant change at end point compared with baseline.

Baseline and end-point parent ratings on the ECI-4 Elimination Disorders and Anxiety Disorders scales, and four items relevant to communication developmental milestones from the Developmental Milestones scale were compared with two-tailed paired *t*-tests to examine the effect of atomoxetine on co-morbid symptoms. These ECI-4 scales were selected because they corresponded to the specific co-morbid disorders (as determined via the PDI) present in 2 or more preschool subjects. The ECI-4 ODD scale was excluded to avoid overlap with the SNAP-IV-ODD subscale.

Because peer-conflict and sleep problems are a common complaint of parents of preschool and older children with ADHD (Campbell et al. 2000; Cohen-Zion and Ancoli-Israel 2004; Hoza 2007) and atomoxetine was originally developed as an antidepressant, the Peer Conflict, Sleep Problems, and Depressive Disorders scales of the ECI-4 were also included. A Bonferroni/Dunn correction was used because multiple subscales per outcome measure were involved. To evaluate the clinical significance of the impact of treatment on outcome, empirically based effect sizes (Cohen *d*, the

standardized difference of the means) were calculated for independent *t*-tests (correcting for the correlation between groups) as $d = t * \sqrt{2(1-r)/n}$ (Dunlap et al. 1996; Rosenthal et al. 2000). Interrater reliability among the 3 raters for the parent-identified target symptoms was estimated with intraclass correlation coefficient using an absolute agreement definition.

Results

Baseline characteristics

Parents of 24 children gave written consent for their child's participation in the study, and 6 of the 24 children failed to return to the clinic to initiate the screening assessments. Of the remaining 18 children, 3 children dropped out before completing all the screening assessments, 1 child did not meet criteria for enrollment, and 1 child met eligibility criteria but moved out of state prior to initiating atomoxetine treatment. The remaining 13 children started treatment with atomoxetine; however, 1 child failed to return to the clinic for any medication follow-up visit. Of the 12 children who started treatment with atomoxetine and had at least one medication follow-up visit, 4 children dropped out before completing the dose maintenance and observation phase; 1 child was termi-

nated from the study after the second titration visit due to flare up of his bronchial asthma and treatment with albuterol inhaler, 1 child was lost to follow up after the first titration visit, and 2 children completed the titration phase but dropped out prior to entering the dose maintenance and observation phase because the parents declined further study participation.

There were no significant differences in the age, gender, or SNAP-IV subscale scores between the 12 children who provided atomoxetine treatment outcome data compared to the 12 children who did not participate in the medication phase of the study. There were no significant differences in the age, gender, baseline SNAP-IV HI, IA, ADHD Composite, or ODD subscale scores between (younger, $n=6$) 4-year-olds and (older, $n=6$) 5-year-olds. Baseline sample characteristics are presented in Table 1.

Primary outcomes

In the intent-to-treat analysis, repeated-measures one-way ANOVA results for the primary outcome measure, parent SNAP-IV-Hyperactivity-Impulsivity (SNAP-IV-HI) subscale ratings, indicated a significant effect of time from baseline to the end of the study ($F[9, 11] = 6.32, p < 0.0001$) as presented

TABLE 1. BASELINE CHARACTERISTICS OF THE OPEN-LABEL INTENT-TO-TREAT STUDY SAMPLE ($N=12$)

<i>Subject variables (N = 12)</i>		
Demographic Variables		
Age, years, mean (SD), [range]	5.02 (0.72)	[3.56–5.76]
Age Group, n (%), [range]		
36–47 month old	1 (8.3)	[42.68]
48–59 month old	5 (41.67)	[50.63–59.4]
60–71 month old	6 (50.0)	[63.77–69.09]
Male, n (%)	9 (75.0)	
Ethnicity, n (%)		
Caucasian	8 (66.67)	
Hispanic or Latino	4 (33.33)	
Child Assessment Variables		
ADHD subtype, n (%)		
Hyperactive-impulsive type	7 (58.3)	
Combined type	5 (41.7)	
Number of DSM-IV Attention Deficit/Hyperactivity Disorder (ADHD) symptoms*, mean (SD), [range]		
Hyperactive/Impulsive	7.83 (1.03)	[6–9]
Inattentive	5.25 (1.91)	[2–9]
Total DSM-IV ADHD symptoms	13.08 (2.27)	[8–17]
ADHD symptoms present since age, years, mean (SD), [range]	2.07 (0.79)	[0.8–3.5]
Duration of ADHD symptoms, years, mean (SD), [range]	2.59 (1.18)	[0.58–5.0]
Parent Swanson Nolan And Pelham-IV (SNAP-IV) Scale score, n , mean (SD), [range]		
Hyperactivity/Impulsivity Subscale	21.58 (4.08)	[14–27]
Inattentive Subscale	16.08 (5.25)	[7–24]
Total ADHD Composite	37.67 (7.13)	[29–49]
ODD Subscale	14.17 (6.49)	[1–23]
Clinical Global Impression-Severity of Illness (CGI-S), mean (SD), [range]		
Clinician CGI-S rating	5.25 (0.62)	[4–6]
Parent CGI-S rating	4.70 (1.06)	[2–6]
Children's Global Assessment Scale (C-GAS), mean (SD), [range]	49.92 (3.70)	[43–58]

*Based on the semistructured Preschoolers with ADHD Treatment Study (PATS) Diagnostic Interview (PDI).

Abbreviation: SD = standard deviation.

