Adverse Events of Atomoxetine in a Double-Blind Placebo-Controlled Study in Children with Autism

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Abstract

Objective: Attention-deficit/hyperactivity disorder (ADHD) symptoms, including inattention and over activity, occur in approximately one-third of children with autism spectrum disorder (ASD). We describe the rate and duration of adverse events in a randomized controlled trial of atomoxetine (ATX) and parent training (PT) for ADHD symptoms and noncompliance in children with ASD.

Methods: We conducted a 10-week, double-blind, 2×2 trial of ATX and PT with 128 children (ages 5–14) randomized to ATX alone, ATX+PT, placebo+PT, or placebo alone. For 6 weeks, ATX (or placebo) doses were clinically adjusted to a maximum of 1.8 mg/(kg·day) and maintained for an additional 4 weeks. An average of seven PT sessions were conducted in the two PT arms. Adverse events (AEs) were assessed through parent ratings of common symptoms on a seven-point Likert severity scale and through direct interviews with study medical staff.

Results: ATX was associated with decreased appetite and fatigue, but was otherwise well tolerated. Most reported AEs lasted 4 weeks or less. Unlike reports with typically developing (TD) children, there were no concerns with QTc changes or suicidal ideation.

Conclusions: This study extends the findings of previous studies of ATX in ASD by documenting that the type of AEs was similar to that of TD children, with no significant safety concerns.

Keywords: atomoxetine, parent training, ADHD, adverse events, autism spectrum disorder

Introduction

THE RISK FOR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) in children with autism spectrum disorder (ASD) is well established, with approximately one-third of these children displaying significant problems with inattention and/or overactivity (Leyfer et al. 2006; Rosenberg et al. 2011). The symptoms of ADHD are often difficult to manage in ASD and contribute to poor functioning at home, at school, and in the community (Sikora et al. 2012). For the past 15 years, studies of traditional pharmacological treatment, such as psychostimulant medication, have reported response rates of around 50%, a rate lower than the 70%–80% response among typically developing (TD) children with ADHD (Handen et al. 2011; Antshel et al. 2013; Benvenuto et al. 2013). In addition, children with ASD may be more prone to psychostimulant drug side effects than TD children (Handen et al. 2000; Aman et al.

2005). Frequent side effects include poor appetite, irritability, abdominal pain, and motor tics. There have been reports of cardiovascular events in children with the use of stimulants (Jiao et al. 2009; Cooper et al. 2011). However, recent guidelines published by the FDA indicate a relatively low risk of such events (FDA Drug Safety Communication 2011).

Alternatives to psychostimulants include the alpha-2 agonists (guanfacine and clonidine) in immediate release and long-acting forms as well as atomoxetine (ATX). A recent randomized clinical trial (RCT) of guanfacine in 80 children with ASD found overall response rates of around 50%, similar to psychostimulants (Scahill et al. 2015). The most common side effects included drowsiness, fatigue, and decreased appetite. A 2014 review of the literature on the use of ATX in children with ASD and developmental disabilities identified 11 studies, only two of which were placebo-controlled RCTs (Aman et al. 2014). Owing to the paucity of RCTs,

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it was difficult to judge the magnitude of reported gains. The largest controlled trial ($N=102$) had an effect size of 1.0, but only about 25% of the sample were determined to be responders, based upon the Clinical Global Impressions Improvement subscale (Harftekamp et al. 2012). A smaller RCT involving a cross-over design with 16 subjects found nearer a 50% response rate (Arnold et al. 2006). The most commonly reported AEs across all studies were appetite decrease, nausea, and irritability. Similar to psychostimulants, irritability appeared to occur more frequently in persons with ASD and/or intellectual disability than in TD individuals. No other differences in the types of reported side effects were noted between children with ASD and TD children.

A recent meta-analysis of ATX studies in TD children and adolescents with ADHD found fatigue, anorexia, gastrointestinal symptoms, and central nervous system-related AEs to be significantly more frequent among those taking ATX. However, the rate of serious AEs, such as suicidal ideation, aggression, and depression, was not statistically different between placebo and ATX (Schwartz and Correl 2014). The potential advantage of ATX over stimulants include smoother effect over time, reduced rebound irritability, less sleep impairment, fewer concerns with growth retardation, and decreased exacerbation of tics. Similar to alpha 2 agonists, ATX may reduce anxiety but could cause fatigue. The potential disadvantages of ATX include longer half-life with its potential for longer lasting side effects, slowing of growth (but less than with stimulants), and gastrointestinal (GI) side effects (Aman et al. 2014).

