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Research Article

ATOMOXETINE TREATMENT IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND COMORBID SOCIAL ANXIETY DISORDER

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Background: *To evaluate the effect of atomoxetine (ATX) on attention-deficit/hyperactivity disorder (ADHD) and comorbid social anxiety disorder in adults.* **Methods:** *Randomized, double-blind, placebo-controlled, conducted in adults with ADHD and social anxiety disorder. Patients received 40–100 mg ATX (n = 224) or placebo (n = 218) for 14 weeks following a 2-week placebo lead-in period. Efficacy measures included the Conners' Adult ADHD Rating Scale: Investigator-Rated: Screening Version (CAARS:Inv:SV), Liebowitz Social Anxiety Scale (LSAS), Clinical Global Impression-Overall-Severity (CGI-O-S), State-Trait Anxiety Inventory (STAI), Social Adjustment Scale-Self Report (SAS), and Adult ADHD Quality of Life Scale-29 (AAQoL). Safety and tolerability were also assessed.* **Results:** *ATX mean change (−8.7 ± 10.0) from baseline (29.6 ± 10.4) on CAARS:Inv:SV Total ADHD Symptoms score was significantly greater than placebo mean change (−5.6 ± 10.2) from baseline (31.2 ± 9.4; P < .001). ATX mean change (−22.9 ± 25.3) from baseline (85.3 ± 23.6) on LSAS Total score was significant compared to placebo mean change (−14.4 ± 20.3) from baseline (82.1 ± 21.3; P < .001). The visit-wise analysis revealed greater improvement on the CAARS:Inv:SV Total ADHD Symptoms score and LSAS Total score for ATX at every time point throughout the study (P values ≤ .012). Mean changes in CGI-O-S, STAI-Trait Anxiety scores, and AAQoL Total score were significantly greater for ATX compared to placebo. Mean change for both groups on STAI-State Anxiety scores was comparable. Improvement on SAS for ATX compared to placebo was not significant. Rates of insomnia, nausea, dry mouth, and dizziness were higher with ATX than with placebo. Discontinuation rates due to treatment-emergent adverse events were similar between groups.* **Conclusions:** *ATX monotherapy effectively improved symptoms of ADHD and comorbid social*

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Key words: ***atomoxetine; ADHD; social anxiety disorder; adults***

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common neuro-psychiatric disorder, affecting 4.4% of adults in the United States.[1] Adults with ADHD have more difficulties with school, work, family relationships, and social interactions than adults without ADHD. A sample of adults reported as having been diagnosed with ADHD by a clinician completed less schooling, were less likely to be employed or be employed full-time, and had significantly lower annual incomes.[2] Adults with ADHD have higher rates of cigarette smoking and substance use, more severe substance use disorders, and driving-related deficits leading to negative social and economic consequences.[2–4] Adult ADHD is associated with increased legal difficulties, medical costs, and psychiatric comorbidities.[1,5,6] Adult ADHD is associated with profound economic and interpersonal issues, causing individuals to have less optimism and an overall decreased quality of life.[2,5] Because of its prevalence and broad impact on quality of life, adult ADHD is a significant public health issue.

Social anxiety disorder is characterized by persistent fear and avoidance of social situations in which embarrassment may occur; a somatic anxiety response upon exposure to the social situation; and, in adults, recognition that this fear is excessive or unreasonable (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; DSM-IV-TR). The National Comorbidity Survey Replication revealed that 29.3% of adults with ADHD had comorbid social anxiety disorder within the previous 12 months, the highest rate of any other anxiety disorder comorbid with ADHD.[1] Although much is known about these two conditions when they occur independently, less is known about the comorbid conditions. Comorbid occurrence of ADHD and anxiety disorders might produce greater impairments or unique treatment challenges compared with either condition alone. For instance, treatment of ADHD has traditionally relied on the use of psychostimulants, such as the amphetamines and methylphenidate. However, the effects of psychostimulants on comorbid anxiety disorders in children with ADHD remain unclear[7–11] and, to our knowledge, have not been systematically evaluated in adults. The available literature guiding clinicians' treatment options is sparse.

Atomoxetine (ATX) is a highly selective inhibitor of the presynaptic norepinephrine transporter. The efficacy of ATX for treating core ADHD symptoms in adults was demonstrated in two similar 10-week, placebo (PBO)-controlled trials.[12] Other studies have confirmed these results in adults[13] and examined the usefulness of ATX in treating ADHD in the presence of comorbid alcohol use disorders.[14] In a recent trial, ATX was effective in treating the symptoms of both ADHD and comorbid anxiety disorders in children and adolescents.[15]

This study was an outpatient, multi-site, randomized, double-blind, PBO-controlled trial testing the hypothesis that ATX would provide significant therapeutic benefit for ADHD symptoms in adult patients with ADHD and comorbid social anxiety disorder. Key secondary objectives included measuring the reduction of social anxiety disorder symptoms, and improvement of social adjustment and quality of life.