FIG. 1. Parent SNAP-IV Hyperactive/Impulsive Subscale Ratings at baseline and each titration and maintenance visit for the intent-to-treat sample ($N = 12$). Error bars depict confidence intervals. SNAP = Swanson, Nolan and Pelham scale; T = titration visit; M = dosage maintenance and observation visit; #¹ = first child completed titration; #² = median and modal number of titration visits; #³ = last child completed titration; § $n = 12$ at each time point, tabulated number represents the number of preschoolers whose dose is still being titrated for the T visits and number of preschoolers completing dosage maintenance and observation phase for the M visits.

in Fig. 1. The mean difference between the baseline and the end of study parent SNAP-IV-HI scores was 10.16 ± 7.3 ($p = 0.0005$; effect size [Cohen $d = 1.54$]). The parent SNAP-IV-HI subscale change scores at the end of the study did not differ between the (younger) 4-year-old and (older) 5-year-old subjects ($df = 1, 10$, $t = 0.047$, $p = 0.96$).

Using our *a priori* definition of 30% or more reduction in the parent SNAP-IV-HI subscale scores and a CGI-I rating of Much Improved or Very Much Improved, 75% children (83% of the younger subjects and 67% of the older subjects) were rated as atomoxetine responders. The Wilcoxon signed rank test indicated a significant change on the CGI-S ratings between baseline and end-point ratings ($z = -0.658$, $p = 0.008$). The C-GAS scores improved significantly over time ($F[9, 11] = 6.24$, $p < 0.001$) from a mean score of 49.9 ± 3.7 at baseline to 60.0 ± 9.0 at the end of the study.

Secondary outcomes

Table 2 shows the mean baseline and end-point scores and effect sizes (where relevant) for the HI, IA, ADHD Composite, and ODD subscales of the parent and teacher SNAP-IV, clinician- and parent-rated CGI-S subscales, C-GAS, and parent-rated ECI-4 communication items of the Developmental Milestones, Elimination Disorders, Anxiety Disorders

(composite of ECI-4 category D pertaining to Separation Anxiety Disorder symptoms and ECI-4 category E pertaining to other anxiety disorders), Depressive Disorders, Peer Conflict, and Sleep Problems scales. Significant improvement was seen in the parent ratings on the SNAP-IV-IA and ADHD Composite (SNAP-IV-ADHD) subscales over time with atomoxetine. After the Bonferroni correction for multiple comparisons, the parent SNAP-IV-IA, SNAP-IV-ADHD, and SNAP-IV-ODD scores showed significant improvement at the endpoint compared to the baseline.

Parents also completed CGI ratings for their child at baseline and at each subsequent follow-up visit. The parent CGI-S ratings indicated a significant effect of time from baseline to end of maintenance ($F[9, 10] = 5.08$, $p < 0.001$). The Wilcoxon signed rank test indicated a significant change on the parent CGI-S ratings between baseline and end-point ratings ($z = -2.366$, $p = 0.018$). The parents rated 7 of 11 (63.6%) children as Very Much Improved or Much Improved on the CGI-I. The intraclass correlation coefficient among the 3 raters for the parent-identified target symptoms was 0.817. The target symptoms were classified into four categories: overactivity, inability to focus, defiance, and anger/aggression. Compared to the baseline, the mean ratings at the end of the study improved for the overactivity, inability to focus, and anger/aggression target symptoms (2.22 ± 1.03 , 2.92 ± 1.87 ,

TABLE 2. OUTCOME MEASURES COMPARING BASELINE AND ENDPOINT SCORES WITH ATOMOXETINE IN PRESCHOOL CHILDREN WITH ADHD

Outcome measure	N	Baseline		Endpoint		Change score		% Change ^a						Effect size ^c
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	t value	p value ^b			
Parent Swanson Nolan And Pelham-IV (SNAP-IV) Scale														
Hyperactive-Impulsive Subscale	12	21.58	4.10	11.42	6.61	10.16	7.30	45.74	30.47	3.355	0.0005		1.54	
Inattentive Subscale	12	16.17	5.24	9.17	5.20	7.00	5.41	43.91	25.98	4.482	0.0009		1.34	
Total ADHD Composite	12	36.75	7.90	20.58	10.80	16.17	12.16	42.38	31.03	4.807	0.0008		1.70	
Oppositional Subscale	12	14.17	6.49	8.42	5.70	5.75	6.48	−10.71	188.40	3.073	0.0108		0.83	
Teacher SNAP-IV Scale														
Hyperactive-Impulsive Subscale	7	19.86	6.34	16.43	7.19	3.43	10.94	2.03	61.54	0.829	0.4390			
Inattentive Subscale	7	19.00	6.68	15.29	7.51	3.71	6.45	16.79	30.89	1.524	0.1783			
Total ADHD Composite	7	38.86	12.33	31.71	13.33	7.14	16.12	9.80	42.09	1.172	0.2855			
Oppositional Subscale	7	12.29	6.53	9.14	5.52	3.15	4.91	21.82	33.78	1.692	0.142			
Parent Early Childhood Inventory-4 (ECI-4) Scale														
Communication Developmental Milestones ^{d,e}	9	10.11	2.08	10.67	1.94	−0.56	2.24	−9.41	30.11	−0.743	0.4790			
Elimination Disorders ^d	9	2.56	3.25	1.67	3.04	0.89	1.97	45.00	51.23	1.357	0.2120			
Anxiety Disorders ^{d,f,g}	9	13.00	7.14	7.87	6.98	5.33	5.45	42.40	37.48	2.833	0.018899		0.75	
Depressive Disorders ^h	9	5.28	2.54	6.28	4.21	−1.00	5.43	−63.91	192.92	−0.552	0.5958			
Peer Conflict Scale ^{g,i}	9	11.78	8.77	4.33	3.20	7.45	7.84	44.00	38.58	2.847	0.0220		0.99	
Sleep Problems ^{g,i}	9	3.67	3.28	2.11	1.90	1.58	1.94	36.39	49.01	2.401	0.0430		0.44	
Clinical Global Impressions (CGI)														
Parent CGI-Severity Score	10	4.70	1.10	3.00	1.49	1.70	1.34	79.17	68.63	4.019	0.0030		1.28	
Clinician CGI-Severity Score	12	5.25	0.60	4.08	0.79	1.17	1.11	33.75	31.17	3.626	0.0040		1.64	
Children’s Global Assessment Scale	12	49.92	3.70	60.00	8.98	10.08	9.71	20.66	19.12	3.598	0.0042		1.47	

