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Atomoxetine Increased Effect over Time in Adults with Attention-Deficit/Hyperactivity Disorder Treated for up to 6 Months: Pooled Analysis of Two Double-Blind, Placebo-Controlled, Randomized Trials

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SUMMARY

Introduction: Changes in the magnitude of efficacy throughout 26 weeks of atomoxetine treatment, along with impact of dosing, were evaluated in adults with ADHD from two randomized, double-blind, placebo-controlled studies. **Aims:** Pooled placebo (n = 485) and atomoxetine (n = 518) patients, dosed 25, 40, 60, 80 (target dose), or 100 mg daily, were assessed. Change from baseline in Conners' Adult ADHD Rating Scale–Investigator Rated Scale: Screening Version (CAARS) total ADHD symptoms score and Adult ADHD Investigator Symptom Rating Scale (AISRS) total score were analyzed using mixed-model repeated measures, with least squares mean change, effect size, and response rate calculated at 1, 2, 4, 8, 12, 16, 22, and 26 weeks. **Results:** Decreases on CAARS for atomoxetine- versus placebo-treated patients were consistently statistically significantly greater at every time point beginning at one week ($P \leq 0.006$, 0.28 effect size). By 4 weeks, comparison was −13.19 compared with −8.84 ($P < 0.0001$, 0.45 effect size). By 26 weeks, mean change was −15.42 versus −9.71 (0.52 effect size); increase in effect size over time was most pronounced in the 80 mg group (0.82 effect size). AISRS demonstrated similar results. Atomoxetine response rate (CAARS 50% decrease) continued to increase throughout 26 weeks. **Conclusions:** Atomoxetine treatment in adults with ADHD was associated with small effect sizes after 4 weeks and moderate effect sizes by 6 months of treatment. The data support increased effect size and response rate over time during longer-term treatment at target dose.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a pattern of inattentiveness, hyperactivity, and impulsiveness that is present in at least 2 settings (e.g., school, work, home, social) and results in impairment [1]. ADHD is a chronic, neurobiological behavioral disorder that begins in childhood, with up to 60% having symptoms continue into adulthood [1,2]. The prevalence of ADHD in adults is estimated to range between 2.5% and 5% [1,3,4].

Atomoxetine is a nonstimulant pharmacotherapy option with demonstrated therapeutic benefit in adults for the treatment of ADHD [5–8]. While short-term studies have suggested a greater effect size for methylphenidate, a stimulant treatment for ADHD, atomoxetine responder rates and effect sizes in adults and children are similar to methylphenidate when longer assessment periods are considered [9,10]. Data across a range of adult and child studies suggest that atomoxetine can have an onset of action within 1–2 weeks of treatment [7,8], but that clinically meaningful response can take 4–6 weeks [11–14]; moreover, for responders, there is evidence that an incremental increasing response occurs in adults up to 24 weeks or longer [10].

The 2 atomoxetine adult ADHD registration trials demonstrated treatment effect sizes of 0.35 and 0.40 for ADHD symptom reduction scales in a 10-week treatment period [5]. In these studies, over 70% of patients were prescribed 90 mg/day or 120 mg/day atomoxetine, which is above the label recommended 80 mg/day target dosing; the mean final dose of atomoxetine for both studies was approximately 95 mg/day [5,15]. Subsequent atomoxetine adult ADHD trials reported treatment effect sizes ranging from 0.40 around 12 weeks of treatment to 0.57 around 24 weeks of treatment [7,8,16]. In these studies, mean or modal atomoxetine

doses were ≥80 mg/day. Understanding atomoxetine dosing practices and its relationship to efficacy results over time is important for putting clinical trial results into clinical practice context, as dosing in trials has been greater than and more aligned with label recommendations than dosing generally observed in real-world settings, where atomoxetine is often underdosed [13,17].