METHODS AND MATERIALS

STUDY DESIGN

This randomized, double-blind, PBO-controlled, parallel-design study was conducted at 30 investigative sites in the US. The first patient was enrolled on July 12, 2005, and the last patient completed the double-blind portion of the trial on May 10, 2007. The study protocol was approved in accordance with the principles of the Declaration of Helsinki.

All patients underwent an initial 2-week (approximately), medication-free evaluation period (Visit 1). Patients taking a stimulant for ADHD were required to be stimulant-free for 24 hr before the second screening visit (Visit 2) and to discontinue these medications for the duration of the study.

This protocol used scores from the Liebowitz Social Anxiety Scale (LSAS) at two separate times to differentiate patients (once during the screening period to compare scores at Visit 1 and Visit 2 and identify patients with inconsistent social anxiety disorder symptoms, and once after the PBO lead-in period to identify high PBO responders). The LSAS was completed at each of the two screening period visits (Visit 1 and Visit 2). At Visit 2, patients who had a decrease in social anxiety symptoms of more than 30% on the LSAS compared to Visit 1 were ineligible and did not participate in the study. Eligible patients were randomized to a treatment group at Visit 2 (Week 0) via a computer algorithm that blindly assigned patients to either study drug or PBO at a 1:1 ratio at the site level. The treatment assignments were kept blinded until after the database was locked. Investigative sites dispensed the blinded study drug, via telephone interactive voice response system, at the end of Visit 2 and instructed patients to begin dosing the next morning. Patients took blinded study drug twice daily (BID), in the morning and in the afternoon or early evening, and were encouraged to take the medication with food. Following randomization and dosing initiation at the end of Visit 2 (Week 0), the recommended time points for patient evaluations were 2, 4, 6, 10, 14, and 16 weeks later (Visits 3–8), which, for the ATX-treated patients, corresponded to 0, 2, 4, 8, 12, and 14 weeks after beginning active medication. Patients were counted as completing the study if they completed all visits. Based on the visit intervals allowed

per protocol, patients who completed the protocol participated in the screening and double-blind phases of the trial ranging from 77 to 172 days.

Following randomization, patients in both the ATX and PBO treatment groups received PBO for 2 weeks. To maintain the double-blind, patients and site personnel were informed that a PBO treatment period would occur at some point during the study but were blinded to the timing and duration. A separate document detailing this PBO lead-in phase was provided to each site's ethical review board. Because research in behavioral and emotional disorders demonstrates that there may be a significant PBO response with reduction in symptoms in the absence of active drug, this PBO lead-in phase was meant to identify and separate high PBO responders (greater than 25% decrease in social anxiety symptoms as measured by the LSAS Total score) from "qualified" patients (*no more* than a 25% decrease of social anxiety symptoms) during the PBO lead-in phase. Although patients with more than a 25% decrease of social anxiety symptoms during the PBO lead-in phase could continue with the study, qualified patients were included in separate statistical analyses (description follows). An earlier study has successfully used a PBO lead-in phase (15).

Following the PBO lead-in, patients in the ATX group began treatment with 40 mg/day for a minimum of 7 days followed by 80 mg/day, the target dose, for a minimum of 7 days. At Week 10, or any subsequent visit, patients with significant residual symptoms could have their dose increased to a maximum 100 mg/day. Dose decreases were allowed, but patients were discontinued if a decrease was requested below 40 mg/day.

PATIENTS

Adult patients, 18–65-years old, meeting the DSM-IV-TR diagnoses for both ADHD and social anxiety disorder, were enrolled. The diagnostic criteria for ADHD were assessed with the Conners' Adult ADHD Diagnostic Interview for DSM-IV and for social anxiety disorder by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders-Research Version. Additionally, patients had an LSAS Total score of at least 50 at Visit 1, no more than a 30% decrease in LSAS Total score at Visit 2, and a Clinical Global Impression-Overall-Severity (CGI-O-S) score of 4 or greater at Visits 1 and 2. Concomitant Axis I diagnoses (current or lifetime)-specific phobias, Generalized Anxiety Disorder (GAD), and dysthymia were allowed. Current diagnosis of major depressive disorder was allowed only if diagnosed more than 6 months before Visit 1.

Exclusionary criteria included current or lifetime diagnosis of obsessive–compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders, and/or current diagnosis of panic disorder, posttraumatic stress disorder, or an eating disorder within the year preceding Visit 1. Current diagnosis of alcohol, drugs of abuse, or prescription medication abuse meeting DSM-IV-TR criteria were also excluded.

Written informed consent was obtained after subjects received a complete description of the study.