^aPairwise difference/baseline score 100.^bBonferroni correction for multiple subscales per measure: Parent SNAP secondary outcome subscales: $\alpha + 3 \approx 0.0167$; Parent ECI subscales: $\alpha + 6 = 0.0083$; CGI-Severity; $\alpha + 2 = 0.025$.^cCohen d for independent tests (correcting the correlation between groups): $d = t^* \sqrt{2(1-r)/n}$.^dThe ECI subscale represents the corresponding comorbid disorder present in 2 or more preschool subjects based on clinical diagnostic assessment.^eIncludes 4 items (relevant to communication milestones) from the Developmental Milestones category of the ECI-4.^fComposite of category D (Separation Anxiety Disorder) and category E (other anxiety disorders) of the ECI-4.^gNot significant after Bonferroni correction.^hDepressive disorders are included to examine effect of atomoxetine on depressive symptoms since atomoxetine was originally developed as an antidepressant.ⁱPeer Conflict Scale and Sleep Problems are included to examine the effect of atomoxetine on peer conflict and sleep since both are common problems in preschool children with ADHD.

Abbreviations: ADHD = Attention-deficit/hyperactivity disorder; SD = standard deviation.

and 2.4 ± 0.76 , respectively) and remained unchanged for defiance (4.0 ± 1.13).

Ten children were in a day care or attended preschool, kindergarten, or a group activity (e.g., summer camp) at the time of initial screening for the study. However, 2 children were expelled from their preschool or day care prior to initiating atomoxetine, and 1 child had teacher ratings for post-treatment follow-up visits but did not have any teacher ratings for the baseline visit. For the remaining 7 children, at least 2 children had 3 different teachers completing the rating scales on different visits. No significant changes were observed in the SNAP-IV-HI, IA, ADHD, and ODD teacher ratings ($n = 7$) at end point compared to baseline.

As shown in Table 2, improvement was seen in comorbid symptoms as rated by parents on the Anxiety Disorders, Peer Conflict, and Sleep Problems scales of the ECI-4 at end point compared to baseline. However, the change was not significant after the Bonferroni correction. There was no change in the Communication Developmental Milestones, Elimination Disorders, and Depressive Disorders subscales of the ECI-4.

Atomoxetine dose. The mean atomoxetine daily dose at the end of study was 31 ± 7.98 mg or 1.59 ± 0.31 mg/kg (range 20–40 mg/day or 1.09–1.89 mg/kg per day). During the study, 8 children took atomoxetine at bedtime, 2 took it in the morning, and 2 children took atomoxetine in two divided doses during the day. The mean duration for completion of dose titration was 5.91 ± 1.79 weeks ($n = 10$; range = 4–10 weeks). Three children completed titration and were stabilized in four visits, 4 children in five visits, 1 child in six visits, and 2 children in seven visits (the mode for titration was five visits). The atomoxetine titration rate and duration differed among the 3- to 5-year-old study participants due to their differential time to response and ability to tolerate the dose increases. The mean duration of the total medication phase (flexible dose titration plus maintenance phase) was 8.24 ± 2.99 weeks (range = 2–12 weeks).

Safety outcomes

Figure 2 shows the side effects endorsed on the parent-completed SERS and spontaneously reported AEs.

FIG. 2. (A) Safety outcome: Side Effect Rating Scale Parent Ratings ($N = 12$). *Highest severity rating at any titration or maintenance visit relative to the baseline rating. (B) Safety outcome: Spontaneously reported adverse events ($N = 12$). *Mean total duration in days and standard deviation of adverse event. **Highest severity rating at any titration or maintenance visit.

Parent-endorsed side effects on the SERS included complaints of their child being tearful, sad, having appetite loss, and trouble sleeping. AEs elicited by direct enquiry occurred in 8 children (66.7%). Complaints of irritability, defiance, and aggression were of most concern to the parents; parents described the children as crying/whiny, grouchy/irritable, or having increased frequency of tantrums, aggression, and agitation. Gastrointestinal complaints were the most common AEs reported by parents, and included stomach upset, reduced appetite, vomiting, constipation/diarrhea, and/or increased thirst. Sleep disturbance experienced by the children included difficulty falling asleep and/or being sleepy and tired. Figure 2B shows the frequency and mean total (noncontinuous) duration for the AEs. Total duration range (noncontinuous) for the AEs was 1–51 days for “irritable, whiny” and “trouble falling asleep,” 2–33 days for “sleepy/tired,” 9–31 days for “reduced appetite,” 1–29 days for “upset stomach,” and 1–3 days for other AEs. One child discontinued the study due to complaints of what his mother termed as “chest-ache” and restless sleep and concurrent flare up of his bronchial asthma necessitating regular use of albuterol inhaler.