The potential for increased efficacy over time and the impact of dosing regimen on treatment outcome has implications for atomoxetine dosing, efficacy assessment, patient education, and patient outcomes. To further investigate the effect of longer duration atomoxetine treatment on symptom improvement effect size over time, the currently described study examines pooled data from 2 similarly designed, 6-month, placebo-controlled atomoxetine clinical trials in adults with ADHD: clinicaltrials.gov registered studies NCT00190736 (B4Z-US-LYCU) [6] and NCT00190775 (B4Z-US-LYCW) [7]. In these two studies, patients were not randomized by treatment dose but instead doses were optimized based on individual efficacy and tolerability. However, because patients within both studies ended the treatment period on different optimized final dosing levels (25–100 mg/day), the current analyses assess the effect of dosing on efficacy measure outcomes in addition to the primary focus of examining response over time. As patients were not randomized by dose, dose-based findings are speculative in nature; however, the results do provide insight into the potential impact, or lack of impact, of various dosing schemes on efficacy outcomes.

Materials and methods

Study details are summarized; for additional details, see the previously published study results for LYCU [6] and LYCW [7].

Participants

In LYCU study, patients were adults aged 18–54 years, with a 1:1 randomization to atomoxetine (n = 250) or placebo (n = 251). To be included, patients had to meet Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision (DSM-IV-TR) criteria for adult ADHD as assessed by the Adult ADHD Clinician Diagnostic Scale version 1.2, as well as a Clinical Global Impressions-ADHD-Severity of Illness score of 4 (moderate symptoms) or higher. Patients were excluded from the study if they met diagnostic criteria for current major depression, a current anxiety disorder, any history of bipolar disorder, or any history of a psychotic disorder.

In LYCW study, patients were adults aged ≥18, with a 2:1:1 randomization to placebo or one of 2 atomoxetine titration strategies. A programming error in a randomization stratification block led to unbalanced arms for the atomoxetine on-label titration (n = 147) versus slower titration (n = 121) groups and for the atomoxetine (n = 268) and placebo (n = 234) groups as a whole [7]. Patients were required to meet DSM-IV-TR criteria for adult ADHD and have a historical diagnosis of ADHD during childhood, both of which were assessed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV. Additionally, patients were required to have a Clinical Global Impressions-ADHD-Severity score of 4 (moderate symptoms). Patients were excluded if diagnostic criteria were met for any history of bipolar or psychotic disorder, current major depression, anxiety disorder, or DSM-IV-TR criteria for substance abuse.

Study Design

LYCU and LYCW were randomized, multicenter, double-blind, placebo-controlled trials conducted at 21 and 42 outpatient sites in the United States, respectively. The last patient completed the double-blind portion of the trials on May 15, 2006 and October 27, 2009, respectively.

For LYCU study, all patients underwent a minimum 5-day medication-free evaluation period (Visit 1), followed by a 6-month double-blind study period. Eligible patients were randomized to a treatment group at Visit 2 (Week 0). After randomization and dosing initiation at the end of Visit 2 (Week 0), the time points for patient evaluations were 2, 4, 6, 10, 14, 22, and 26 weeks later (Visits 3–9, Table 1).

For LYCW study, there was a minimum 8-day screening period, followed by a 24-week double-blind study period. After an initial washout, screening, and entry period (Visit 1–3), patients were randomized to either placebo or atomoxetine. Patients were assessed after 1 and 2 weeks during titration treatment and then at weeks 4, 8, 12, 16, 20, and 24 (Table 1).

Dosing

In LYCU study, patients were randomized to the atomoxetine group with a lower/slower titration scheme compared with recommended labeling. They were started on 25 mg/day for a minimum of 7 days and then titrated to 40 mg/day for a minimum of 7 days, after which their dose was increased at the end of Visit 3 to a target dose of 80 mg/day. Patients had their dose increased at the end of Visit 5 to a maximum dose of 100 mg/day, unless precluded due to tolerability at the investigators discretion. After Visit 3, the investigator could also lower a patient's dose, allowing for 25, 40, 80, or 100 mg/day final dosing. A patient's dose was to remain stable from Visit 6 to Visit 7 and for 14 days immediately following Visit 7 unless a dose decrease was required. Dose increases could not occur by more than one level at a time, and only one decrease was allowed during the randomized study period.