EFFICACY ASSESSMENTS

The primary ADHD efficacy measure was the mean change from baseline on the Conners' Adult ADHD Rating Scale: Investigator-Rated: Screening Version (CAARS:Inv:SV)[16] Total ADHD Symptoms score. The three subscales (inattention, hyperactivity–impulsivity, and the ADHD index) were also evaluated. The CAARS:Inv:SV was administered with adult ADHD prompts for the 18 items making up the Total ADHD Symptoms score, to create a semistructured interview scored by qualified raters at each investigative site. Prompts are a set of questions with adult-specific language that a rater can use to document the presence, breadth, and severity of ADHD symptoms. These prompts have been used in previous ATX trials.[12] The use of prompts is becoming a common practice in adult ADHD trials to ensure adequate exploration of adult symptoms.[1,14,17,18]

Each investigator received scale training for the CAARS:Inv:SV, LSAS, and CGI-O-S following standard guidelines[19] before initiating the trial. The LSAS[20] Total score mean change from baseline was the key secondary measure used to assess change in symptoms of social anxiety disorder. This investigator-rated scale assesses the range of social interaction and performance situations that individuals with social anxiety disorder may fear and/or avoid. The LSAS Total score is the sum of the fear and avoidance item scores. The four subscales of the LSAS are (1) performance fear, (2) performance avoidance, (3) social fear, and (4) social avoidance.

The CGI-O-S[21,22] is a single-item rating of the clinician's assessment of the severity of the patient's ADHD and social anxiety symptoms in relation to the clinician's total experience with adults with ADHD and comorbid social anxiety disorder. Severity is rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill patients). Additional secondary efficacy measures included the Social Adjustment Scale-Self Report (SAS) to measure instrumental and expressive role performance over the past 2 weeks;[23] the State-Trait Anxiety Inventory (STAI)[24] to assess anxiety or worry; and the Adult ADHD Quality of Life Scale-29 (AAQoL) to examine the disease-specific functional impairments and quality of life for adults with ADHD.[25] The AAQoL produces an overall score and four subscale scores.

SAFETY

Safety measures recorded at every visit included spontaneously reported treatment-emergent adverse events (TEAEs) and vital signs. Safety analyses were performed for all randomized patients who took at least one dose.

STATISTICAL ANALYSIS

The sample size provided at least 85% power to detect a treatment difference of 3.64 points on the CAARS:Inv:SV Total ADHD Symptoms score between treatment groups, assuming an overall standard deviation of no more than 9.89 points based on a two-sided significance level of 0.05 using a two-sample t test.

The primary analysis for the primary efficacy variable (CAARS:Inv:SV Total ADHD Symptoms score) was an analysis of covariance (ANCOVA) on the mean change from baseline to last observation carried forward (LOCF) endpoint scores for all qualified patients. The model contains terms for baseline value, treatment group, and investigational site. To assess the overall robustness, the mean changes of the CAARS:Inv:SV Total ADHD Symptoms score, LSAS Total score, and CGI-O-S were also analyzed using a restricted maximum likelihood-based mixed model repeated measures (MMRM) technique. The analysis included fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction; and the continuous, fixed covariate of baseline score (last of scores at Visit 1 through Visit 3). The unstructured, compound-symmetric, autoregressive of order 1, and the heterogeneous versions of each were considered to model the within-patient errors, and the covariance structure that produced the best Akaike's Information Criteria score was selected for this analysis. An analysis was done to compare ATX and PBO at the end of the double-blind phase using a contrast on the treatment-by-visit interaction term from the MMRM model. The Kenward–Rogers method was used for the denominator degrees of freedom in the t test at the final visit.

The key secondary variables (LSAS and CGI-O-S) were analyzed by both LOCF ANCOVA and MMRM methods (as described) for all

randomized patients. Other secondary variables (STAI, SAS, and AAQoL) were analyzed using LOCF ANCOVA (as described). For the CAARS:Inv:SV and LSAS measures, two separate statistical analyses were conducted, one including all randomized patients and one including only the qualified patients. Efficacy analyses were conducted on an intent-to-treat basis except for the CAARS:Inv:SV Total ADHD Symptoms score and the LSAS Total score analyzed on qualified patients.

Further analyses were conducted to compare data from patients diagnosed with GAD and patients without a GAD diagnosis. Mean change from baseline to LOCF data from the CAARS:Inv V and LSAS were analyzed using an ANCOVA model with the same terms as the primary analysis with a GAD by treatment interaction term added.

The incidence rates of TEAEs were compared across treatment groups using Fisher's exact test. Treatment differences were assessed for changes from baseline (last data from Visits 1 and 2) to endpoint for vital signs using LOCF ANCOVA (as described). Within-group changes were assessed with paired *t* tests for vital signs.

Patient characteristics were compared across treatment groups using Fisher's exact test for categorical data and an analysis of variance (ANOVA) with treatment and investigator in the model for the quantitative data in the double-blind phase.

This clinical trial was registered at www.clinicaltrials.gov [NCT00190879].

