Efficacy and Safety Extrapolation Analyses for Atomoxetine in Young Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objectives: This extrapolation analysis qualitatively compared the efficacy and safety profile of atomoxetine from Lilly clinical trial data in 6–7-year-old patients with attention-deficit/hyperactivity disorder (ADHD) with that of published literature in 4–5-year-old patients with ADHD (two open-label [4–5-year-old patients] and one placebo-controlled study [5-year-old patients]).

Methods: The main efficacy analyses included placebo-controlled Lilly data and the placebo-controlled external study (5-year-old patients) data. The primary efficacy variables used in these studies were the ADHD Rating Scale-IV Parent Version, Investigator Administered (ADHD-RS-IV-Parent:Inv) total score, or the Swanson, Nolan and Pelham (SNAP-IV) scale score. Safety analyses included treatment-emergent adverse events (TEAEs) and vital signs. Descriptive statistics (means, percentages) are presented.

Results: Acute atomoxetine treatment improved core ADHD symptoms in both 6–7-year-old patients ($n = 565$) and 5-year-old patients ($n = 37$) (treatment effect: -10.16 and -7.42). In an analysis of placebo-controlled groups, the mean duration of exposure to atomoxetine was ~ 7 weeks for 6–7-year-old patients and 9 weeks for 5-year-old patients. Decreased appetite was the most common TEAE in atomoxetine-treated patients. The TEAEs observed at a higher rate in 5-year-old versus 6–7-year-old patients were irritability (36.8% vs. 3.6%) and other mood-related events (6.9% each vs. $<3.0\%$). Blood pressure and pulse increased in both 4–5-year-old patients and 6–7-year-old patients, whereas a weight increase was seen only in the 6–7-year-old patients.

Conclusions: Although limited by the small sample size of the external studies, these analyses suggest that in 5-year-old patients with ADHD, atomoxetine may improve ADHD symptoms, but possibly to a lesser extent than in older children, with some adverse events occurring at a higher rate in 5-year-old patients.

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is one of the most frequently diagnosed neuropsychological disorders in children and adolescents (Biederman 2005; Biederman and Faraone 2005). Atomoxetine is approved for the treatment of ADHD in children and adolescents 6–18 years of age, although the disorder can present with impairing symptoms in children <6 years of age (Baker et al. 2010; Ayaz et al. 2012). The American Academy of Pediatrics recently developed guidelines suggesting that children as young as 4 years of age who meet criteria for ADHD can be treated with medication (American Academy of

Pediatrics 2011). The first-line intervention in preschool ADHD is parent management training (Kratochvil et al. 2004; Gleason et al. 2007). This includes parent- and/or teacher-administered behavior therapy, and if this does not work, the physician may prescribe medication after evaluating the risks of starting medication versus delaying treatment (American Academy of Pediatrics 2011). Extensive data are available for children and adolescents (6–18 years of age), from previous studies of atomoxetine conducted by Eli Lilly and Company. However, there is little information available about the use of atomoxetine for the treatment of ADHD in children <6 years of age. Hence, an extrapolation exercise related to efficacy and safety was conducted on available atomoxetine data

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from children 6–7 years of age from clinical trials sponsored by Eli Lilly and Company, and supported by available literature in 4–5-year-old children.

When developing an extrapolation strategy, the two main patient factors that affect the pharmacokinetics of atomoxetine, namely CYP2D6 genotype and body weight, were considered. The CYP2D6 genotype is the primary metabolic pathway for atomoxetine, and this enzyme is thought to reach adult competency at several months of age (Kearns 1995). Phenotyping studies in infants have shown that dextromethorphan phenotype is concordant with the CYP2D6 genotype by 2 weeks of age (Leeder et al. 2000), suggesting that CYP2D6 activity is well developed by 2 weeks of age. Therefore, differences in CYP2D6 activity and function were not expected in 4–5-year-old patients compared with older children. Exposure in a younger child was expected to be comparable to that in an older child. Atomoxetine is dosed according to weight in children <70 kg, and the recommended starting dose of atomoxetine is 0.5 mg/kg daily with the target maintenance dose being 1.2 mg/kg daily. The weight of 6–7-year-old patients is close to the weight of 4–5-year-old patients, hence this strategy of using data from 6–7-year-old patients to attempt to further understand the efficacy and safety of atomoxetine in 4–5-year-old patients was considered to be appropriate, given the closeness of age.

Methods

Overview

The atomoxetine clinical trial database consisting of studies conducted by Eli Lilly and Company was used to assess the efficacy and safety of atomoxetine in children 6–7 years of age with ADHD. In addition to summarizing the Lilly clinical trial data in children 6–7 years of age, the available efficacy and safety data from studies conducted by external investigators in 4–5-year-old patients were also summarized. The efficacy and safety of atomoxetine in preschool-aged children were from three independent studies funded by the United States National Institutes of Mental Health (NIMH). Two of the studies were pilot, open-label studies, and one was a placebo-controlled study. In all three studies, atomoxetine was titrated to a maximum of 1.8 mg/kg per day. The external data involved in these analyses included data from children 5 years of age with ADHD from the 8 week, double-blind, placebo-controlled study (mean final dose was 1.4 mg/kg) that enrolled children 5 and 6 years of age (Kratochvil et al. 2011); data from children 5 years of age with ADHD from an open-label study (mean final dose was 1.25 mg/kg) that enrolled children 5 and 6 years of age (Kratochvil et al. 2007); and data from children 4 and 5 years of age with ADHD from an open-label study (mean final dose was 1.59 ± 0.3 mg/kg) that enrolled children 3–5 years of age (Ghuman et al. 2009).

Analysis groups

Results from four analysis groups are presented in this document. Two analysis groups contain Lilly clinical trial data from children 6–7 years of age (Lilly Pediatric Placebo-controlled ADHD Analysis Group; Lilly Pediatric Overall ADHD Analysis Group) and two analysis groups contain external data from children 4–5 years of age (External Placebo-controlled Dataset [5-year-old patients only]; External Overall Dataset [4–5-year old patients]). A description of the analysis groups is provided in Table 1.