In LYCW study, for the first 2 weeks on treatment, atomoxetine patients were randomized 1:1 to one of two titration schemes: (1) on-label titration with a starting dose of 40 mg/day for 3 days, increased to target dose of 80 mg/day; or (2) slower titration with a starting dose of 40 mg/day for 7 days, increased to 80 mg/day. At the end of Visit 5, regardless of titration scheme, at the discretion of investigators, patients could have their dose increased to a maximum dose of 100 mg/day. Patients could also be lowered from 80 to 60 mg/day if 80 mg/day was not tolerable, allowing for 60, 80, and 100 mg/day final dosing. Patients were allowed only one dose decrease. In both studies, patients were dosed once daily in the morning.

Measures

In both studies, Adult ADHD Investigator Symptom Rating Scale (AISRS) and Conners' Adult ADHD Rating Scale–Investigator

Table 1 Schedule of collection of ADHD efficacy measures from studies LYCU and LYCW

Study week	0	1	2	4	6	8	10	12	14	16	20	22	24	26
Time in window, weeks	0	1	2	4	6–8		10–12		14–16		20–22		24–26	
Study LYCU	V2		V3	V4	V5		V6		V7			V8		V9
	CAARS AISRS		AISRS	AISRS	AISRS		CAARS AISRS		AISRS			AISRS		CAARS AISRS
Study LYCW	V3	V4	V5	V6		V7		V8		V9	V10		V11	
	CAARS AISRS	CAARS	CAARS	CAARS		CAARS		CAARS AISRS		CAARS	CAARS		CAARS AISRS	

AISRS, Adult ADHD Investigator Symptom Rating Scale; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale; V, visit.

Rated Scale: Screening Version (CAARS) data were collected. The prespecified primary efficacy measure was AISRS total score and CAARS total ADHD symptoms score for LYCU and LYCW, respectively. The CAARS total ADHD symptoms score and the AISRS total score both measure the 18 core ADHD symptoms from DSM criteria for adult ADHD, although the questions are worded differently. Both diagnostic tools are well established [18,19].

For the current pooled analyses, the *a priori* CAARS total ADHD symptoms score (hereafter, CAARS total score) analyses were primary and the AISRS total score analyses secondary, as the CAARS is more commonly used, including for responder definitions. The following were assessed throughout the duration of the studies: (1) effect size, (2) CAARS total score mean change, (3) AISRS total score mean change, (4) response rate based on 25% and 50% improvement from baseline in CAARS total score, and (5) incidence of treatment-emergent adverse events (TEAEs) among the three distinct titration strategies.

Statistical Analyses

Baseline characteristics were summarized using means and standard deviation for continuous variables and frequencies and percentages for categorical variables. Treatment groups were compared using an analysis of variance (ANOVA) model with the terms treatment and pooled investigator for continuous variables or Fisher's exact test for categorical variables. Changes from baseline in CAARS and AISRS total score were analyzed by week using mixed-model repeated measures (MMRM). The MMRM model included treatment, investigator, visit, treatment-by-visit interaction, and baseline score of the outcome measure. Effect size was calculated using Cohen's d methodology. Patient incidence of TEAEs between atomoxetine dosing titration strategies and placebo were compared using Fisher's exact test in all treated patients.

Data were analyzed at 1, 2, 4, 8, 12, 16, 22, and 26 weeks. *P*-values ≤0.05 were considered statistically significant. For the analyses of CAARS and AISRS total score by dose level, mean change and Cohen's d effect size were presented by week as descriptive analyses.

Results

Baseline demographics and characteristics were similar between patients treated with atomoxetine compared to placebo (Table 2).