RESULTS

BASELINE CHARACTERISTICS

Of the 590 patients who entered screening for the study, 442 were randomized to either ATX ($n = 224$) or PBO ($n = 218$; Fig. 1). Of the randomized patients, 176 in the ATX group and 166 in the PBO group met criteria as qualified patients, of which 171 in the ATX group and 158 in the PBO group had a post-PBO lead-in phase observation. During the PBO lead-in phase, 15 patients randomized to ATX and 14 patients randomized to PBO discontinued the study (most for the reason "unable to contact"). Of randomized patients, 56.7% (127/224) randomized to ATX and 62.8% (137/218) randomized to PBO completed the study. The mean age was 38 years and most patients were Caucasian (74.0%). Male patients were 53.6%, 57.2% met criteria for the combined ADHD subtype (both inattentive and hyperactive/impulsive symptoms), 86.9% were diagnosed with generalized social anxiety disorder, and 23.3% also had a diagnosis of GAD. Weight was 85.1 kg in the ATX group and 81.3 kg in the PBO group. There were no differences between the groups in baseline characteristics. The mean final ATX dose for all randomized patients was 82.9 mg/day. This dose is consistent with the ATX label and with previous adult ADHD trials.

EFFICACY

From the LOCF data analysis (baseline to endpoint) of qualified patients, mean scores from the Total ADHD Symptoms score of the ATX-treated patients decreased from 29.6 (standard deviation [*SD*] = 10.4) at baseline to 20.9 ($SD = 11.3$) at endpoint compared with decreases from 31.2 ($SD = 9.4$) to 25.6 ($SD = 10.6$) for the PBO group (95% CI, −6.0, −2.2; $P < .001$; Table 1). Significant symptom reductions were also noted for ATX on the CAARS:Inv:SV subscales. Results were similar when data from all randomized patients were analyzed (*P* values $< .001$).

MMRM analysis of data from the qualified patient subset for CAARS:Inv:SV Total ADHD Symptoms score demonstrated that ATX was statistically superior to PBO overall ($P < .001$) and at every postbaseline visit (Fig. 2). Results were similar for the three subscales (inattention, hyperactivity-impulsivity, and ADHD index), with significant overall effects (*P* values $< .001$) and at every postbaseline visit. Results were similar when data from all randomized patients were analyzed.

The MMRM analysis from the qualified patient subset showed that ATX produced statistically significant reductions on the LSAS Total scores relative to PBO overall ($P < .001$) and at every postbaseline visit (Fig. 3). Statistically significant reductions in symptom severity were also demonstrated with ATX on the four subscales overall and at 15 of the 20 postbaseline time points. Similar results were seen when data from all randomized patients were analyzed. The LOCF analysis from the qualified patient subset demonstrated a significant benefit for ATX on the LSAS Total score. Mean scores for the ATX group decreased from 85.3 ($SD = 23.6$) at baseline to 62.4 ($SD = 29.7$) at endpoint compared with decreases from 82.1 ($SD = 21.3$) to 67.7 ($SD = 26.9$) for the PBO group (95% CI, −13.4, −3.9; $P < .001$; Table 1). In addition, ATX was superior to PBO on all four LSAS subscales. Results were similar when data from all randomized patients were analyzed.

A Pearson's correlation post hoc analysis of the CAARS:Inv:SV Total ADHD Symptoms scores and the LSAS Total scores mean change from baseline to LOCF endpoint revealed a statistically significant, positive correlation ($r = .61$; 95% CI, 0.54, 0.67), suggesting that patients whose scores improved on one measure also showed improvement on the other.

The MMRM analysis of the CGI-O-S data showed that ATX was superior to PBO overall ($P = .014$) and at the last three time points. The LOCF analysis demonstrated ATX superiority over PBO (95% CI, −0.39, −0.03; $P = .022$), with decreases from 4.3 ($SD = 0.8$) to 3.5 ($SD = 1.1$) and from 4.4 ($SD = 0.9$) to 3.8 ($SD = 1.0$) for ATX and PBO, respectively. STAI-Trait scores from ATX-treated patients declined significantly more than scores from PBO-treated patients (95% CI, −4.7, −0.7; $P = .008$). Scores for the STAI-Trait decreased from 56.2 ($SD = 10.4$) to 47.3 ($SD = 13.1$) in the ATX group and from 54.7 ($SD = 10.2$) to 48.7 ($SD = 12.2$) in the PBO group. There was no significant difference between ATX and PBO on the STAI-State LOCF scores (95% CI, −3.6, 1.0; $P = .273$). Benefit of ATX as measured by the SAS