No significant changes were observed in the children’s weight (baseline = 19.30 ± 3.03 kg, end point = 19.22 ± 2.80 kg), height (baseline = 110.79 ± 7.43 cm, end point = 111.67 ± 7.30 cm), pulse (baseline = 97.4 ± 4.22 , end point = 102.1 ± 13.7), blood pressure (systolic blood pressure at baseline = 98.5 ± 10.6 hg and at end point = 98.2 ± 9.4 hg, and diastolic blood pressure at baseline = 61.3 ± 6.4 hg and at end point = 64.3 ± 7.02 hg) and ECG parameters at end point compared to the baseline values.

Discussion

To the best of our knowledge, this is the first systematic assessment of the effectiveness and tolerability of atomoxetine in a sample of 3- to 5-year-old children with ADHD. By including 3- and 4-year-old children, this study extends the current knowledge beyond the Kratchovil et al. (2007) report of open-label atomoxetine treatment in 5-year-old children. Atomoxetine improved parent-rated hyperactive, impulsive, and inattentive behaviors of preschool children diagnosed with ADHD. A significant improvement (45.7%) was

observed over baseline on the parent rated SNAP Hyperactivity/Impulsivity subscale, and a similar improvement was seen on the SNAP Inattentive subscale (43.9%) and the total ADHD Composite (42.4%); effect sizes were large ranging from 1.34 to 1.7.

Improvement in the ADHD symptoms experienced by the preschool children with atomoxetine in the current trial is comparable to the previously mentioned open-label atomoxetine study in 5- and 6-year-old children (Kratochvil et al. 2007) and in school-aged children with ADHD (Michelson et al. 2001; Spencer et al. 2002). There were no differences in response to treatment by age between the younger 4-year-old and the older 5-year-old children in the current study. Greater improvement with atomoxetine was reported in the younger 5-year-old subgroup compared to the older 6-year-old subgroup by Kratochvil et al. (2007). However, given the smaller sample size and open-label nature of both these studies, it is difficult to draw any firm conclusions about the effects of age. No significant difference in overall response was found in a meta-analysis comparing efficacy of atomoxetine in children and adolescents with ADHD (Wilens et al. 2006a).

In contrast to the parent reports of improvement, teachers did not report improved ADHD symptoms in the preschool children treated with atomoxetine. The finding of negative teacher outcome with atomoxetine in the current pilot study differs from the PATS report of greater sensitivity of teacher ratings to MPH effects than parent ratings (Greenhill et al. 2006). Several reasons may have contributed to the negative teacher outcome. First, the sample size was small and teacher data were available for only 7 children. Second, the type, structure, and setting of the school/group activity attended by the preschool children varied widely; and finally, different teachers may have completed the ratings on different visits.

A high proportion (66.7%) of the preschoolers in the current study experienced side effects with atomoxetine. Defiance, tantrums, aggression, and agitation led to dose reduction in 3 children and a slower modified titration in 3 children (with dose increment at 2 weeks instead of the weekly scheduled increase as per protocol). Upset stomach and vomiting also led to dose reduction in 1 child. One child was terminated from the study due to complaints of what his mother termed as "chest ache," and restless sleep and flare up of his bronchial asthma necessitating regular use of albuterol inhaler. There were no changes in cardiovascular measures.

The frequency and profile of the AEs in the current trial were similar to the results reported for the mixed-age sample of 5- and 6-year-old children with ADHD (Kratochvil et al. 2007). Parents complained of irritability, defiance, agitation, and crying/whiny in 41.7% of the preschool children in the current study. These complaints are similar to the "mood lability" reported in 50% of the 5- and 6-year-old children by Kratochvil et al. (2007). Adverse effects of behavioral activation have been reported in younger children treated with psychopharmacological agents. High rates of behavioral activation were reported with selective serotonin reuptake inhibitors (SSRIs) to treat anxiety and depressive disorders in children younger than 7 years (Zuckerman et al. 2007). Higher prevalence of activation or restlessness was reported with SSRIs in younger children compared to older children (Safer and Zito 2006). High rates of emotional lability were also reported in preschool children treated with MPH in the PATS (Greenhill et al. 2006). In contrast to the 3- to 5-year-old chil-

dren, emotional lability and/or irritability are not commonly reported in school-aged children treated with atomoxetine (Michelson et al. 2001; Kelsey et al. 2004).

There were no significant changes in height, weight, pulse, systolic and diastolic blood pressure, and ECG with atomoxetine in the current trial, a finding similar to the Kratochvil et al. (2007) study with two exceptions. Kratochvil et al. (2007) reported a mean decrease in weight of 1.04 ± 0.80 kg ($p < 0.001$) and a mean increase in systolic blood pressure of 2.98 ± 5.68 ($p = 0.03$) in the 5- to 6-year-old children. However, because information was not provided separately for the 5- and 6-year-old subgroups, it is difficult to determine the impact of atomoxetine on weight and systolic blood pressure of the 5-year-olds. Moreover, given the smaller sample size and open-label nature of both these studies, it is difficult to draw any firm conclusions about the effects of atomoxetine on weight and systolic blood pressure in preschool-aged children.