All studies included in the extrapolation analysis required patients to have ADHD as defined by *The Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) or the DSM-IV

Text Revision (DSM-IV-TR) (American Psychiatric Association 1994, 2000). Both Lilly analysis groups allowed patients who had comorbid tics or oppositional defiant disorder. In the Kratochvil et al. 2007 study, patients had comorbidities such as oppositional defiant disorder, enuresis, simple phobia, and phonological disorder (Kratochvil et al. 2007). In the Kratochvil et al. 2011 study, patients had comorbidities that included oppositional defiant disorder, enuresis, separation anxiety, phobia, tics, and other comorbidities (Kratochvil et al. 2011). In the Ghuman et al. study, the comorbidities included oppositional defiant disorder, communication disorders, elimination disorders, anxiety disorders, conduct disorder, adjustment disorder, reactive attachment disorder, and pica (Ghuman et al. 2009).

In the atomoxetine clinical trial database, all studies used a core set of exclusion criteria, most of which were intended to ensure safety and minimize risk in a research setting. Patients with serious acute medical conditions were generally excluded from studies, as were patients with a history of a seizure disorder (other than febrile seizures), patients with uncontrolled hypertension, patients at serious risk for suicide, patients with bipolar disorder, and patients with ongoing alcohol or drug abuse. Pediatric patients who weighed <20 kg at study entry were generally excluded. A number of medications were also grounds for exclusion, including primarily medications with psychoactive effects that could confound efficacy analyses (e.g., antidepressants or antipsychotics) and medications that could have unwanted pharmacodynamic or other interactions with atomoxetine, such as additive sympathomimetic effects. In the external studies, some of the exclusion criteria included concurrent treatment with medications that have central nervous system effects; current treatment with atomoxetine or failure to respond to a previous trial of atomoxetine; and current diagnosis of adjustment disorder, autism, psychosis, bipolar disorder, suicidality, or hepatic disease (Kratochvil et al. 2007; Ghuman et al. 2009; Kratochvil et al. 2011).

In addition to the above analysis populations, sensitivity analyses that were run on subsets of the Lilly Pediatric Overall ADHD Analysis Group are also presented. These subsets included patients 6 years of age only and patients 6–7 years of age who had a body weight <25.1 kg. These subpopulations were chosen for sensitivity analyses in order to provide support for the primary analyses conducted in 6–7-year-olds, but with data from patients who had characteristics closer to the age subset of interest (4–5-year-old patients). A body weight of 25.1 kg is equal to the 5-year-old patients' 90th percentile (Centers for Disease Control and Prevention 2009).

Variables and statistical analyses

Efficacy analyses were conducted on the placebo-controlled analysis groups by using all randomized patients with a baseline and a postbaseline measurement. All other analyses were performed on the safety population (all enrolled patients receiving at least one dose of the study drug). Results from the External Placebo-controlled Dataset are described in terms of qualitative differences between the treatment groups rather than statistically significant differences, because of the small sample sizes. All *p* values are provided as supplemental information. In addition, because of limitations in statistical comparisons and the post-hoc nature of the analyses, statistical significance should be interpreted with caution.

For all analysis groups, the number of patients exposed to the study drug and the duration of study drug exposure in days and total

TABLE 1. ANALYSIS POPULATIONS FOR THE EXTRAPOLATION ANALYSES

<i>Analysis Group</i>	<i>Age (years)</i>	<i>n</i>	<i>Source</i>	<i>Description</i>	<i>Number of studies included</i>	<i>Mean duration exposure (days)</i>	<i>Analyses</i>
Lilly Pediatric Placebo-controlled ADHD Analysis Group	6–7	6 years 6–7 years with weight <25.1 kg	Lilly clinical trial database	Data from children 6–7 years of age with ADHD, or ADHD and comorbid tics, or ODD, from double-blind phase of placebo-controlled studies	16 studies	ATX (<i>n</i> = 393): 49.74 PBO (<i>n</i> = 186): 47.14	Efficacy, safety, disposition, demographics
Lilly Pediatric Overall ADHD Analysis Group	6–7	6 years 6–7 years with weight <25.1 kg	Lilly clinical trial database	Data from children 6–7 years of age with ADHD, or ADHD and comorbid tics, or ODD	39 studies	ATX (<i>n</i> = 1294): 352.46	Safety, disposition, demographics
External Placebo-controlled Dataset	5 ^a	ATX = 19 PBO = 19	Kratochvil et al. 2011	Data from children 5 years of age with ADHD from an 8 week, double-blind, placebo-controlled study	1 study	ATX (<i>n</i> = 19): 62.42 PBO (<i>n</i> = 19): 58.37	Efficacy, safety, disposition, demographics
External Overall Dataset	4–5	ATX = 40	Kratochvil et al. 2011, 2007; Ghuman et al. 2009	Data from children 4–5 years of age with ADHD from 1 placebo-controlled study and 2 open-label studies	3 studies	ATX (<i>n</i> = 40): 63.53	Safety, disposition, demographics

^aThis study did not include 4-year-old patients.

ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine treatment group; ODD, oppositional defiant disorder; PBO, placebo treatment group.

patient-years of exposure were calculated, the patient baseline characteristics were summarized by treatment, and the number and percentage of patients who completed or discontinued the study were summarized by treatment group and overall. For the Lilly Pediatric Placebo-controlled ADHD Analysis Group and External Placebo-controlled Dataset, treatment group differences for continuous demographic data were compared by using an analysis of variance model with terms for treatment and study; treatment group differences for categorical data were compared using Fisher's exact test.