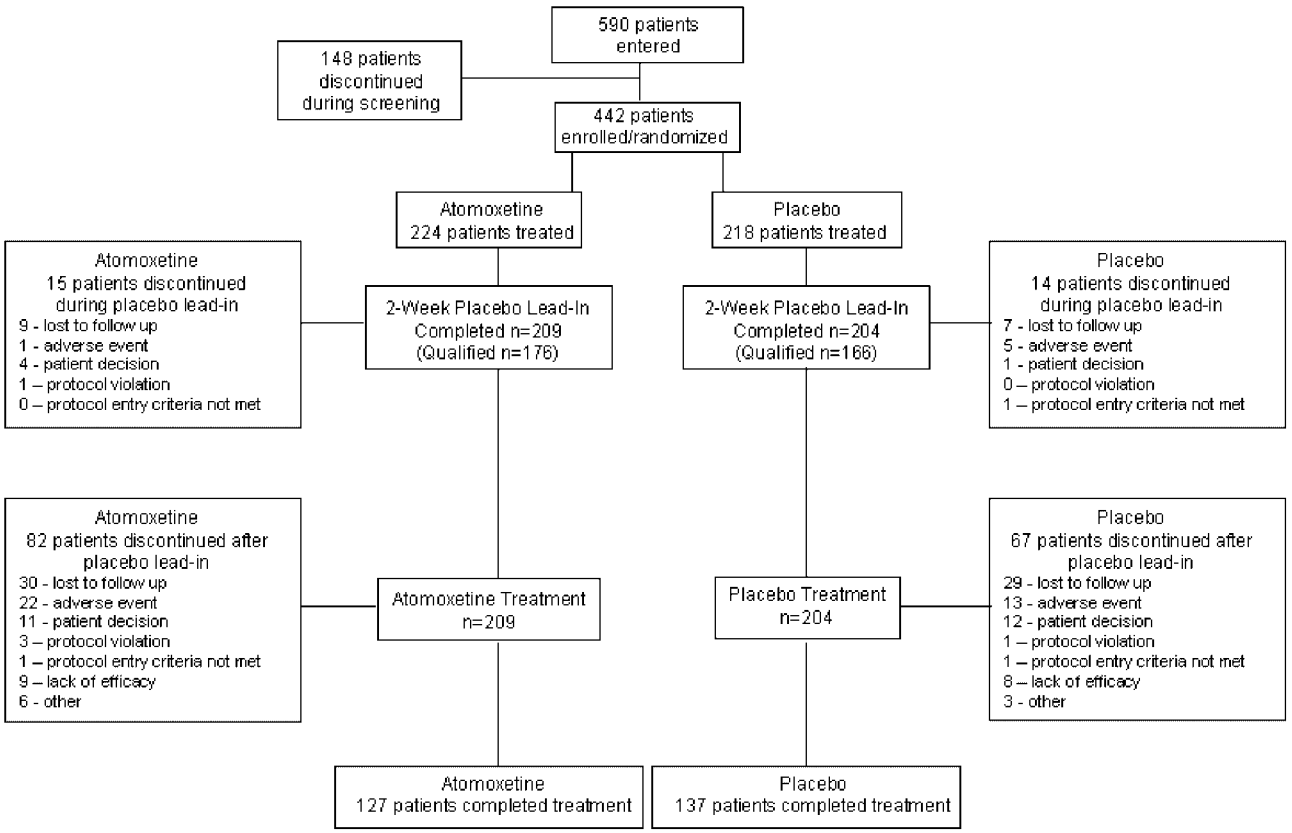

Figure 1. Patient disposition for the double-blind phase. There were no significant differences in the number of patients who completed the study or in the number of patients who discontinued due to the reasons listed.

scores failed to reach statistical significance ($P = .0504$; 95% CI, −0.1, 0.0). The LOCF analysis for the AAQoL Total score indicated that ATX was statistically superior to PBO (95% CI, 0.35, 7.0; $P = .030$), with scores increasing from 44.1 ($SD = 15.2$) to 59.1 ($SD = 18.3$) for ATX-treated patients and from 45.3 ($SD = 13.6$) to 56.4 ($SD = 16.5$) for PBO-treated patients. On the four AAQoL subscores, ATX was statistically superior to PBO on the psychological health subscore ($P = .030$; Table 1).

EFFICACY IN PATIENTS WITH GENERALIZED ANXIETY DISORDER

When patients were divided based upon the presence or absence of GAD, the tests of interaction showed no differential advantage of ATX versus PBO on reduction of the CAARS:Inv:SV Total ADHD Symptoms scores ($P = .586$) or LSAS Total scores ($P = .526$) comparing patients with GAD and those without. For patients without GAD, Total ADHD Symptoms scores for ATX-treated patients ($n = 151$) decreased significantly more than for PBO-treated patients ($n = 155$). Mean decreases were −8.40 and −4.69, for ATX and PBO, respectively ($P < .001$). For patients with GAD, there was no statistically significant difference between Total ADHD Symptoms scores for ATX-treated ($n = 50$) and PBO-treated ($n = 44$) patients (mean decreases of −8.26 and −5.52, respectively; $P = .295$). For patients without GAD, LSAS Total scores for ATX-treated patients ($n = 151$) decreased significantly more than for PBO-treated patients ($n = 155$). Mean decreases were −21.82 and −12.16, for ATX and PBO, respectively ($P < .001$). For patients with GAD, there was no statistically significant difference between LSAS Total scores for ATX-treated ($n = 50$) and PBO-treated ($n = 44$) patients (mean decreases of −18.16 and −13.39, respectively; $P = .556$).