The mean end-point dose of 1.59 ± 0.31 mg/kg per day in the current study was higher than the 1.25 mg/kg per day in the Kratochvil et al. (2007) study. It is possible that the higher mg/kg atomoxetine dose in the current study was related to the fact that Kratochvil et al. (2007) had access to noncommercial smaller atomoxetine dosage strengths (2.5 mg, 5 mg, and 20 mg), allowing them to make smaller dose increases than possible in the current study.

The preschool children in the current study had high rates of co-morbidity, a finding consistent with other preschool ADHD samples (Ghuman et al. 2001; Greenhill et al. 2006; Ghuman et al. 2007; Kratochvil et al. 2007). Oppositional defiant disorder was the most common co-morbid psychiatric disorder, and parents reported benefit from atomoxetine in the SNAP-IV-ODD. Improvement in parent-rated oppositional behavior with atomoxetine has also been reported in school-aged children with ADHD (Michelson et al. 2001). No improvement was reported in the communications domain, affective symptoms, or elimination problems. Even though the parent-reported benefit from atomoxetine in anxiety symptoms, peer conflict, and sleep problems was not significant after Bonferroni correction, it is still of clinical interest. Similar to the findings in the current study, improvement in anxiety symptoms with atomoxetine was reported in 8- to 17-year-old children with ADHD and co-morbid anxiety disorders (Geller et al. 2007); and no evidence of efficacy for major depressive disorder was reported in 12- to 18-year-old adolescents (Bangs et al. 2007). Preschool children with ADHD symptoms and coexisting peer problems are likely to have persistent impairment at a later age (Campbell and Ewing 1990). Hence improvement in peer conflict by using atomoxetine may have a role in mitigating longer-term impairment in preschool children with ADHD.

Limitations

Although these data suggest the potential utility of atomoxetine in treating ADHD in preschool children, the findings should be viewed with caution because of the methodological limitations and small sample size of the current study. The study was conducted in an open-label manner and thus may be subject to observer bias and placebo effect. Lack of a control group in the study makes it impossible to determine whether the positive effects were due to atomoxetine or to nonspecific factors, such as closely

monitored weekly visits. The semistructured diagnostic interview was specifically developed for the PATS, although no validity studies in preschool children have been conducted. A reliable and valid semistructured diagnostic parent interview, Preschool Age Psychiatric Assessment (PAPA) (Egger et al. 2006), is available for use in research studies. The small sample size limits any meaningful comparisons between younger and older preschoolers, boys and girls, and ethnic subgroups; it also limits the generalizability of the findings. Lack of consistent teacher data limits our ability to assess preschool children's response to atomoxetine in school settings. Another limitation of the study was that about a third of the preschoolers were unable to swallow the atomoxetine capsules and their parents poured the capsule into a small amount of liquid. However, opening of the atomoxetine capsules is not advised because atomoxetine is an eye irritant. On the other hand, none of the parents reported any problem with eye irritation or refusal on their child's part to take atomoxetine due to unpleasant taste. Finally, the children were treated for a short time, and no data are available regarding long-term tolerability and safety of atomoxetine in preschool children.

Conclusion

The results of this prospective, open-label naturalistic study suggest that atomoxetine may be a useful treatment for ADHD in preschool children. Treatment-emergent AEs were common with high rates of irritability, crying, whining, and gastrointestinal symptoms, and they were mostly mild to moderate. One child discontinued the study due to complaints of what his mother characterized as "chest ache." These findings suggest that controlled investigations of the efficacy, safety, and tolerability of atomoxetine in preschool children with ADHD should be conducted. In the meantime, any preschool children treated with atomoxetine should have very gradual titration and close monitoring for side effects.

Disclosures

The following financial disclosures indicate potential conflicts of interest among the investigators and industry sources. ¹Honoraria/Consultant, ²Research Support, ³Speaker's Bureau, ⁴Significant Equity (>\$50,000). Dr. J. Ghuman: Bristol Myers-Squibb²; Dr. Aman: Bristol-Myers-Squibb^{1,2}, Johnson & Johnson^{1,2}, Forest Research², and NeuroPharm²; Dr. Gelenberg: Eli Lilly^{1,2}, Pfizer Pharmaceuticals^{1,3}, Best Practice¹, Astra/Zeneca, Wyeth^{1,3}, Cyberonics¹, Novartis¹, Forest¹, GlaxoSmithKline^{1,3}, ZARS Pharma¹, Jazz Pharmaceuticals¹, Lundbeck¹, Takeda¹, eResearch Technology¹, and Healthcare Technology Systems, Inc.⁴ Drs. Reichenbacher, Wright, and Rice, and Ms. Fort have no conflicts of interest or financial ties to disclose.

Acknowledgments

The authors thank Natalie Mai-Dixon, Meagan Hastings, Allison Lee, James Eudeikis, and Dawn Begaye for their help in conducting this study.