Recently, our group reported findings from an RCT of ATX and parent training (PT) in 128 children with ASD and ADHD (Handen et al. 2015; Smith et al. 2016). The RCT started with a 10-week, double-blind, placebo-controlled acute trial of ATX and PT. Treatment responders subsequently entered a 24-week extension trial. This article offers a detailed analysis of the AE results from this RCT to address the following questions: (1) How did the rate, severity, and duration of reported AEs compare between ATX and placebo? (2) Did the addition of PT have an impact on AE reporting? and (3) What AEs were reported for children remaining on ATX for the 24-week extension trial?

Methods

The RCT involved a 10-week, double-blind, placebo-controlled trial of ATX and PT (Handen et al. 2015). Subjects were randomly assigned to one of four treatment arms: (1) ATX plus PT, (2) ATX alone, (3) PT plus placebo, and (4) placebo alone. After determining study eligibility and obtaining baseline assessment measures, subjects were assessed weekly during weeks 1–6 and then every other week until the week 10 visit (study visits included assessing AEs and obtaining vital signs). ATX was titrated for a 6-week period to optimal effect, with dose capped at 1.8 mg/(kg·day), and then held steady for 4 weeks. Families assigned to PT met weekly with a clinician for 1 hour. At week 10, responders were offered the option of continuing in their assigned condition for a 24-week extension and were seen monthly for monitoring. Subjects who had been randomly assigned to receive PT (either in combination with ATX or with placebo) continued to be seen for monthly PT sessions (Smith et al. 2016).

Subjects

Inclusion criteria included (1) age 5.0–14.11 years, (2) diagnosis of autistic disorder, pervasive developmental disorder or Asperger's disorder [based on the Autism Diagnostic Interview–Revised

(Rutter et al. 2003)] and expert clinical evaluation using a *Diagnostic and Statistical Manual of Mental Disorders–4th edition–Text Revision* (DSM-IV-TR) Interview [DSM-IV-TR (2000) 4th ed., text rev.], (3) mental age >24 months [based upon the Stanford–Binet 5th Edition (Roid 2003) or Mullen Scales of Early Learning (Mullen 1989)], (4) mean item score of >1.50 points on both the parent and teacher SNAP ADHD scale (Bussing et al. 2008), and (5) a CGI-severity score ≥ 4 for ADHD symptoms (Guy 1976). Exclusion criteria included (1) use of other psychotropic drugs, (2) more than one anticonvulsant for seizure control (or changing dose or having a seizure within the past 6 months), (3) Rett's disorder, childhood disintegrative disorder, lifetime diagnosis of schizophrenia, other psychotic disorder, bipolar disorder, or current diagnosis of major depression or obsessive compulsive disorder (OCD), (4) significant medical conditions (e.g., heart, renal, or pulmonary disease) or significant abnormalities on routine laboratory tests and EKG, (5) a prior adequate trial of ATX (minimum 4 weeks, with at least 1 week at >1.0 mg/kg) within the past 2 years, (6) regular use of beta adrenergic blocking agents or asthma medicine such as albuterol (because of potential for drug interaction), and (7) prior involvement in a highly structured PT program.

Outcome measures

The following measures related to potential AEs were obtained.

Side effects checklist. At each visit, parents completed a questionnaire on the presence, frequency, and severity of the 16 most common side effects for ATX, according to the package insert (Eli Lilly, 2002). Severity was rated on a seven-point Likert scale from “0” (not a concern) to 6 (severe).

Side effects review. Caregivers and subjects were asked about possible side effects during each visit by study medical staff. Side effects were tracked on a form that included the presence of an AE, date first noted (or date ended), and severity. Staff also indicated the possible relationship to the study medication. In addition, suicidal ideation was assessed at each visit.

Concomitant medications. This form was completed by staff at each visit, providing information on all prescription and nonprescription medications, doses, and recent dose changes.

Vital signs/laboratory. Blood pressure, pulse, height, and weight were obtained at each clinic visit. Blood pressure and pulse were assessed with subjects seated after 2 minutes at rest. Weight and height were measured twice (with cold weather clothes and shoes removed), using the mean of the two measurements. Temperature was taken only if clinically indicated. An EKG and blood work (complete blood count [CBC] and liver function tests) were obtained at baseline (required) and at week 10 (based upon subject cooperation).