Efficacy over Time

After 1 week of treatment, the atomoxetine group had statistically significant symptom reduction measured by the CAARS total score ($P \leq 0.006$) compared with the placebo group. For the remaining time points in the analysis, the atomoxetine group demonstrated symptom reduction that continued to be statistically significantly greater than reductions in the placebo group ($P < 0.0001$ from 4 weeks onward, Figure 1A). After 2 weeks of treatment, the effect size was 0.23, increased to 0.45 by 4 weeks, and then remained consistent throughout subsequent timepoints (Table 3). By 26 weeks, a moderate effect size of 0.52 was achieved. The mean change and effect sizes for the atomoxetine

Table 2 Baseline demographics and characteristics for pooled analyses

Variable	Atomoxetine (N = 518)	Placebo (N = 485)	*P*-value[†]
Age, years, mean	39.5	39.3	0.7542
Range, years	18–59	19–62	–
Gender, male, n (%)	261 (50.4)	232 (47.8)	0.4483
Final prescribed mean daily dose, mg (SD)	76.6 (15.0)	N/A	–
Modal dose, mg, mean (SD)	85.5 (19.4)	N/A	–
Weight, lb, mean[‡]	186.9	186.7	0.9551
ADHD subtype, n (%)			0.5537
Hyperactive/impulsive	3 (0.6)	5 (1.0)	
Inattentive	155 (29.9)	134 (27.6)	–
Combined	360 (69.5)	346 (71.3)	
Previous stimulant exposure, yes, n (%)	104 (20.1)	105 (21.6)	0.5863
CYP2D6 poor metabolizer, n (%)	10 (1.9)	14 (2.9)	0.2954
CAARS total score, mean[§]	35.1	35.8	0.1888
AISRS total score, mean[¶]	37.1	37.9	0.1124
CGI-ADHD-S, mean	4.6	4.7	0.1616

ADHD, attention-deficit/hyperactivity disorder; AISRS, Adult ADHD Investigator Symptom Rating Scale; ANOVA, analysis of variance; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale; CGI-ADHD-S, Clinical Global Impressions-ADHD-Severity; CYP2D6, cytochrome P450 2D6; N/A, not applicable; SD, standard deviation. [†]Differences between groups were not statistically significant (Fisher's exact test for categorical variables; ANOVA model with the terms treatment and pooled investigator for continuous variables). [‡]Only patients with a baseline value were included in the analyses; atomoxetine n = 517; placebo n = 483. [§]Atomoxetine n = 514; placebo n = 479. [¶]Atomoxetine n = 511; placebo n = 481.

group as measured by the AISRS followed a similar trajectory as seen with the CAARS, with an effect size range 0.21–0.48 (Table 3; Figure 1B).

Impact of Dosing on Efficacy

The endpoint effect size was greater for the 80 mg/day group (0.82) than that for all patients (0.52) (Tables 3 and 4), and an increase in effect size in this group was apparent over 1 to 22 weeks. In the other dose groups with a relevant number of patients (60 and 100 mg/day), effect size did not generally appear to increase after 6 weeks. When analyzed by mean change in CAARS or AIRS total scores, an atomoxetine dose–response across potential patient doses (25, 40, 60, 80, and 100 mg/day) was not observed (Table 4).

Based upon a 25% and 50% CAARS total score improvement, the response rate for atomoxetine patients across dose groups was similar after 6 weeks for the 25% symptom reduction definition and ranged from about 70–85% at endpoint. Using the 50% symptom reduction definition, there was an increase in response rate over 1–26 weeks, most noticeably in the 80 mg/day group, where endpoint response rate was 71.1%. Placebo patients had a response rate at study endpoint of 51.6% (with 25% symptom reduction) and 29.7% (with 50% symptom reduction) (Table 5).

The mean ± standard error baseline CAARS and AISRS total scores for atomoxetine-treated patients were 35.07 ± 0.38 and 37.37 ± 0.35, respectively. Mean CAARS and AISRS baseline scores for patients by dose group at 24–26 weeks were between 34 and 39, with no by dose trend.