Efficacy analyses were conducted separately on the Lilly and External analysis groups that contained placebo-controlled data in order to compare 6–7-year-old patients with 5-year-old patients. For this extrapolation report, the primary efficacy variable was the ADHD Rating Scale-IV Parent Version, Investigator Administered (ADHD-RS-IV-Parent:Inv) total score. Three Lilly studies that specifically included patients with comorbid oppositional defiant disorder used the Swanson, Nolan, and Pelham Rating Scale-Revised [SNAP-IV]; the ADHD component of SNAP-IV (i.e., the 18-item scores from SNAP-IV, that were from DSM-IV criteria for ADHD) were used in these analyses. Given the similarity to the ADHD-RS-IV-Parent:Inv, studies that used the SNAP-IV were pooled with the studies that used the ADHD-RS-IV-Parent:Inv. Secondary efficacy variables included two subscale scores (inattentive subscale and hyperactive-impulsive subscale) that were computed from the above-mentioned efficacy measures, and studies were pooled for analysis purposes.

For analysis of ADHD-RS-IV-Parent:Inv total and subscale scores, change from baseline to the last observation carried forward (LOCF) endpoint during the treatment phase was calculated for each patient. An analysis of covariance (ANCOVA) on the mean change from baseline was conducted including terms for baseline, treatment, and study in the model, for both the Lilly Pediatric Placebo-controlled ADHD Analysis Group and the External Placebo-controlled Dataset.

Safety analyses were conducted on adverse events (AEs) and vital signs including weight, blood pressure, and pulse. Treatment-emergent adverse events (TEAEs) were defined as events that first occurred or worsened in severity, relative to baseline, any time during a study treatment period. All TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0.

In the open-label study conducted by Ghuman et al. (2009), AEs (or “side effects”) were reported at each visit via the parent-completed Side Effects Rating Scale (SERS), which addressed potential atomoxetine-specific AEs (Greenhill et al. 2003). Events from the Ghuman study were not mapped to MedDRA preferred terms because of complications and uncertainties related to the use of the SERS; specifically, many side effects on the questionnaire were groups of events that precluded mapping to a single MedDRA preferred term. Additionally, it was not considered appropriate to integrate the AE data from the Ghuman et al. study into the External Overall Dataset because of the differences in AE reporting methods (solicited) (Ghuman et al. 2009) compared with the two external studies (spontaneous) conducted by Kratochvil et al. (2007, 2011). The Lilly studies collected TEAEs via spontaneous reporting. Therefore, the AE summaries for the External Overall Dataset only include the two studies conducted by Kratochvil et al. (which did not include 4-year-old patients) (Kratochvil et al. 2007, 2011).

Sensitivity analyses of safety data were conducted for the Lilly Pediatric Overall ADHD Analysis Group using only data from 6-year-old patients and from 6–7-year-old patients weighing <25.1 kg.

Mean change from baseline to LOCF endpoint in vital signs and weight were assessed for all analysis groups. The ANCOVA model used for the Lilly Pediatric Placebo-controlled ADHD Analysis Group contained terms for baseline value, treatment, and study. For the External Placebo-controlled Dataset, the ANCOVA model contained terms for baseline value, treatment, and study.

Categorical analyses of change in vital signs and weight at endpoint were assessed for Overall Analysis groups. Categorical changes in pulse were defined as a decrease of at least 20 beats per minute (bpm) to a value of at most 65 bpm or an increase of at least 25 bpm to a value of at least 110 bpm. Categorical change in weight was defined as a decrease of at least 3.5% from baseline. Categorical change in systolic and diastolic was defined as an increase of at least 5 mm Hg to a value above the 95th percentile (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004).

Results

Patient exposure

Lilly data in 6–7-year-old patients. In the Lilly Pediatric Placebo-controlled ADHD Analysis Group, the mean duration of exposure to atomoxetine was 49.74 days (median: 49.00 days) and to placebo was 47.14 days (median: 44.5 days). In the Lilly Pediatric Overall ADHD Analysis Group, patients were exposed to atomoxetine for a mean of 352.46 days (median: 106.0 days).

External data in 4–5-year-old patients. In the External Placebo-controlled Dataset, the mean duration of exposure to atomoxetine was 62.42 days (median: 62.00 days), and to placebo was 58.37 days (median: 61.00 days). In the External Overall Dataset, patients were exposed to atomoxetine for a mean of 63.53 days (median: 60.50 days).

Comparison across age groups. In the placebo-controlled analyses, the mean duration of exposure to placebo and atomoxetine was similar between the Lilly Pediatric Placebo-controlled ADHD Analysis Group (47 [placebo] to 50 [atomoxetine] days) and the External Placebo-controlled Dataset (58 [placebo] to 62 [atomoxetine] days). Patient-years of exposure to atomoxetine were greater in the Lilly Pediatric Placebo-controlled ADHD Analysis Group than in the External Placebo-controlled Dataset (53.39 patient-years vs. 3.25 patient-years).

In the overall analyses, mean duration of exposure and patient-years of exposure were greater for the Lilly Pediatric Overall ADHD Analysis Group (352.46 days; 1246.75 patient-years) compared with that for the External Overall Dataset (63.53 days; 6.61 patient-years); the disparity was not as great when medians were compared (106.00 days for the Lilly data vs. 60.50 days) for the External Overall Dataset.

Demographics

Lilly data in 6–7-year-old patients. In the Lilly Pediatric Placebo-controlled ADHD Analysis Group, a majority of patients in both treatment groups were male and white, with mixed ADHD subtype and no prior stimulant use (Table 2). There was no statistically significant difference between treatment groups in baseline ADHD symptom severity, as measured by ADHD-RS-IV-Parent:Inv total score, and treatment groups were comparable for other characteristics except ethnic origin, for which there was a statistically significant difference between treatment groups ($p=0.039$).