Statistical analyses

All randomized subjects were included in the analysis of AEs based on the intention-to-treat principle. We tabulated the number and percentage of subjects who experienced AEs in each randomized treatment group. The duration of an AE was calculated from the initiation of the AE to the time the AE resolved, or the end of the acute phase study (including early exit). For subjects who exited the acute trial early (before week 10), the last postbaseline side effect severity was considered as the end-point (week 10)

TABLE 1. SUBJECT DEMOGRAPHICS

Variable	ATX+PT (N=32)	ATX (N=32)	Placebo+PT (N=32)	Placebo (N=32)	p Value comparing groups
Age (in years)	8.0 (1.9)	8.6 (2.3)	7.7 (1.5)	8.2 (2.4)	0.29
IQ (standard score)	83.3 (21.6)	78.7 (25.9)	77.9 (25.7)	86.7 (23.7)	0.43
Percentage of autistic disorder	37.5	43.8	43.8	53.1	0.70
Percentage of Asperger's	15.6	21.9	15.6	12.5	0.84
Percentage of PDD-NOS	46.9	34.4	40.6	34.3	0.73
Percentage of male	96.9	81.3	84.4	78.1	0.13
Percentage of Caucasian	87.5	84.4	81.3	75.0	0.67
Percentage of African American	3.1	6.3	6.3	15.6	
Percentage of other	9.4	9.3	12.4	9.4	

ATX, atomoxetine; PDD-NOS, pervasive developmental disorder-not otherwise specified; PT, parent training.

severity level. All comparisons among treatment groups were exploratory without multiple comparison adjustment. The chi-square test was used for categorical variables (yes or no for occurrence of side effect or AE) and *t*-test for continuous variables with proper data transformation as needed. Sensitivity analyses were conducted to ensure that the results reported here were robust to the selection of the statistical procedure and method of data transformation.

Results

Subject characteristics

Two hundred potential subjects were screened for the acute 10-week trial with 128 (64%) randomized to one of four treatments (32 per condition) (Arnold et al. 2006). Twenty-nine subjects withdrew before the end of the 10-week acute trial. A total of 25 (19.5%) subjects were taking melatonin for sleep (ATX+PT, 7; ATX alone, 8; PT+placebo, 6; placebo alone, 4) and 1 subject was taking an anti-convulsant (stable dose throughout) for treatment of a seizure disorder.

Fifty-eight (45.3%) subjects had received prior treatment for ADHD. Of these, 49 had been prescribed one or more stimulants and 13 had been treated with alpha-2 agonists or complementary and alternative interventions. Table 1 summarizes subject demographics by treatment group in the acute trial. There were no significant differences between the groups on any of the measures. The sample had a mean age of 8.1 (± 2.1) years and mean full-scale IQ of 81.7 (± 24.3). Males comprised 85% of the sample; 82% were Caucasian, 8% African American, 8% multiracial, and 2% other. Final ATX doses ranged from 0.3 mg to 1.8 mg/(kg·day). The average ATX doses at the end of the 10-week acute trial were 49.8 mg (± 23.3) for the ATX arm, 40.0 mg (± 18.4) for the ATX plus PT arm, 42.4 mg (± 14.3) for the placebo plus PT arm, and 45.6 mg (± 20.3) for the placebo arm.

Side effects checklist

Table 2 summarizes the frequency of subjects whose caregivers reported a severity level of ≥ 2 (mild) at baseline and week 10 on the