SAFETY

Of the TEAEs reported by at least 5% of patients in either treatment group, insomnia (17 versus 9%; $P = .020$), nausea (16 versus 7.6%; $P = .010$), dry mouth (15.6 versus 4.3%; $P < .001$), and dizziness (7.5 versus 2.4%; $P = .023$) were reported significantly more often with ATX than with PBO (Table 2). Total numbers of adverse events and discontinuations due to adverse events did not differ significantly between treatment groups. Two patients assigned to ATX treatment reported serious adverse events (gallstones and biliary dyskinesia). These events were not attributed to study drug.

Compared with PBO, ATX-treated patients had statistically significantly increased diastolic blood

TABLE 1. Means, *P* values, and effect sizes for key efficacy variables from the LOCF[a] ANCOVA

	Atomoxetine						Placebo							
	Baseline		Endpoint		Change		Baseline		Endpoint		Change			
Efficacy variable	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	*P* value	Effect Size (Cohen's *d*)
CAARS:Inv:SV Total ADHD Symptoms Score[b]	29.6	10.4	20.9	11.3	−8.7	10.0	31.2	9.4	25.6	10.6	−5.6	10.2	**<.001**	.47
CAARS:Inv:SV ADHD index subscale[b]	19.8	6.8	14.1	7.7	−5.7	7.3	20.5	5.8	17.3	7.1	−3.2	6.7	**<.001**	
CAARS:Inv:SV hyperactivity/ impulsivity subscale[b]	12.7	5.9	8.7	5.6	−3.9	5.3	12.7	5.6	10.7	5.7	−2.0	5.2	**<.001**	
CAARS:Inv:SV inattention subscale[b]	17.0	6.0	12.2	6.9	−4.8	5.7	18.5	5.4	14.9	6.0	−3.6	6.2	**.001**	
LSAS Total score[b]	85.3	23.6	62.4	29.7	−22.9	25.3	82.1	21.3	67.7	26.9	−14.4	20.3	**<.001**	.40
LSAS Performance Fear score[b]	22.4	6.6	17.0	8.0	−5.4	6.7	22.2	5.9	18.3	7.3	−3.9	5.9	**.01**	
LSAS Performance Avoidance score[b]	22.0	7.1	15.7	8.2	−6.2	7.7	21.2	6.6	17.3	7.7	−4.0	6.0	**.002**	
LSAS Social Fear score[b]	20.5	6.1	15.4	7.9	−5.1	6.1	19.5	5.4	16.3	6.9	−3.2	5.3	**.002**	
LSAS Social Avoidance score[b]	20.5	6.5	14.2	7.7	−6.3	6.8	19.1	6.3	15.8	7.4	−3.4	6.0	**<.001**	
CGI-O-S[c]	4.3	0.8	3.5	1.1	−.76	1.1	4.4	0.9	3.8	1.0	−.60	1.0	**.02**	.23
STAI-State[c]	50.0	11.9	42.8	13.2	−7.2	13.9	48.2	11.6	43.2	12.5	−5.0	12.0	.27	–
STAI-Trait[c]	56.2	10.4	47.3	13.1	−8.9	11.2	54.7	10.2	48.7	12.2	−6.0	9.0	**.008**	.27
SAS[c]	2.4	0.4	2.1	0.5	−0.3	0.4	2.4	0.5	2.1	0.5	−0.2	0.4	.05	–
AAQoL Total score[c]	44.1	15.2	59.1	18.3	14.9	17.1	45.3	13.6	56.4	16.5	11.1	15.0	**.03**	.24
AAQoL Life Outlook Domain[c]	46.1	15.5	57.6	18.8	11.5	17.6	46.1	14.3	54.9	16.8	8.8	14.9	.07	
AAQoL Life Productivity Domain[c]	41.7	19.3	58.9	22.6	17.2	21.9	42.9	18.2	55.8	20.8	12.9	19.8	.09	
AAQoL Psychological Health Domain[c]	41.2	20.0	57.0	22.7	15.8	21.9	42.1	18.5	53.3	20.8	11.2	19.3	**.03**	
AAQoL Quality of Relationships Domain[c]	50.5	18.9	64.2	18.4	13.7	20.5	53.0	19.0	62.8	18.6	9.8	19.1	.10	

[a]LOCF, last observation carried forward; ANCOVA, analysis of covariance; *SD*, standard deviation; CAARS:Inv:SV, Conners' Adult ADHD Rating Scale: Investigator-Rated: Screening Version; ADHD, attention-deficit/hyperactivity disorder; LSAS, Liebowitz Social Anxiety Scale; CGI-O-S, Clinical Global Impression-Overall-Severity; STAI, State-Trait Anxiety Inventory; SAS, Social Adjustment Scale-Self Report; AAQoL, Adult ADHD Quality of Life Scale-29.
[b]All qualified patients (those who had no more than a 25% decrease in LSAS Total score during placebo lead-in).
[c]All randomized patients.