TABLE 2. DEMOGRAPHIC AND BASELINE CHARACTERISTICS: PLACEBO-CONTROLLED ANALYSIS GROUPS

Variable	Lilly Pediatric Placebo-controlled ADHD Analysis Group (6–7-year-old patients)			External Placebo-controlled Dataset (5-year-old patients)		
	ATX (n = 393)	PBO (n = 186)	p value	ATX (n = 19)	PBO (n = 19)	p value
Age, years, mean (SD)	7.188 (0.570)	7.159 (0.555)	0.463	5.49 (0.35)	5.53 (0.26)	0.721
Gender, n (%)			0.501			0.605
Male	320 (81.42)	147 (79.03)		15 (78.95)	12 (63.16)	
Ethnic origin, n (%)			0.039			0.105
White	279 (70.99)	137 (73.66)		19 (100.00)	14 (73.68)	
Asian	66 (16.79)	17 (9.14)		0 (0.00)	0 (0.00)	
Hispanic	21 (5.34)	9 (4.84)		0 (0.00)	0 (0.00)	
Black or African American	18 (4.58)	15 (8.06)		0 (0.00)	4 (21.05)	
Other	9 (2.29)	8 (4.30)		0 (0.00)	0 (0.00)	
Native American	0 (0.00)	0 (0.00)		0 (0.00)	1 (5.26)	
ADHD subtype, n (%)			0.393			0.698
Hyperactive/Impulsive	21 (5.34)	6 (3.23)		3 (15.79)	1 (5.26)	
Inattentive	60 (15.27)	24 (12.90)		2 (10.53)	1 (5.26)	
Mixed	312 (79.39)	156 (83.87)		14 (73.68)	17 (89.47)	
Prior stimulant use, n (%)	n = 371	n = 177	0.768	n = 19	n = 19	1.00
No	257 (69.27)	120 (67.80)		18 (94.74)	19 (100.00)	
Yes	114 (30.73)	57 (32.20)		1 (5.26)	0 (0.00)	
ADHD-RS total score, mean (SD)	41.43 (8.22)	41.82 (7.75)	0.775	38.21 (5.40)	39.84 (6.05)	0.385
Hyperactive/Impulsive, mean (SD)	20.25 (5.55)	20.55 (5.11)	0.694	19.26 (5.26)	20.42 (4.14)	0.434
Inattentive subscale, mean (SD)	21.19 (4.10)	21.27 (4.08)	0.977	18.95 (5.02)	19.42 (4.32)	0.771

ADHD, attention-deficit/hyperactivity disorder; ADHD-RS, Attention-Deficit/Hyperactivity Disorder Rating Scale; ATX, atomoxetine treatment group; PBO, placebo treatment group.

This difference appears to be primarily driven by a higher proportion of Asian patients in the atomoxetine treatment group. A similar demographic profile was seen for patients in the Lilly Pediatric Overall ADHD Analysis Group (Table 3).

External data in 4–5-year-old patients. Demographic and baseline characteristics for the External Placebo-controlled Dataset were similar to those for patients in the Lilly Pediatric Placebo-controlled ADHD Analysis Group (Table 2). The demographic characteristics for patients in the External Overall Dataset (Table 3) were consistent with those for patients in the External Placebo-controlled Dataset (Table 2).

Comparison across age groups. Most of the patient demographics and baseline characteristics were similar between patients 6–7 years of age in the Lilly atomoxetine clinical trial database and patients 4–5 years of age in the external atomoxetine studies, except for ADHD subtype (hyperactive/impulsive) and no prior stimulant use (Table 3), which were more frequent in the external studies.

Disposition

Lilly data in 6–7-year-old patients. In the Lilly Pediatric Placebo-controlled ADHD Analysis Group, a total of 59.3% of atomoxetine- and 52.2% of placebo-treated patients completed the studies, with no statistically significant difference between the atomoxetine and placebo treatment groups. Statistically significantly more placebo-treated patients discontinued because of lack of efficacy compared with atomoxetine-treated patients (15.6% vs. 7.1%; $p=0.003$) (Table 4). More patients in the placebo treatment group discontinued because of AEs than did those in the atomoxetine treatment group, but the difference was not statistically significant (5.4% vs. 2.3%; $p=0.077$). In the Lilly Pediatric Overall ADHD Analysis Group, a total of 41.6% of atomoxetine-treated

patients completed the studies. The primary reason for discontinuation was lack of efficacy (16.7%). The percentage of atomoxetine-treated patients who discontinued because of AEs was relatively low (4.9%), but it was higher than the percentage observed in the placebo-controlled analysis (2.3%).

TABLE 3. DEMOGRAPHIC AND BASELINE CHARACTERISTICS: OVERALL ANALYSIS GROUPS

Variable	Lilly Pediatric Overall ADHD Analysis Group (6–7- year-old patients)	External Overall Dataset (4–5-year-old patients)
	ATX (n = 1294)	ATX (n = 40)
Age, years, mean (SD)	7.133 (0.577)	5.26 (0.45)
Gender, n (%)	n = 1294	n = 39
Male	1042 (80.53)	30 (76.92)
Ethnic origin, n (%)	n = 1294	n = 39
White	954 (73.72)	35 (89.74)
Asian	167 (12.91)	0 (0.00)
Hispanic	79 (6.11)	0 (0.00)
Black or African American	58 (4.48)	2 (5.13)
Other	36 (2.78)	2 (5.13)
ADHD subtype, n (%)	n = 1264	n = 39
Hyperactive/Impulsive	72 (5.70)	12 (30.77)
Inattentive	172 (13.61)	2 (5.13)
Mixed	1020 (80.70)	25 (64.10)
Prior stimulant use, n (%)	n = 1269	n = 40
No	800 (63.04)	38 (95.00)
Yes	469 (36.96)	2 (5.00)

ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine treatment group.