TABLE 2. SIDE EFFECTS REVIEW (PARENT COMPLETED)—SEVERITY SUMMARIES

Side effects review	Baseline		Week 10	
	ATX	Placebo	ATX	Placebo
N ^a	64	63	63	63
Mean severity score, mean (SD) ^b	0.61 (0.49)	0.67 (0.46)	0.38 (0.47)	0.44 (0.44)
Severity frequency, n (%)				
Upset stomach	9 (14.1)	7 (11.1)	7 (11.1)	7 (11.1)
Decreased appetite	8 (12.5)	10 (15.9)	11 (17.5)	7 (11.1)
Nausea/vomiting	5 (7.8)	1 (1.9)	5 (7.9)	3 (4.8)
Dizziness	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Tiredness/fatigue	14 (21.9)	10 (15.9)	14 (22.2)	7 (11.1)
Mood swings	29 (45.3)	34 (54.0)	16 (25.4)	19 (30.2)
Restless	41 (64.1)	51 (81.0)	19 (30.2)	34 (54.0)
Insomnia	17 (26.6)	13 (20.6)	10 (15.9)	9 (14.3)
Shaking/tremor	2 (3.1)	4 (6.3)	0 (0.0)	3 (4.8)
Headache	3 (4.7)	6 (9.5)	3 (4.8)	5 (7.9)
Tics ^c	7 (10.9)	4 (6.3)	3 (4.8)	4 (7.9)
Diarrhea	4 (6.3)	1 (1.6)	1 (1.6)	4 (6.3)
Constipation ^c	11 (17.2)	13 (20.6)	7 (11.1)	5 (7.9)
Dry mouth	1 (1.6)	2 (3.2)	3 (4.8)	4 (6.3)
Itchy rash	7 (10.9)	7 (11.1)	2 (3.2)	2 (3.2)
Racing heart	2 (3.1)	4 (6.3)	1 (1.6)	0 (0.0)

^aTotal sample size not equal to 128 because one subject from placebo+PT did not have any side effects review data.

^bBased on the average severity rating (0–6) for all 16 items combined.

^cAt baseline, severity frequency sample size decreased for tics and constipation because of missing item data (total N=126; ATX+PT n=32, ATX n=31, placebo+PT n=31, placebo n=32).

ATX, atomoxetine; PT, parent training.

TABLE 3. ADVERSE EVENTS DURING ACUTE PHASE

Adverse event	Any ATX n=64		Any Placebo n=64		Total n=128		p ^a
	n	%	n	%	n	%	
General—constitutional	33	52	34	53	67	52	0.5954
Fatigue	28	44	32	50	60	47	
Cardiac	4	6	3	5	7	5	
Hypertension	0	0	1	2	1	1	1.0000
Tachycardia	3	5	2	3	5	4	1.0000
Cardiac, NOS	1	2	0	0	1	1	1.0000
Gastrointestinal	49	77	43	67	92	72	1.0000
Appetite increase	0	0	1	2	1	1	
Appetite decrease	33	52	21	33	54	42	
Constipation	11	17	12	19	23	18	1.0000
Diarrhea	9	14	16	25	25	20	0.1803
Gastrointestinal, abdominal pains (excluding oral and throat)	13	20	6	9	19	15	0.1343
Nausea	19	30	14	22	33	26	0.4192
Vomiting	13	20	11	17	24	19	0.8213
Neurological	26	41	25	39	51	40	0.6865
Headache	18	28	15	23	33	26	
Behavioral	51	80	46	72	97	76	
Aggression	1	2	5	8	6	5	0.2076
Hyperactivity	13	20	10	16	23	18	0.6459
Irritability	10	16	5	8	15	12	0.1802
Difficulty initiating sleep	20	31	16	25	36	28	0.5557
Difficulty maintaining sleep	2	3	3	5	5	4	1.0000
Restlessness	8	13	11	17	19	15	0.6200

^aComparing any ATX versus any placebo.
ATX, atomoxetine.

16-item side effects checklist. The table combines data from the two ATX groups (ATX alone and ATX+PT) and the two placebo groups (placebo alone and placebo+PT). One subject had no side effect severity reported at all and one had no postbaseline report. No statistically significant differences in AEs were reported between the ATX and placebo groups at either baseline or week 10, with both groups reporting numerous side effects. The two most frequently reported side effects were mood swings and restlessness. GI symptoms were also commonly reported, including upset stomach, decreased appetite, and constipation. About one-fifth of families also reported that their children had difficulty sleeping. Overall, the number of subjects reporting severity scores of ≥ 2 decreased by more than 50% when comparing baseline and week 10 during the acute trial.

Adverse events review

Table 3 summarizes the data from the adverse events report, again with data for the two ATX and two placebo groups from the acute trial combined. The only significant differences between ATX and placebo were the higher rate of appetite decrease in ATX ($p < 0.04$). Although 77% of the two ATX groups reported GI complaints, so did 67% of the placebo groups. Similarly, differences were not detected for other previously reported concerns with ATX, such as fatigue or irritability. Despite previous reports of possible cardiac side effects, cardiac AEs were not detected. Also, although there is a black box warning for ATX, only a single subject reported suicidal ideation. Unblinding revealed that the subject had been on placebo.