References

- Adler LA, Spencer TJ, Milton DR, Moore RJ, Michelson D: Long-term, open-label study of the safety and efficacy of atomoxetine in adults with attention-deficit/hyperactivity disorder: An interim analysis. *J Clin Psychiatry* 66: 294–299, 2005.
- Allen A, Michelson D, Kelsey DK, Heiligenstein JH, Faries DE, Sumner CR, Thomason CK: Once or twice-daily atomoxetine treatment in children and adolescents with ADHD—Does it make a difference? *Biolog Psychiatry* 53:206S–206S, 2003.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR). Washington (DC): American Psychiatric Association; 2000.
- Arnold LE, Vitiello B, McDougall C, Scahill L, Shah B, Gonzalez NM, Chuang S, Davies M, Holloway J, Aman MG, Cronin P, Koenig K, Kohn AE, McMahon DJ, Tierney E: Parent-defined target symptoms respond to risperidone in RUPP Autism Study: Customer approach to clinical trials. *J Am Acad Child Adolesc Psychiatry* 42:1443–1450, 2003.
- Bangs ME, Emslie GJ, Spencer TJ, Ramsey JL, Carlson C, Bartky EJ, Busner J, Duesenberg DA, Harshawat P, Kaplan SL, Quintana H, Allen AJ, Sumner CR: Efficacy and safety of atomoxetine in adolescents with attention-deficit/hyperactivity disorder and major depression. *J Child Adolesc Psychopharmacol* 17:407–420, 2007.
- Beck MH, Cataldo M, Slifer KJ, Pulbrook V, Guhman JK: Teaching children with attention deficit hyperactivity disorder (ADHD) and autistic disorder (AD) how to swallow pills. *Clin Pediatr* 44:515, 2005.
- Biederman J, Spencer TJ: Psychopharmacological interventions. *Child Adolesc Psychiatr Clin N Am* 17:439–458, xi, 2008.
- Biederman J, Heiligenstein JH, Faries DE, Galil N, Dittmann R, Emslie GJ, Kratochvil CJ, Laws HF, Schuh KJ: Efficacy of atomoxetine versus placebo in school-age girls with attention-deficit/hyperactivity disorder. *Pediatrics* 110:e75; 2002.
- Biederman J, Arnsten AF, Faraone SV, Doyle AE, Spencer TJ, Wilens TE, Weiss MD, Safren SA, Culppepper L: New developments in the treatment of ADHD. *J Clin Psychiatry* 67:148–159, 2006a.
- Biederman J, Monuteaux MC, Mick E, Spencer T, Wilens TE, Silva JM, Snyder LE, Faraone SV: Young adult outcome of attention deficit hyperactivity disorder: A controlled 10-year follow-up study. *Psychol Med* 36:167–179, 2006b.
- Bird HR, Yager TJ, Staghezza B, Gould MS, Canino G, Rubio-Stipec M: Impairment in the epidemiological measurement of childhood psychopathology in the community. *J Am Acad Child Adolesc Psychiatry* 29:796–803, 1990.
- Birnbaum HG, Kessler RC, Lowe SW, Secnik K, Greenberg PE, Leong SA, Swensen AR: Costs of attention deficit-hyperactivity disorder (ADHD) in the US: Excess costs of persons with ADHD and their family members in 2000. *Curr Med Res Opin* 21:195–206, 2005.
- Campbell SB, Ewing LJ: Follow-up of hard-to-manage preschoolers: Adjustment at age 9 and predictors of continuing symptoms. *J Child Psychol Psychiatry* 31:871–889, 1990.
- Campbell SB, Shaw DS, Gilliom M: Early externalizing behavior problems: Toddlers and preschoolers at risk for later maladjustment. *Dev Psychopathol* 12:467–488, 2000.
- Cohen-Zion M, Ancoli-Israel S: Sleep in children with attention-deficit hyperactivity disorder (ADHD): A review of naturalistic and stimulant intervention studies. *Sleep Med Rev* 8:379–402, 2004.
- Connor DF: Preschool attention deficit hyperactivity disorder: A review of prevalence, diagnosis, neurobiology, and stimulant treatment. *J Dev Behav Pediatr* 23:S1–S9, 2002.
- Dulcan MK, Benson RS: AACAP Official Action. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. *J Am Acad Child Adolesc Psychiatry* 36:1311–1317, 1997.