TABLE 4. PATIENT DISPOSITION

Variable, n (%)	Lilly Pediatric Placebo-controlled ADHD Analysis Group (6–7-year-olds)		Lilly Pediatric Overall ADHD Analysis Group 6–7-year olds		External Placebo-controlled Dataset (5-year-olds)		External Overall Dataset (4–5-year-olds)
	ATX (n=393)	PBO (n=186)	ATX (n=1294)		ATX (n=19)	PBO (n=19)	ATX (n=40)
Completed	233 (59.3)	97 (52.2)	538 (41.6)		14 (73.7)	11 (57.9)	32 (80.0)
Discontinued for any reason	160 (40.7)	89 (47.8)	756 (58.4)		5 (26.3)	8 (42.1)	8 (20.0)
Reason for discontinuation							
Lack of efficacy	28 (7.1)*	29 (15.6)	216 (16.7)		0 (0.0)	3 (15.8)	0 (0.0)
Sponsor decision	34 (8.7)	14 (7.5)	72 (5.6)		0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	25 (6.4)	10 (5.4)	67 (5.2)		0 (0.0)	0 (0.0)	0 (0.0)
Parent/caregiver decision	18 (4.6)	10 (5.4)	47 (3.6)		0 (0.0)	0 (0.0)	0 (0.0)
Subject decision	17 (4.3)	7 (3.8)	113 (8.7)		0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	9 (2.3)	10 (5.4)	63 (4.9)		0 (0.0)	2 (10.5)	0 (0.0)
Lost to follow-up	10 (2.5)	3 (1.6)	76 (5.9)		2 (10.5)	0 (0.0)	2 (5.0)
Entry criteria exclusion	9 (2.3)	3 (1.6)	15 (1.2)		0 (0.0)	0 (0.0)	0 (0.0)
Physician decision	9 (2.3)	3 (1.6)	37 (2.9)		0 (0.0)	0 (0.0)	0 (0.0)
Satisfactory response	1 (0.3)	0 (0.0)	18 (1.4)		0 (0.0)	0 (0.0)	0 (0.0)
Relapse	0 (0.0)	0 (0.0)	32 (2.5)		0 (0.0)	0 (0.0)	0 (0.0)
Inability to adhere to visit schedule	0 (0.0)	0 (0.0)	0 (0.0)		1 (5.3)	1 (5.3)	1 (2.5)
Family had to leave country	0 (0.0)	0 (0.0)	0 (0.0)		2 (10.5)	0 (0.00)	2 (5.0)
Unable to find transportation	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	1 (5.3)	0 (0.0)
No reason given	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	1 (5.3)	3 (7.5)

* $p < 0.01$.

ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine treatment group; PBO, placebo treatment group.

External data in 4–5-year-old patients. In the External Placebo-controlled Dataset, the percentage of patients completing the study was higher in the atomoxetine treatment group than in the placebo treatment group (73.7% vs. 57.9%) (Table 4). More placebo-treated patients discontinued because of lack of efficacy (15.8%) and AEs (10.5%) compared with atomoxetine-treated patients (0% for both). In the External Overall Dataset, the percentage of patients completing the studies was high (80.0%). The most common primary reasons for discontinuation were being lost to follow-up and family having to leave the country (5.0% each). No atomoxetine-treated patient discontinued the studies because of AEs. In the Ghuman et al. study (2009) of 12 patients who started treatment with atomoxetine and had at least one medication follow-up visit, four patients dropped out before completing the dose maintenance and observation phase, one patient was terminated from the study after the second titration visit because of flare-up of his bronchial asthma and treatment with an albuterol inhaler, one patient was lost to follow-up after the first titration visit, and two patients completed the titration phase but dropped out prior to entering the dose maintenance and observation phase, because the parents declined further study participation.

Comparison across age group. Disposition was generally similar between patients 6–7 years of age in the Lilly atomoxetine clinical trial database and patients 4–5 years of age in the external atomoxetine studies. Lack of efficacy was a common reason for discontinuation in placebo-treated patients for both 6–7-year-old patients and 4–5-year-old patients, and it was more common for placebo-treated patients than for atomoxetine-treated patients in both age groups. The proportion of atomoxetine-treated patients who discontinued because of an AE was low in both age groups; in the external studies of 4–5-year-old patients, no atomoxetine-treated patients discontinued because of an AE.

In the overall analysis populations, the percentage of atomoxetine-treated patients who completed the studies was lower in Lilly trials of 6–7-year-old patients compared with the external studies in 4–5-year-old patients (41.6% versus 80.0%) (Table 4).

Efficacy

Lilly data in 6–7-year-old patients. For the mean change from baseline to LOCF endpoint in ADHD-RS-IV-Parent:Inv total score as well as hyperactive/impulsive and inattentive subscores for the Lilly Pediatric Placebo-controlled ADHD Analysis Group, there was a statistically significant greater mean improvement with atomoxetine treatment compared with placebo in 6–7-year-old patients at endpoint (Table 5).

Results of the sensitivity analyses were consistent with and support the primary and secondary analyses in 6–7-year-old patients.

External data in 5-year-old patients. For the mean change from baseline to LOCF endpoint in ADHD-RS-IV-Parent:Inv total score and inattentive subscore for the External Placebo-controlled Dataset, there was a statistically significant greater mean improvement with atomoxetine treatment compared with placebo in 5-year-old patients at endpoint (Table 5).

Comparison across age groups. In both the 6–7-year-old and 5-year-old age groups, atomoxetine treatment was associated with a greater mean improvement on the ADHD-RS-IV-Parent:Inv total score, inattentive subscore, and hyperactive/impulsive subscore compared with placebo. The overall magnitude of the treatment difference (treatment effect: –10.16 and –7.42) was greater in the Lilly Pediatric Placebo-controlled ADHD Analysis Group than in the External Placebo-controlled Group (Table 5).