To examine the potential impact of PT on the reported rate of AEs, we more closely examined reports of irritability. This AE had been identified in our 2014 ATX review as common, and possibly

more frequent, in children with ASD than in TD children (Aman et al. 2014). A composite category, called mood dysregulation, was created, combining the symptoms of irritability, crying, depressed mood, and labile mood. Table 4 shows that mood dysregulation was significantly less common in ATX+PT than in ATX and in the two PT groups than in the two no-PT groups. These findings suggest that PT may have mitigated mood dysregulation and that ATX did not exacerbate it.

Adverse events duration

Table 5 summarizes the average number of weeks that reported AEs lasted for each of the four treatment groups. Because this analysis was exploratory and involved a large number of comparisons, statistical tests of group differences were not performed. However, the addition of PT may have had a positive effect on some AEs. For example, the duration of difficulty initiating and

TABLE 4. RATE OF REPORTED MOOD DYSREGULATION

	ATX+PT	ATX	p
	n=32	n=32	
Mood dysregulation	9 (28%)	18 (56%)	0.04
	PT (ATX+PT; PT+placebo)	No PT (ATX; placebo)	p
	n=64	n=64	
Mood dysregulation	20 (31%)	36 (56%)	0.007

ATX, atomoxetine; PT, parent training.

TABLE 5. DURATION (MEAN NUMBER OF WEEKS) OF ADVERSE EVENTS BY TREATMENT GROUP

Adverse event	ATX+PT	ATX	PT+placebo	Placebo
Aggression				
Mean (SD)	3.00 (0)	NO ^a	1.79 (1.72)	4.14 (0.38)
Min–Max	3.00–3.00		0.57–3	3.86–4.57
Appetite decrease				
Mean (SD)	5.60 (3.45)	6.34 (3.71)	4.02 (2.64)	2.75 (2.27)
Min–Max	0.43–10.57	1.29–11.86	0.29–7.57	0.57–7.86
Appetite increase				
Mean (SD)	NO ^a	NO ^a	NO ^a	9.57 (0)
Min–Max				9.57–9.57
Cardiac, NOS				
Mean (SD)	0.14 (0)	NO ^a	NO ^a	NO ^a
Min–Max	0.14–0.14			
Constipation				
Mean (SD)	3.09 (3.62)	3.07 (2.72)	3.40 (3.43)	3.17 (3.82)
Min–Max	0.29–8.57	0.57–7.14	0.43–7.71	0.14–8.14
Diarrhea				
Mean (SD)	1.45 (2.72)	1.62 (1.15)	0.75 (1.55)	0.96 (0.83)
Min–Max	0.14–7	0.43–2.71	0.14–4.57	0.14–2.14
Difficulty initiating sleep				
Mean (SD)	3.80 (3.68)	5.73 (4.00)	1.84 (1.92)	3.71 (3.09)
Min–Max	0.29–10.86	0.29–11.00	0.43–6.29	0.43–9.71
Difficulty maintaining sleep				
Mean (SD)	3.00 (0)	10.71 (0)	2.29 (0)	3.50 (3.74)
Min–Max	3.00–3.00	10.71–10.71	2.29–2.29	0.86–6.14
Fatigue				
Mean (SD)	4.09 (2.75)	4.44 (3.55)	3.31 (2.82)	3.30 (3.34)
Min–Max	0.43–8.86	0.86–11.00	0.14–9.86	0.57–10.29
Gastrointestinal, abdominal pains (excluding oral and throat)				
Mean (SD)	1.12 (1.38)	2.29 (2.99)	1.80 (3.55)	0.43 (0)
Min–Max	0.14–3.86	0.29–6.43	0.14–8.14	0.43–0.43
Headache				
Mean (SD)	0.44 (0.45)	2.97 (2.58)	0.51 (0.51)	1.98 (3.47)
Min–Max	0.14–1.57	0.29–7.14	0.14–1.57	0.29–10.29
Hyperactivity				
Mean (SD)	4.19 (1.39)	5.9 (2.41)	7.69 (2.51)	3.18 (2.53)
Min–Max	3.00–5.71	1.86–9.71	3.00–9.86	1–5.71
Hypertension				
Mean (SD)	NO ^a	NO ^a	1.14 (0)	NO ^a
Min–Max			1.14–1.14	
Irritability				
Mean (SD)	2.43 (1.48)	3.18 (1.98)	3.24 (4.37)	2.14 (2.42)
Min–Max	0.71–3.29	1.00–5.57	0.57–8.29	0.43–3.86
Nausea				
Mean (SD)	2.14 (3.86)	2.37 (2.64)	0.43 (0.32)	1.14 (0.88)
Min–Max	0.14–11.14	0.14–8.43	0.14–1	0.14–2.29
Restlessness				
Mean (SD)	5.29 (4.06)	6.29 (4.58)	5.21 (4.94)	5.55 (3.66)
Min–Max	1.29–10.86	1.57–10.43	0.29–11.57	1.29–9.86
Tachycardia				
Mean (SD)	0.14 (0)	7.14 (0)	3.71 (0)	0.14 (0)
Min–Max	0.14–0.14	7.14–7.14	3.71–3.71	0.14–0.14
Vomiting				
Mean (SD)	0.60 (0.84)	1.98 (3.09)	0.45 (0.56)	0.97 (0.92)
Min–Max	0.14–2.29	0.14–8.43	0.14–1.57	0.14–2.43