Metabolic status was only available for LYCW of which only 5 patients were poor metabolizers with week 24–26 results: two patients at 80 mg/day, CAARS mean change −13.00; 3 patients at 100 mg/day, CAARS mean change −20.00.

Impact of Titration Strategy on Tolerability

The number of patients with at least 1 TEAE was not statistically significantly different between the on-label titration and the slower titration or lower/slower titration strategies (Table 6). Frequency of TEAEs reported in ≥5% of patients was not statistically significantly different when patients were titrated as recommended by the atomoxetine-prescribing label (on label) compared with slower or lower/slower titration. No statistically significant differences were observed between the slower and lower/slower titration strategies in the proportions of patients with at least 1 TEAE or frequency of TEAEs reported in ≥5% of patients, with the exception of decreased appetite, which occurred more frequently in the slower titration group.

All three titration strategies had a statistically significantly greater number of patients with at least 1 TEAE compared to placebo and the frequency of TEAEs reported in ≥5% of patients was generally greater in any atomoxetine titration strategy compared to placebo (Table 6). TEAEs occurring more frequently with atomoxetine compared with placebo were consistent with TEAEs reported in previous atomoxetine trials in adults with ADHD.

The overall discontinuation percentage was statistically significantly less in the placebo (49.3%) than lower/slower titration (62.4%, $P < 0.001$) but not the on-label titration (52.7%) or slower titration (58.3%) groups, which were not significantly different from each other. The discontinuation percentage due to adverse events was similar across the on-label titration (21.9%), slower titration (20.0%), and lower/slower titration strategies (17.2%), all of which were significantly greater than placebo (7.4%, $P < 0.001$). Discontinuation due to lack of efficacy was significantly less in the lower/slower titration group (4.8%) compared to the placebo (9.7%, $P = 0.022$) and on-label titration (11.0%, $P = 0.026$) but not slower titration (10.0%) groups.