TABLE 5. MEAN CHANGE FROM BASELINE TO LAST OBSERVATION CARRIED FORWARD ENDPOINT—ADHDRS-IV-PARENT:INV

	Lilly Pediatric Placebo-controlled ADHD Analysis Group (6–7-year-old patients)		External Placebo-controlled Dataset (5-year-old patients)	
	ATX n = 384	PBO n = 181	ATX n = 18	PBO n = 19
ADHDRS-IV-Parent:Inv, mean change (SD)/p value				
Total score	–13.87 (12.79)	–3.71 (9.88)	–12.89 (9.07)	–5.47 (8.09)
		$p < 0.001$		$p = 0.023$
Hyperactivity/Impulsive subscore	–6.86 (6.83)	–1.73 (5.43)	–6.33 (6.12)	–3.16 (4.89)
		$p < 0.001$		$p = 0.073$
Inattentive subscore	–7.01 (6.85)	–1.98 (5.31)	–6.56 (4.23)	–2.32 (4.94)
		$p < 0.001$		$p = 0.006$

p value from ANCOVA model: change = treatment + study center + baseline value.

ATX, atomoxetine treatment group; PBO, placebo treatment group.

Safety: AEs

Lilly data in 6–7-year-old patients. The common TEAEs reported in at least 10% of atomoxetine-treated patients in the Lilly Pediatric Overall ADHD Analysis Group included decreased appetite, headache, abdominal pain, vomiting, nasopharyngitis, cough, pyrexia, nausea, and somnolence (Table 6).

Overall, the TEAEs that occurred in atomoxetine-treated 6-year-old patients were similar to those experienced by atomoxetine-treated 6–7-year-old patients. The common TEAEs reported, which occurred in at least 10% of atomoxetine-treated 6–7-year-old patients, were also observed in at least 10% of atomoxetine-treated 6–7-year-old patients with a body weight <25.1 kg. The only exception was nausea, which fell below the 10% cutoff in patients with low body weight.

Sensitivity analyses. The same TEAEs as reported were identified in at least 10% of atomoxetine-treated 6-year-old patients.

External data in 4–5-year-old patients. The analyses of TEAEs for the External Overall Dataset only included the Kratochvil

TABLE 6. SPONTANEOUSLY REPORTED TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥5% OF ATOMOXETINE-TREATED PATIENTS

	Lilly Pediatric Overall ADHD Analysis Group (6–7-year-old patients)	Lilly Pediatric Overall ADHD Analysis Subgroup (6-year-old patients)	Lilly Pediatric Overall ADHD Analysis Subgroup (6–7-year-old patients, <25.1 kg)	External Overall Dataset (5-year-old patients) ^a
Preferred term TEAE	ATX n = 1294	ATX n = 444	ATX n = 603	ATX n = 29
Patients with ≥1 TEAE	1037 (80.1)	354 (79.7)	484 (80.3)	28 (96.6)
Decreased appetite	329 (25.4)	118 (26.6)	132 (21.9)	13 (44.8)
Headache	295 (22.8)	92 (20.7)	137 (22.7)	2 (6.9)
Abdominal pain	267 (20.6)	88 (19.8)	113 (18.7)	3 (10.3) ^b
Vomiting	226 (17.5)	76 (17.1)	99 (16.4)	4 (13.8)
Nasopharyngitis	180 (13.9)	56 (12.6)	85 (14.1)	1 (3.4)
Cough	172 (13.3)	65 (14.6)	78 (12.9)	0
Pyrexia	162 (12.5)	62 (14.0)	69 (11.4)	1 (3.4)
Nausea	157 (12.1)	50 (11.3)	57 (9.5)	2 (6.9)
Somnolence	138 (10.7)	48 (10.8)	71 (11.8)	2 (6.9)
Upper respiratory tract infection	109 (8.4)	39 (8.8)	58 (9.6)	2 (6.9)
Irritability	107 (8.3)	33 (7.4)	50 (8.3)	9 (31.0)
Fatigue	101 (7.8)	34 (7.7)	34 (5.6)	5 (17.2)
Oropharyngeal pain	89 (6.9)	23 (5.2)	41 (6.8)	0
Influenza	82 (6.3)	30 (6.8)	38 (6.3)	0
Diarrhea	75 (5.8)	30 (6.8)	36 (6.0)	1 (3.4)
Constipation	71 (5.5)	23 (5.2)	39 (6.5)	0
Nasal congestion	60 (4.6)	19 (4.3)	33 (5.5)	0
Sedation	18 (1.4)	7 (1.6)	8 (1.3)	5 (17.2)
Thirst	10 (0.8)	6 (1.4)	5 (0.8)	3 (10.3)
Altered mood	6 (0.5)	3 (0.7)	4 (0.7)	2 (6.9)
Tearfulness	18 (1.4)	5 (1.1)	7 (1.2)	2 (6.9)
Emotional disorder	20 (1.5)	5 (1.1)	4 (0.7)	2 (6.9)
Mood swings	36 (2.8)	6 (1.4)	11 (1.8)	2 (6.9)

^aExcludes Ghuman et al. 2009 study that solicited adverse events.

^bSpecifically, upper abdominal pain.

ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine treatment group; TEAE, treatment-emergent adverse event.

et al. studies that collected TEAEs via spontaneous reporting (Kra-tochvil et al. 2007, 2011). The common TEAEs reported in at least 10% of atomoxetine-treated patients 5 years of age were decreased appetite, irritability, sedation, fatigue, vomiting, thirst, and upper abdominal pain (Table 6).

Comparison across age groups. Table 6 displays TEAEs occurring in at least 5% of atomoxetine-treated patients across all overall analysis populations. Decreased appetite was very common (>10%) in atomoxetine-treated patients in all analysis populations, and was reported in a higher percentage of patients 5 years of age in the external studies than in patients 6–7 years of age in the Lilly clinical trial database (44.8% vs. 25.4%). Similarly, a higher percentage of 5-year-old patients experienced irritability compared with 6–7-year-old patients (31.0% vs. 8.3%). Mood altered, tearfulness, emotional disorder, and mood swings were also reported more frequently in 5-year-old patients than in 6–7-year-old patients. In addition to having these mood-related AEs, atomoxetine-treated patients also demonstrated fatigue, sedation, and thirst at least twice as frequently in the 5-year-old group than in the 6–7-year-old group. Conversely, headache, abdominal pain, nasopharyngitis, cough, pyrexia, oropharyngeal pain, influenza, constipation, and nasal congestion were reported more than twice as infrequently in atomoxetine-treated 5-year-old patients than in atomoxetine-treated 6–7-year-old patients (Table 6).