^aNO: No event was observed.

ATX, atomoxetine; PT, parent training; SD, standard deviation.

maintaining asleep appears to be shortest for those in the ATX+PT (vs. ATX alone) and placebo+PT (vs. placebo alone) treatment arms. Similarly, the duration of headaches and complaints of vomiting may have been shorter in ATX+PT and placebo+PT than in ATX alone and placebo alone. Overall symptom duration was usually 4 weeks or less. The only symptoms that appeared to last longer were difficulty maintaining sleep and decreased appetite.

Study dropout rate

Of 29 subjects who exited the acute trial early, 15 left because of an AE. Of these, 10 were on placebo and left the study because of either increased behavioral difficulties or physical side effects (e.g., GI issues and insomnia). The remaining five subjects were on ATX, all of whom experienced increased behavioral difficulties or irritability, leading to study exit.

Laboratory results

No significant group differences were found on EKG, height, weight, and pulse. However, seven subjects were noted to have an increase in blood pressure of >20 mm Hg during the acute phase of the study. Six of the subjects were assigned to one of the two placebo groups and one was from the ATX alone group. No significant difference of changes in laboratory tests was noted between the placebo and ATX groups. Among all tests, 14.5% were abnormal for the two ATX groups and 14% for the two placebo groups.

Long-term results

Twenty-eight subjects who were ATX responders at the conclusion of the 10-week acute trial were enrolled in the 24-week double-blind extension. Of these, 12 had been in ATX+PT and 16 in ATX alone. Twenty-four (85%) continued taking ATX until the end of the trial. Of the four dropouts, two were lost to follow-up (one 2 weeks after the acute trial and one 30 weeks after the trial); one had increased moodiness 12 weeks after the acute trial; and one subject's parents decided to stop their child's medication (ending 20 weeks after the acute trial). Finally, two subjects exited early (12 weeks after the acute trial) because study funding had run out. Overall, long-term (≥6 months) use of ATX appeared to have been well tolerated, with 85% of ATX responders continuing until the end of the extension trial.

Discussion

This is the largest and most carefully quantified evaluation of AEs related to ATX treatment in children with ASD/ADHD. Overall, the types of side effects reported by children with ASD who were prescribed ATX appeared similar to those reported by TD children, although at a higher rate for some. The most commonly reported ATX AEs for both ATX and placebo groups were abdominal pain, nausea, and poor appetite, along with increased irritability, agitation, and headaches. Reports of cardiac side effects were not as frequent as in TD children, with AEs limited to tachycardia and increased blood pressure in seven subjects. QTc changes, which have been reported among TD children (as well as other serious CV effects), were not seen in this sample of children with ASD. Suicidal ideation was also rare (reported in only a single subject, who was later found to be taking placebo). The results indicate that ATX is generally safe in children with ASD, even at doses up to 1.8 mg/kg. In addition, PT was found to reduce the frequency of mood dysregulation such as irritability. Although irritability is often listed as an AE of ATX in the literature (Aman

et al. 2014), our data suggest that irritability occurred no more frequently with ATX than with placebo. Indeed, irritability seems to be a common comorbidity of ASD. In terms of symptom duration, issues related to both falling asleep and remaining asleep appeared to be of shorter duration if PT training was also provided, although this was not formally tested.