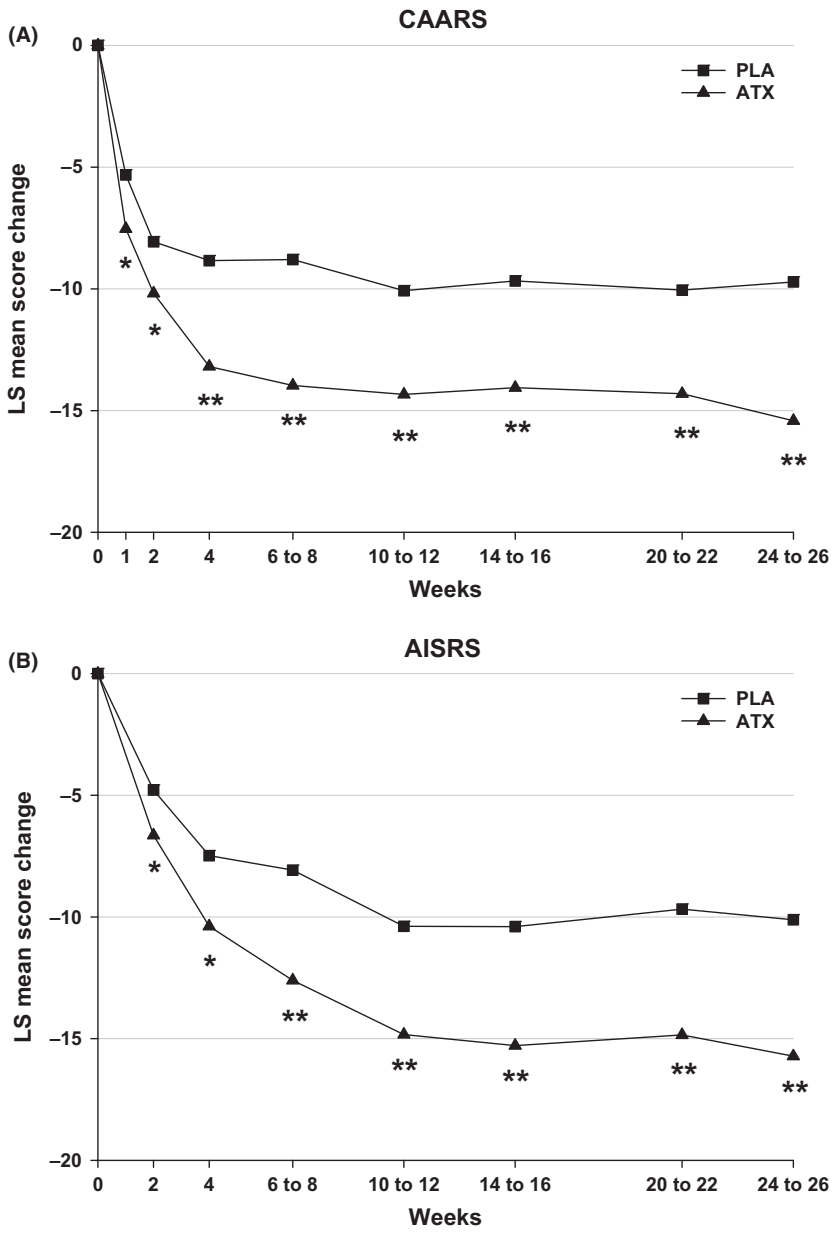

Figure 1 CAARS and AISRS total score LS mean change over 26 weeks. *(**A**) $P \leq 0.006$ atomoxetine versus placebo; (**B**) $P \leq 0.012$; atomoxetine versus placebo. **$P < 0.0001$ atomoxetine versus placebo. AISRS, Adult ADHD Investigator Symptom Rating Scale; ATX, atomoxetine; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale; LS, least squares; PLA, placebo.

Discussion

Atomoxetine Efficacy over Time

The current study pooled data from two adult, double-blind 6-month studies examining atomoxetine versus placebo for the treatment of ADHD and assessed changes in efficacy over time, as well as effect of dosing on symptom improvement. Results align with previously published data that atomoxetine has an initial onset of action within 1–2 weeks of treatment (small changes in ADHD symptoms), clinically meaningful response can take 4–6 weeks, and optimal or maximal response can potentially take an additional several weeks. These results, based upon effect size, also align with data showing that adult patients have an incremental increasing response to atomoxetine treatment potentially up to 24 weeks or longer [10]. Increasing atomoxetine response over time has been demonstrated in other adult long-term studies [20–22], as well as in child studies [23–27]. For example, in a long-term, open-label adult study (N = 384) following two 10-week double-blind studies, 39% of patients who failed to respond to atomoxetine during the 10-week treatment period responded to atomoxetine at a later time point during the open-label extension [22]. After 10 weeks of treatment in the feeder studies, there was a 4-week washout period, followed by atomoxetine open-label treatment. Patients who had previously responded to atomoxetine during the double-blind studies subsequently achieved a maximum response in the open-label study after 8 weeks of treatment.

Table 3 Effect size and LS mean change and difference for CAARS and AISRS total scores by week