Safety: Mean change in vital signs and weight

Lilly data in 6–7-year-old patients. In the Lilly Pediatric Overall ADHD Analysis Group, mean increases in blood pressure and pulse were observed with atomoxetine treatment and were of a similar magnitude to the placebo-controlled analysis. There was a mean increase (+2.3 kg) in weight in atomoxetine-treated patients in the Lilly Pediatric Overall ADHD Analysis Group (Table 7).

External data in 4–5-year-old patients. In the External Overall Dataset, mean increases from baseline with atomoxetine treatment were observed for systolic blood pressure, diastolic blood pressure, and pulse. A mean decrease from baseline was observed in weight (–0.4 kg) (Table 7).

Safety: Categorical analyses of vital signs and weight

Lilly data in 6–7-year-old patients. In the Lilly Pediatric Overall ADHD Analysis Group, with the exception of weight, the proportion of patients who met the predefined threshold values for changes in vital signs with atomoxetine treatment was similar

to the placebo-controlled analysis. Fewer patients had weight decrease of at least 3.5% at endpoint in the Lilly Pediatric Overall ADHD Analysis Group compared with the Lilly Pediatric Placebo-controlled ADHD Analysis Group (15.3% vs. 22.2%).

External data in 4–5-year-old patients. In the External Overall Dataset, no atomoxetine-treated patient met the predefined criteria for categorical increases in diastolic blood pressure or systolic blood pressure at endpoint. One (2.6%) atomoxetine-treated patient met the categorical threshold for increase in pulse at endpoint. A total of 20.5% of patients met the threshold for decrease in weight at endpoint.

Comparison across age groups. The mean change from baseline to LOCF endpoint for vital signs and weight for all age groups in the overall analysis populations is shown in Table 7. In the categorical analyses, no atomoxetine-treated patients 4–5 years of age in the External Overall Dataset met the criteria for increased systolic or diastolic blood pressure, although this is not unexpected given the size of the analysis population. In comparison, approximately 7% of atomoxetine-treated patients 6–7 years of age in the Lilly Overall ADHD Analysis Group met the threshold for high systolic (7.1%) or diastolic (6.5%) blood pressure. A similar proportion of patients across all age groups met the threshold for increased pulse (~2–3%). The proportion of patients across all age groups that met the criteria for decreased weight ranged from ~11% to 21%.

Discussion

This efficacy and safety extrapolation analysis provided supplemental and comparative information regarding the use of atomoxetine in children <6 years of age as compared with children 6–7 years of age. There was a difference in the median duration of exposure in the overall analyses between 6–7-year-old patients in the Lilly clinical trial data (15 weeks) and the 4–5-year-old patients in the external studies (~8 weeks).

A majority of patients were male and white, which is not unexpected for an ADHD population, and is consistent with studies of atomoxetine in patients 6–18 years of age (Donnelly et al. 2009). In the overall analysis populations, the percentage of atomoxetine-treated patients who completed the studies was lower in Lilly trials of 6–7-year-old patients than in the external studies in 4–5-year-old patients. This difference may be the result of a number of factors, including the number of long-term studies that ran up to 8 years in

TABLE 7. MEAN CHANGE FROM BASELINE TO ENDPOINT FOR VITAL SIGNS AND WEIGHT

	Lilly Pediatric Overall ADHD Analysis Group (6–7-year-old patients) mean change (SD)	Lilly Pediatric Overall ADHD Analysis Subgroup (6-year-old patients) mean change (SD)	Lilly Pediatric Overall ADHD Analysis Subgroup (6–7-year-old patients, <25.1 kg) mean change (SD)	External Overall Dataset (4–5-year-old patients) mean change (SD)
	ATX n = 1294	ATX n = 444	ATX n = 603	ATX n = 40
Pulse (bpm)	+4.70 (13.70)	+4.73 (14.44)	+4.45 (14.20)	+1.22 (12.70)
SBP (mmHg)	+3.06 (10.84)	+2.76 (10.98)	+3.04 (10.64)	+1.09 (6.69)
DBP (mmHg)	+2.92 (9.71)	+2.89 (9.96)	+2.94 (9.96)	+2.36 (6.45)
Weight (kg)	+2.32 (6.92)	+1.91 (5.47)	+2.42 (5.68)	–0.40 (0.67)

ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine treatment group; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure.

duration, contributing to the Lilly clinical trial database, as well as other differences (e.g., number of study sites, investigator-patient relationship, and total number of patients within sites).

Acute atomoxetine treatment was effective in improving core ADHD symptoms in both the 6–7-year-old patients and 5-year-old patients. The treatment effect in the 5-year-old patients was smaller than that observed in the 6–7-year-old patients. The overall magnitude of the treatment difference was greater in the Lilly Pediatric Placebo-controlled ADHD Analysis Group than in the External Placebo-controlled Group.

With regard to the safety extrapolation analyses, decreased appetite was the most common TEAE in atomoxetine-treated patients in both 6–7-year-old patients and 5-year-old patients, and it was observed with a higher incidence in 5-year-old patients. Irritability was observed at a much higher rate in 5-year-old patients than in 6–7-year-old patients (36.8% vs. 3.6%). In addition, other mood-related TEAEs, such as altered mood, tearfulness, emotional disorder, and mood swings were observed in a higher percentage of 5-year-old patients (6.9% each) than in 6–7-year-old patients (<3%) based on the overall analysis populations. These trends were described by the external investigators in their publications of the data (Kratochvil et al. 2007; Ghuman et al. 2009; Kratochvil et al. 2011), and they noted that the results of studies with selective serotonin reuptake inhibitors (Safer and Zito 2006) and stimulants (Greenhill et al. 2006) suggest that younger children may be more prone to mood-related side-effects than older children.