Despite no significant differences in the reported rate of side effects between our ATX and placebo groups, the rate of reported AEs in our ASD sample was considerably higher than among TD children. For example, almost 50% of participants reported feeling fatigue at some point during the 10-week trial, compared with 22% in a meta-analysis of TD children with ADHD alone (Schwartz and Correll 2014). Similarly, reports of constipation and diarrhea were quite high (77%), compared with frequency of only 22% in TD children. Although prior reports suggest that rates of AEs are higher in children with ASD than in TD children during controlled drug trials, it is also the case that this population has a larger incidence of GI issues, sleep issues, and behavioral concerns than TD peers. Therefore, these concerns may arise frequently, independent of whether a child with ASD has initiated a new medication regimen. In fact, the pretreatment reports of GI symptoms, sleep problems, and mood dysregulation for the children with ASD were higher than among TD children after having been treated with ATX. Therefore, the high baseline rate of problems, later considered AEs, necessitates a thorough pretreatment assessment of possible AEs to determine whether subsequent problematic reports reflect a true change in the base rate for the ASD population.

Duration of reported symptoms is not typically published in controlled trials, but provides insight into the course of any reported AE. Many side effects endorsed by parents were not transient, but persisted across a number of visits. This study's results suggest that most AEs lasted 4 weeks or less. With the exception of a single subject (who experienced sleep problems and had a delayed final study visit), no AEs lasted the entire 10 weeks of the acute trial. It is also possible that the duration of some of the AEs may have been an underestimate, as 29 subjects exited the study before the 10-week visit. Comparisons among groups were not possible because of this early drop-out rate.

Finally, families assigned to the ATX+PT group may have reported slightly fewer AEs than those assigned to ATX alone. For example, the rate of mood dysregulation was significantly lower among children whose parents received PT. Similarly, the duration of reported sleep problems, headaches, and vomiting may have been shorter for the ATX+PT group. The latter are areas where increased parental skills could have had an impact. Yet, it is also possible that the provision of individualized, weekly support to families led to fewer reports of side effects, independent of the material covered during sessions. Certainly, such support could have decreased parental anxiety and stress, increasing their ability to manage behavioral concerns in the home (Hollway et al. 2015). Finally, the fact that concomitant PT allowed a lower optimal dose of ATX may have spared some side effects based on dose.

Limitations

Although there was a planned, step-wise dose titration protocol, final doses were based on clinical response and side effects. Therefore, the effect of medication dose on side effects could not be easily examined (as subjects were taking different final doses). Although in one sense a limitation, this actually mirrors standard practice and may therefore be an overall strength of the study. Long-term AE data were only available on a smaller subset of

subjects who continued to take ATX. As only subjects who tolerated ATX and showed a favorable behavioral response remained in the 24-week extension, this was a selected group that may have experienced fewer AEs than would occur with random assignment to active drug for that length of time. Conversely, longer term use of ATX (or any drug, for that matter) is only likely in patients having beneficial clinical responses. Long-term use of ATX is likely if the benefits and response to the medication outweigh the side effects.

Conclusions

ATX treatment was associated with decreased appetite and fatigue, but was otherwise well tolerated in this group of children with ADHD and ASD. Most reported AEs lasted 4 weeks or less. Unlike reports with typically developing children, there were no concerns with QTc changes or suicidal ideation. This study extends the findings of previous studies of ATX in ASD by documenting that the type of AEs was similar to that of typically developing children, with no significant safety concerns.

Clinical Significance

Overall, ATX was well tolerated by children with ASD. The study withdrawal rate during the acute trial was not different with ATX than placebo. Consistent with TD children, the most commonly reported AEs were fatigue, poor appetite, and poor sleep. There were no concerns with QTc changes or suicidal ideation. Those continuing on ATX for 24 weeks also tolerated the medication with few significant AEs. Overall, the rate of AEs in children with ASD was higher than among TD children. However, it should also be noted that there is a high base rate of behaviors, such as mood dysregulation, sleep, and GI issues. Therefore, the practitioner should carefully note the rate of any such concerns before initiating medication. In addition, the practitioner may be able to provide education and support to address emerging or worsening AEs, potentially mitigating these symptoms.

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