CAARS total scores	Atomoxetine			Placebo			LS mean change	
Time on treatment, weeks	n[†]	LS mean, (SD)	LS mean change, (95% CI)[‡]	n[†]	LS mean, (SD)	LS mean change, (95% CI)[‡]	difference[§¶]	Effect size
1	261	27.7 (10.1)	−7.5 (−8.7, −6.4)	226	29.9 (10.3)	−5.3 (−6.5, −4.2)	−2.2	0.28
2	263	25.0 (10.8)	−10.18 (−11.4, −9.0)	225	27.1 (11.1)	−8.06 (−9.3, −6.9)	−2.1	0.23
4	244	22.0 (11.3)	−13.2 (−14.4, −12.0)	211	26.4 (11.4)	−8.8 (−10.1, −7.6)	−4.4	0.45
6–8	215	21.2 (11.0)	−14.0 (−15.2, −12.7)	196	26.4 (11.8)	−8.8 (−10.1, −7.5)	−5.2	0.53
10–12	367	20.9 (10.8)	−14.3 (−15.5, −13.1)	358	25.1 (11.8)	−10.1 (−11.3, −8.9)	−4.3	0.41
14–16	166	21.1 (11.1)	−14.1 (−15.4, −12.7)	153	25.5 (11.7)	−9.7 (−11.0, −8.3)	−4.4	0.41
20–22	165	21.0 (11.9)	−14.31 (−15.7, −12.9)	174	25.2 (12.3)	−10.1 (−11.4, −8.7)	−4.3	0.38
24–26	221	19.8 (11.3)	−15.42 (−16.8, −14.1)	240	25.5 (12.3)	−9.7 (−11.0, −8.4)	−5.7	0.52
AISRS total scores								
2	254	31.5 (11.2)	−6.6 (−8.0, −5.3)	255	33.4 (9.7)	−4.8 (−6.2, −3.4)	−1.9	0.21
4	240	27.6 (10.9)	−10.4 (−11.8, −9.0)	235	30.7 (10.7)	−7.5 (−8.9, −6.1)	−2.9	0.30
6–8	229	25.5 (10.8)	−12.6 (−14.0, −11.2)	246	30.1 (11.3)	−8.1 (−9.5, −6.7)	−4.5	0.45
10–12	360	23.3 (11.4)	−14.8 (−16.2, −13.5)	361	27.8 (12.1)	−10.4 (−11.7, −9.1)	−4.5	0.41
14–16	171	22.9 (11.1)	−15.3 (−16.8, −13.7)	185	27.6 (12.4)	−10.4 (−11.9, −8.9)	−4.9	0.43
20–22	146	23.3 (12.5)	−14.9 (−16.5, −13.2)	159	28.5 (12.5)	−9.7 (−11.3, −8.1)	−5.2	0.43
24–26	224	22.4 (12.2)	−15.7 (−17.3, −14.2)	249	28.0 (12.7)	−10.1 (−11.6, −8.6)	−5.6	0.48

AISRS, Adult ADHD Investigator Symptom Rating Scale; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale; CI, confidence interval; LS, least squares; MMRM, mixed-model repeated measures; SD, standard deviation. [†]The n fluctuates over time (weeks) based upon scale assessment schedule as outlined in Table 1; baseline was the last value during baseline period. [‡]$P < 0.0001$ within-group change from baseline for all time intervals. [§]$P \leq 0.006$ atomoxetine versus placebo (CAARS) (MMRM, model included treatment, investigator, visit, treatment-by-visit interaction, and baseline score of the outcome measure). [¶]$P \leq 0.012$; atomoxetine versus placebo (AISRS).

Table 4 Effect size and mean change for CAARS and AISRS total scores by dose and by week