Other TEAEs with atomoxetine treatment that occurred more frequently (twice or more often) in 5-year-old patients than in 6–7-year-old patients included fatigue and sedation. Abdominal pain was reported half as frequently in 5-year-old patients than in 6–7-year-old patients, and this difference was likely attributable, at least in part, to the difference in median duration of exposure between the Lilly Pediatric Overall ADHD Analysis Group and the External Overall Dataset (106.00 days vs. 60.50 days). The common TEAEs that occurred in at least 10% of atomoxetine-treated 6–7-year-old patients regardless of weight were also observed in at least 10% of atomoxetine-treated 6–7-year-old patients with a body weight <25.1 kg, with the exception of nausea, which fell below the 10% cutoff in the low-body-weight patients.

There was a mean increase in weight in atomoxetine-treated patients in the Lilly Pediatric Overall ADHD Analysis Group. An increase in weight would be expected in this population given the inclusion of longer-term studies (versus placebo-controlled studies that were of shorter duration) and natural growth patterns in children over time. In addition, this is consistent with findings in a previous study that the initially observed decreased weight gain tends to recover with long-term exposure to atomoxetine (Wernicke and Kratochvil 2002). In the overall analysis group containing 4–5-year-old patients from the external studies, a mean decrease in weight was observed at endpoint. This difference between 4–5-year-old patients in the External Overall Dataset and 6–7-year-old patients in the Lilly Pediatric Overall ADHD Analysis Group is likely attributable to the difference in median duration of exposure between the analysis groups (60.50 days vs. 106.00 days). Increases in blood pressure and heart rate are known responses to atomoxetine, and weight decreases have been previously observed with acute atomoxetine treatment (Garnock-Jones and Keating 2009). Changes in vital signs and body weight in 4–5-year-old patients and 6–7-year-old patients were in line with what is known for atomoxetine (Wernicke and Kratochvil 2002; Adler et al. 2006) but appeared to be less pronounced in the 4–5-year-old patients.

This could be attributable to the smaller sample size and shorter duration of treatment in the 4–5-year-old patients.

With regard to categorical analyses, no atomoxetine-treated patient 4–5 years of age in the External Overall Dataset met the criteria for increased systolic or diastolic blood pressure, although this was not unexpected, given the size of the analysis population. Sensitivity analyses, conducted in 6-year-olds and in 6–7-year-old patients with a body weight <25.1 kg, confirmed the results of the safety analyses in all 6–7-year-old patients, suggesting that comparing the external data in younger children to Lilly data in 6–7-year-old patients was a reasonable approach for the extrapolation exercise.

Based on these analyses in 4–5-year-old patients and 6–7-year-old patients, it could be expected that a 4–5-year-old patient with ADHD who is administered atomoxetine at a dose in line with the label recommendations (dosing based on body weight) could benefit from an improvement in ADHD symptoms after acute treatment, possibly to a lesser extent than an older child. The Preschool ADHD Treatment Study (PATS) that examined immediate-release methylphenidate in the treatment of ADHD also determined that preschoolers with ADHD did benefit from treatment with methylphenidate (Greenhill et al. 2006). However, the effect sizes for methylphenidate in the PATS study were smaller than those reported in the NIMH Multimodal Treatment Study of ADHD (MTA) (Greenhill et al. 2001) for school-aged children, implying that preschoolers do not benefit from methylphenidate as much as their school-age counterparts. The PATS study reported that this may have been attributed to the fact that the severity of ADHD symptoms in the preschool children in the study was greater than in the school-aged children recruited for the MTA study (Greenhill et al. 2006). In the analyses reported here, the baseline severity of ADHD symptoms in the 5-year-old patients was not greater than the symptoms of the 6–7-year old patients; therefore, the results may not be attributed to severity of patient symptoms. The AE profile was generally similar for the 4–5-year-old patients and the 6–7-year-old patients, although there was some evidence of frequency differences with regard to decreased appetite, mood-related events, fatigue, and sedation (higher in 5-year-old patients) and abdominal pain (lower in 5-year-old patients). It would be anticipated that changes in vital signs and weight would be similar between the two age groups.

Limitations

Some limitations to this analysis need to be considered. As this was an extrapolation analysis, direct statistical comparisons between the age groups could not be made. The external dataset had a smaller sample size and included studies of a shorter duration, in comparison with the Lilly clinical trial data. It is possible that the differences in incidence may be greatly affected by this small sample size. Lastly, it is possible that the 5-year-old patients were enrolled into the study because the parent, teacher, and/or clinicians may have identified them as having a more severe form of the disorder. Although a theoretical limitation, the mean ADHD scores at baseline do not suggest that 5-year-old patients had more severe ADHD.

Conclusions

Although limited by the small total sample size in the 4–5-year-old patients, these analyses suggest that 5-year-old patients with ADHD may respond similarly to atomoxetine as do 6–7-year-old patients, but possibly to a lesser extent and with some AEs

occurring at a higher rate in 4–5-year-old patients. There is lack of data to suggest if combining atomoxetine with psychosocial interventions or parent- and/or teacher-administered behavior therapy is more efficacious in preschool-age children. Hence, to the extent that there is a perceived need to expand ADHD medication treatment indications to include children <6 years of age, future studies comparing atomoxetine with other medications and psychosocial treatments, as well as studies examining combining treatments, may be useful.

Clinical Significance

This extrapolation analysis qualitatively compared the efficacy and safety profile of atomoxetine from Lilly clinical trial data in 6–7-year-old patients with ADHD with that of published external data in 4–5-year-old patients with ADHD. Based on these analyses, it could be expected that a 4–5-year-old patient with ADHD who is administered atomoxetine could benefit from an improvement in ADHD symptoms after acute treatment, but possibly to a lesser extent than an older child. Tolerability could be expected to be generally similar with some AEs (e.g., mood-related ones) possibly occurring at a higher rate.

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