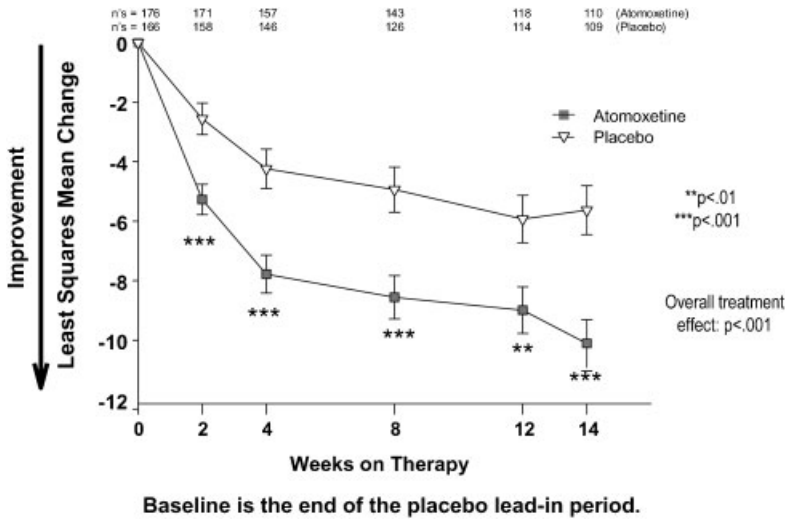

Figure 2. Change of CAARS:Inv:SV Total ADHD Symptoms scores for all qualified patients. CAARS:Inv:SV, Conners' Adult ADHD Rating Scale: Investigator-Rated: Screening Version; ADHD, attention-deficit/hyperactivity disorder.

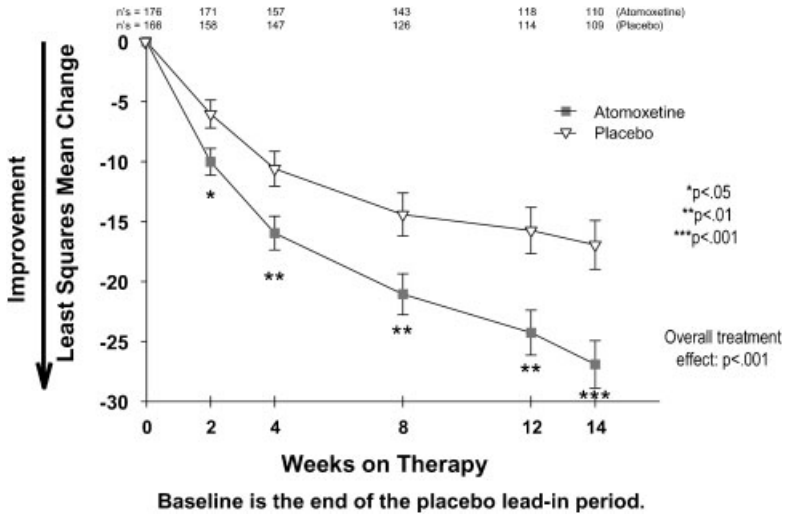

Figure 3. Change of LSAS Total scores for all qualified patients. LSAS, Liebowitz Social Anxiety Scale.

pressure (1.4 and −0.4 mmHg for ATX and PBO, respectively; $P = .003$) and pulse (3.6 and 1.3 bpm for ATX and PBO, respectively; $P < .001$). Mean changes from baseline in weight (−0.41 and −0.08 kg for ATX and PBO, respectively) were not statistically different ($P = .190$).

DISCUSSION

This 16-week, randomized, double-blind, PBO-controlled trial evaluated the effect of ATX on ADHD and social anxiety symptoms in adults with ADHD and comorbid social anxiety disorder. Epidemiological studies suggest that ADHD is seen in as many as 1 in 22 adults, with significant adverse impact on quality of life, and anxiety disorders are prevalent in about half of adults with ADHD. Despite this prevalence and impact on quality of life, to the best of our knowledge, this study is the only large clinical trial ($N = 442$) examining ADHD and social anxiety disorder comorbidities in adults. Patients had substantial levels of impairment for both ADHD and social anxiety disorder as evidenced by baseline CAARS:Inv:SV total scores near 30 and baseline total LSAS scores near 84.

Consistent with previous trials in adults with ADHD,[12] ATX was effective in treating patients with ADHD in this trial. Results from the CAARS:Inv:SV showed that ATX was statistically superior to PBO at every postbaseline visit based upon an MMRM analysis and when using a change from baseline-to-endpoint LOCF analysis. It appears that the amount of symptom decrease was somewhat less in this study compared with previous studies. In previous studies,[12] ATX decreased the CAARS:Inv:SV Total ADHD Symptoms scores by 9.5 and 10.5, compared with 8.7 in this study. However, the amount of symptom decrease for PBO was also less in this study resulting in an effect size of 0.47 compared with 0.35 and 0.40 in the previous studies. Whether differences were due to patients in this study having comorbid social anxiety disorder in addition to ADHD is unclear. Interestingly, ATX was also superior to PBO in producing clinically meaningful and statistically significant decreases in symptoms of social anxiety. Because ADHD and social anxiety disorder frequently co-occur, this suggests that ATX might be particularly beneficial for these patients.