- Dunlap WP, Cortina JM, Vaslow JB, Burke MJ: Meta-analysis of experiments with matched groups or repeated measures designs. *Psycholog Methods* 1:170–177, 1996.
- Egeland B, Kalkoske M, Gottesman N, Erickson MF: Preschool behavior problems: Stability and factors accounting for change. *J Child Psychol Psychiatry* 31:891–909, 1990.
- Egger HL, Angold A: Common emotional and behavioral disorders in preschool children: Presentation, nosology, and epidemiology. *J Child Psychol Psychiatry Allied Discipl* 47: 313–237, 2006.
- Gadow KD, Sprafkin J, Nolan EE: DSM-IV symptoms in community and clinic preschool children. *J Am Acad Child Adolesc Psychiatry* 40:1383–1392, 2001.
- Geller D, Donnelly C, Lopez F, Rubin R, Newcorn J, Sutton V, Bakken R, Paczkowski M, Kelsey D, Sumner C: Atomoxetine treatment for pediatric patients with attention-deficit/hyperactivity disorder with comorbid anxiety disorder. *J Am Acad Child Adolesc Psychiatry* 46:1119–1127, 2007.
- Ghuman JK, Ginsburg GS, Subramaniam G, Ghuman HS, Kau AS, Riddle MA: Psychostimulants in preschool children with attention-deficit/hyperactivity disorder: Clinical evidence from a developmental disorders institution. *J Am Acad Child Adolesc Psychiatry* 40:516–524, 2001.
- Ghuman JK, Cataldo MD, Beck MH, Slifer KJ: Behavioral training for pill-swallowing difficulties in young children with autistic disorder. *J Child Adolesc Psychopharmacol* 14:601–611, 2004.
- Ghuman JK, Riddle MA, Vitiello B, Greenhill LL, Chuang SZ, Wigal SB, Kollins SH, Abikoff HB, McCracken JT, Kastelic E: Comorbidity moderates response to methylphenidate in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *J Child Adolesc Psychopharmacol* 17:563–580, 2007.
- Greenhill LL, Vitiello B, Riddle MA, Fisher P, Shockey E, March JS, Levine J, Fried J, Abikoff H, Zito JM, McCracken JT, Findling RL, Robinson J, Cooper TB, Davies M, Varipatis E, Labellarte MJ, Scahill L, Walkup JT, Capasso L, Rosengarten J: Review of safety assessment methods used in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry* 42:627–633, 2003.
- Greenhill L, Kollins S, Abikoff H, McCracken J, Riddle M, Swanson J, McGough J, Wigal S, Wigal T, Vitiello B, Skrobala A, Posner K, Ghuman J, Cunningham C, Davies M, Chuang S, Cooper T: Efficacy and safety of immediate-release methylphenidate treatment for preschoolers with ADHD. *J Am Acad Child Adolesc Psychiatry* 45:1284–1293, 2006.
- Guy W: ECDEU Assessment Manual for Psychopharmacology (Revised). Washington (DC): Department of Health Education and Welfare, 1976.
- Heiligenstein JH, Michelson D: Atomoxetine—a selective and specific noradrenergic uptake inhibitor for the treatment of pediatric and adult attention-deficit/hyperactivity disorder. *Nordic J Psychiatry* 57:91–91, 2003.
- Higgins ES: A comparative analysis of antidepressants and stimulants for the treatment of adults with attention-deficit hyperactivity disorder. *J Fam Pract* 48:15–20, 1999.
- Hollingshead AB: Four factor index of social status. Unpublished manuscript, New Haven, (Connecticut): Yale University, 1975.
- Hoza B: Peer functioning in children with ADHD. *J Pediatr Psychol* 32:655–663, 2007.
- Keenan K, Shaw DS, Walsh B, Delliquadri E, Giovannelli J: DSM-III-R disorders in preschool children from low-income families. *J Am Acad Child Adolesc Psychiatry* 36:620–627, 1997.
- Kelsey DK, Sumner CR, Casat CD, Coury DL, Quintana H, Saylor KE, Sutton VK, Gonzales J, Malcolm SK, Schuh KJ, Allen AJ: Once-daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder, including an assessment of evening and morning behavior: A double-blind, placebo-controlled trial. *Pediatrics* 114:e1–e8, 2004.
- Kessler RC, Adler LA, Barkley R, Biederman J, Conners CK, Faraone SV, Greenhill LL, Jaeger S, Secnik K, Spencer T, Ustun TB, Zaslavsky AM: Patterns and predictors of attention-deficit/hyperactivity disorder persistence into adulthood: Results from the national comorbidity survey replication. *Biol Psychiatry* 57:1442–1451, 2005.
- Kratochvil CJ, Vaughan BS, Mayfield-Jorgensen ML, March JS, Kollins SH, Murray DW, Ravi H, Greenhill LL, Kotler LA, Paykina N, Biggins P, Stoner J: A pilot study of atomoxetine in young children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 17:175–185, 2007.
- Lavigne JV, Gibbons RD, Christoffel KK, Kaufer K, Arend R, Rosenbaum D, Binns H, Dawson N, Sobel H, Isaacs C: Prevalence rates and correlates of psychiatric disorders among preschool children. *J Am Acad Child Adolesc Psychiatry* 35:204–214, 1996.
- Lee SS, Lahey BB, Owens EB, Hinshaw SP: Few preschool boys and girls with ADHD are well-adjusted during adolescence. *J Abnorm Child Psychol* 36:373–83, 2008.
- Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, Newcorn J, Sallee FR, Sangal RB, Saylor K: Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: A randomized, placebo-controlled study. *Am J Psychiatry* 159:1896, 2002.
- Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, Spencer T, Atomoxetine A: Atomoxetine in the treatment of children and adolescents with attention-deficit. *Pediatrics* 108:E83, 2001.
- Molina BS, Flory K, Hinshaw SP, Greiner AR, Arnold LE, Swanson JM, Hechtman L, Jensen PS, Vitiello B, Hoza B, Pelham WE, Elliott GR, Wells KC, Abikoff HB, Gibbons RD, Marcus S, Conners CK, Epstein JN, Greenhill LL, March JS, Newcorn JH, Severe JB, Wigal T: Delinquent behavior and emerging substance use in the MTA at 36 months: Prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry* 46:1028–1040, 2007.
- Newcorn JH, Spencer TJ, Biederman J, Milton DR, Michelson D: Atomoxetine treatment in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry* 44:240–248, 2005.
- National Institute of Mental Health: Special feature: Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull* 12:1077–1080, 1985.
- Pelham WE, Chacko A, Wymbs BT: Diagnostic and assessment issues of attention deficit/hyperactivity disorder in the young child. In: *Handbook of Infant, Toddler, and Preschool Mental Health Assessment*. Eds: Delcarmen-Wiggins R, Carter A. New York: Oxford University Press, 2004. pp 399–420.
- Posner K, Melvin GA, Murray DW, Gugga SS, Fisher P, Skrobala A, Cunningham C, Vitiello B, Abikoff HB, Ghuman JK, Kollins S, Wigal SB, Wigal T, McCracken JT, McGough JJ, Kastelic E, Boorady R, Davies M, Chuang SZ, Swanson JM, Riddle MA, Greenhill LL: Clinical presentation of attention-deficit/hyperactivity disorder in preschool children: The Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). *J Child Adolesc Psychopharmacol* 17:547–562, 2007.

- Rappley MD, Mullan PB, Alvarez FJ, Eneli IU, Wang J, Gardiner JC: Diagnosis of attention-deficit/hyperactivity disorder and use of psychotropic medication in very young children. *Arch Pediatr Adolesc Med* 153:1039–1045, 1999.
- Rappley MD, Eneli IU, Mullan PB, Alvarez FJ, Wang J, Luo Z, Gardiner JC: Patterns of psychotropic medication use in very young children with attention-deficit hyperactivity disorder. *J Dev Behav Pediatr* 23:23–30, 2002.
- Richman N, Stevenson J, Graham P: *Pre-school to School: A Behavioural Study*. London: Academic Press, 1982.
- Rosenthal R, Rosnow RL, Rubin DB: *Contrasts and Effect Sizes in Behavioral Research: A Correlational Approach*. Cambridge: Cambridge University Press, 2000.
- Safer DJ, Zito JM: Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: Children versus adolescents. *J Child Adolesc Psychopharmacol* 16:159–169, 2006.
- Shaffer D, Gould M, Brasic J, Ambrosini P, Fisher P, Bird H, Aluwalia S: A children's global assessment scale (C-GAS). *Arch Gen Psychiatry* 40:1228–1231, 1983.
- Silver LB: Alternative (nonstimulant) medications in the treatment of attention-deficit/hyperactivity disorder in children. *Pediatr Clin N Am* 46:965–975, 1999.
- Spencer T, Heiligenstein JH, Biederman J, Faries DE, Kratochvil CJ, Conners CK, Potter WZ: Results from 2 proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 63:1140–1147, 2002.
- Sprafkin J, Volpe RJ, Gadow KD, Nolan EE, Kelly K: A DSM-IV-referenced screening instrument for preschool children: The Early Childhood Inventory-4. *J Am Acad Child Adolesc Psychiatry* 41:604–612, 2002.
- Swanson J, Greenhill L, Wigal T, Kollins S, Stehli A, Davies M, Chuang S, Vitiello B, Skrobala A, Posner K, Abikoff H, Oatis M, McCracken J, McGough J, Riddle M, Ghuman J, Cunningham C, Wigal S: Stimulant-related reductions of growth rates in the PATS. *J Am Acad Child Adolesc Psychiatry* 45:1304–1313, 2006.
- Swanson JM: *School-Based Assessments and Interventions for ADD Students*. Irvine (California): KC Publishing, 1992.
- Van Brunt DL, Johnston JA, Ye WY, Pohl GM, Sun PJ, Sterling KL, Davis ME: Predictors of selecting atomoxetine therapy for children with attention-deficit-hyperactivity disorder. *Pharmacotherapy* 25:1541–1549, 2005.
- Weissman MM, Warner V, Fendrich M: Applying impairment criteria to children's psychiatric diagnosis. *J Am Acad Child Adolesc Psychiatry* 29:789–795, 1990.
- Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, Swanson J, Wigal S, Abikoff H, Kollins S, McCracken J, Riddle M, Posner K, Ghuman J, Davies M, Thorp B, Stehli A: Safety and tolerability of methylphenidate in preschool children with ADHD. *J Am Acad Child Adolesc Psychiatry* 45:1294–1303, 2006.
- Wilens TE: A controlled clinical trial of bupropion for attention deficit hyperactivity disorder in adults. *Am J Psychiatry* 158:282–288, 2001.
- Wilens TE: Mechanism of action of agents used in attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 67(Suppl 8):32–38, 2006.
- Wilens TE: The nature of the relationship between attention-deficit/hyperactivity disorder and substance use. *J Clin Psychiatry* 68(Suppl 11):4–8, 2007.
- Wilens TE, Biederman J, Brown S, Monuteaux M, Prince J, Spencer TJ: Patterns of psychopathology and dysfunction in clinically referred preschoolers. *J Dev Behav Pediatr* 23:S31–S36, 2002a.
- Wilens TE, Biederman J, Spencer TJ: Attention deficit/hyperactivity disorder across the lifespan. *Ann Rev Med* 53:113–131, 2002b.
- Wilens TE, Kratochvil C, Newcorn JH, Gao H: Do children and adolescents with ADHD respond differently to atomoxetine? *J Am Acad Child Adolesc Psychiatry* 45:149–157, 2006a.
- Wilens TE, Newcorn JH, Kratochvil CJ, Gao H, Thomason CK, Rogers AK, Feldman PD, Levine LR: Long-term atomoxetine treatment in adolescents with attention-deficit/hyperactivity disorder. *J Pediatr* 149:112–119, 2006b.
- Zito JM, Safer DJ, Valluri S: Psychotherapeutic medication prevalence in Medicaid-insured preschoolers. *J Child Adolesc Psychopharmacol* 17:195, 2007.
- Zuckerman ML, Vaughan BL, Whitney J, Dodds A, Yakhkind A, MacMillan C, Raches D, Pravdova I, DeMaso DR, Beardslee WR, Gonzalez-Heydrich J: Tolerability of selective serotonin reuptake inhibitors in thirty-nine children under age seven: A retrospective chart review. *J Child Adolesc Psychopharmacol* 17:165–174, 2007.

Address reprint requests to:
Jaswinder K. Ghuman, M.D.
University of Arizona
Room AHSC 7304
1501 N. Campbell Ave
Tucson, AZ 85724-5002

E-mail: jkghuman@email.arizona.edu