Item analyses were completed to examine the correlation of the CAARS:Inv:SV and LSAS to determine internal consistency of the scales.[26] There was a moderate correlation between the change scores of the two scales and the internal consistency of both scales was strong. (A subsequent article will report these analyses.)

When patients were divided based upon the presence or absence of GAD, the tests of interaction showed no differential advantage of ATX versus PBO on reduction of the CAARS:Inv:SV Total ADHD Symptoms scores or LSAS Total scores comparing patients with GAD and those without. For patients without GAD, ATX-treated patients experienced significant symptom reductions on these two measures compared with PBO-treated patients. On these measures, there were no statistically significant differences between ATX and PBO for patients with GAD. It is likely that a lack of power due to smaller numbers of patients with GAD contributed to this lack of statistical significance.

ATX was also superior to PBO on the STAI-Trait scale, indicating that ATX-treated patients experienced a decrease in anxiety symptoms that was measurable on more than one anxiety scale. However, the decrease for ATX (8.9) was only 2.9 greater than the decrease for PBO (6.0). There was no significant difference between ATX and PBO on the STAI-State scale. The lack of a significant difference on the STAI-State might be expected because this subscale reflects anxiety at the time it is being administered and is more reactive to temporary

TABLE 2. TEAEs for all randomized patients occurring in at least 5% of patients in either treatment group

	Atomoxetine ($N = 212$)		Placebo ($N = 211$)		
TEAE	*n*	%	*n*	%	*P* value
Patients with at least one TEAE[a]	183	86.3	167	79.1	.05
Headache	43	20.3	30	14.2	.12
Insomnia	36	17.0	19	9.0	.02
Nausea	34	16.0	16	7.6	.01
Dry mouth	33	15.6	9	4.3	<.001
Nasopharyngitis	23	10.8	17	8.1	.41
Decreased appetite	22	10.4	12	5.7	.11
Constipation	16	7.5	8	3.8	.14
Dizziness	16	7.5	5	2.4	.02
Fatigue	13	6.1	12	5.7	1.00
Initial insomnia	12	5.7	6	2.8	.23
Irritability	11	5.2	15	7.1	.43
Somnolence	11	5.2	7	3.3	.47
Anxiety	10	4.7	13	6.2	.53
Pharyngolaryngeal Pain	9	4.2	12	5.7	.51
Erectile Dysfunction[b]	6	5.2	1	0.9	.12
Upper respiratory tract infection	6	2.8	11	5.2	.23

[a]TEAE, treatment-emergent adverse event.
[b]Percentage based on men only (atomoxetine $n = 115$; placebo $n = 109$).

conditions than to stable change. ATX was also superior to PBO on the overall score of the AAQoL scale. These results support previous findings,[27,28] suggesting that ATX can improve the impairments and consequences of ADHD that negatively impact quality of life.

This study is important from a patient-care perspective because it is the first large-scale treatment trial in this patient population, it produced a clearly positive response, and results are statistically significant and clinically meaningful on both sets of symptoms. Furthermore, both ADHD and social anxiety disorder symptoms showed significant improvement at the first postbaseline visit, 2 weeks after beginning active treatment. This suggests that ATX directly affects both symptom sets (i.e., the improvement of anxiety symptoms is not merely a downstream secondary effect of the improvement in ADHD symptoms). When considered along with the results of the trial by Geller et al.,[15] which demonstrated significant efficacy for treating ADHD and anxiety symptoms in a pediatric population with the comorbid conditions, the results of the current trial extend our knowledge of the treatment of ADHD and comorbid anxiety across the age spectrum.

The tolerability profile was similar to that found in previous studies of ATX in adults.[12] Patients in the ATX group reported insomnia, nausea, dry mouth, and dizziness significantly more often than patients in the PBO group. ATX also produced statistically but not clinically significant increases in pulse and diastolic blood pressure compared with PBO.

The 14-week, active-treatment period could be considered a limitation of this clinical trial. It appears that scores from the two treatment groups were continuing to separate at endpoint. Thus, the ultimate long-term treatment benefits remain uncertain. This might be especially true for the quality of life measures, which might require more time to demonstrate maximum treatment benefit. Furthermore, to the best of our knowledge, this is the first clinical trial to use these scales with this comorbid population. Therefore, it is possible that the results may be somewhat influenced by interactions of each condition (social anxiety disorder or ADHD) on the alternate condition's scale (CAARS:Inv:SV or LSAS), as the original validation of the CAARS:Inv:SV and LSAS scales were not in specific populations with each of these conditions. The issues of possible effects of social anxiety disorder on the CAARS:Inv:SV and ADHD on the LSAS are beyond the scope of this article but warrant further investigation.

CONCLUSIONS

In summary, this study demonstrates that ATX is efficacious for decreasing symptoms of ADHD and anxiety in adult patients with ADHD and comorbid social anxiety disorder, while improving quality of life. The medication was well tolerated, and the safety profile was similar to previous ATX trials.

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Analysis and interpretation of data: Adler, Liebowitz, Kronenberger, Qiao, Rubin, Hollandbeck, Deldar, Schuh, Durell.

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