	ATX 25 mg			ATX 40 mg			ATX 60 mg			ATX 80 mg			ATX 100 mg		
Time on treatment, weeks	n†	Mean change	effect size	n†	Mean change	Effect size	n†	Mean change	Effect size	n†	Mean change	Effect size	n†	Mean change	Effect size
CAARS total scores															
1	–	–	–	119	−7.6	0.30	–	–	–	144	−7.9	0.33	–	–	–
2	–	–	–	–	–	–	–	–	–	254	−10.8	0.30	–	–	–
4	–	–	–	–	–	–	9	−10.2	0.12	95	−14.2	0.51	136	−13.5	0.44
6–8	–	–	–	–	–	–	10	−15.9	0.68	61	−15.8	0.66	140	−14.3	0.53
10–12	5	−15.0	0.4	15	−20.7	0.91	14	−14.0	0.30	67	−15.9	0.47	268	−14.5	0.35
14–16	–	–	–	–	–	–	6	−18.0	0.71	36	−18.1	0.71	113	−15.4	0.48
20–22	–	–	–	–	–	–	6	−15.5	0.41	37	−21.3	0.89	96	−15.1	0.38
24–26	2	−31.5	1.7	9	−20.8	0.79	6	−19.2	0.67	45	−21.1	0.82	160	−15.8	0.39
AISRS total scores															
2	–	–	–	240	−7.2	0.16	–	–	–	–	–	–	–	–	–
4	7	−11.6	0.3	30	−12.8	0.44	–	–	–	185	−10.8	0.24	–	–	–
6–8	6	−12.0	0.3	18	−17.7	0.78	–	–	–	186	−13.1	0.37	–	–	–
10–12	5	−18.0	0.6	15	−19.3	0.72	14	−13.4	0.22	67	−15.5	0.41	268	−15.1	0.36
14–16	3	−17.3	0.4	15	−23.1	0.87	–	–	–	29	−19.2	0.58	115	−15.7	0.29
20–22	2	−23.5	0.9	17	−19.5	0.58	–	–	–	27	−17.0	0.41	93	−15.4	0.28
24–26	2	−26.0	1.2	10	−20.4	0.74	6	−18.5	0.60	45	−19.6	0.70	163	−16.2	0.41

AISRS, Adult ADHD Investigator Symptom Rating Scale; ATX, atomoxetine; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale. †The n fluctuates over time (weeks) based upon scale assessment schedule as outlined in Table 1; baseline was the last nonmissing value during baseline period. In cases where the N is less than the non-by-dose analyses, it is because dosing information was missing.

Table 5 Response rate by dose and by week based upon 25% or 50% reduction in CAARS total score

Time on treatment, weeks	Placebo			ATX 60 mg†			ATX 80 mg†			ATX 100 mg†		
	N‡	25% n (%)	50% n (%)	N‡	25% n (%)	50% n (%)	N‡	25% n (%)	50% n (%)	N‡	25% n (%)	50% n (%)
1	232	64 (27.6)	16 (6.9)	–	–	–	144	69 (47.9)	16 (11.1)	–	–	–
2	225	95 (42.2)	34 (15.1)	–	–	–	254	141 (55.5)	62 (24.4)	–	–	–
4	210	96 (45.7)	43 (20.5)	9	4 (44.4)	4 (44.4)	95	69 (72.6)	36 (37.9)	136	87 (64.0)	45 (33.1)
6–8	194	85 (43.8)	44 (22.7)	10	8 (80.0)	4 (40.0)	61	49 (80.3)	32 (52.5)	140	98 (70.0)	53 (37.9)
10–12	362	186 (51.4)	93 (25.7)	14	10 (71.4)	6 (42.9)	67	48 (71.6)	33 (49.3)	268	179 (66.8)	108 (40.3)
14–16	153	81 (52.9)	41 (26.8)	6	5 (83.3)	3 (50.0)	36	28 (77.8)	20 (55.6)	113	83 (73.5)	47 (41.6)
20–22	146	81 (55.5)	44 (30.1)	6	5 (83.3)	3 (50.0)	37	30 (81.1)	26 (70.3)	96	67 (69.8)	36 (37.5)
24–26	246	127 (51.6)	73 (29.7)	6	5 (83.3)	4 (66.7)	45	38 (84.4)	32 (71.1)	160	115 (71.9)	67 (41.9)

25%, 25% improvement in CAARS Total Score; 50%, 50% improvement in CAARS Total Score; ATX, atomoxetine; CAARS, Conners' Adult ADHD Rating Scale–Investigator Rated Scale. †ATX 25 mg and ATX 40 mg are not shown due to low N and lack of data across weeks. ‡The n fluctuates over time (weeks) based upon scale assessment schedule as outlined in Table 1; baseline was the last nonmissing value during baseline period. In cases where the N is less than the non-by-dose analyses, it is because dosing information was missing.

Of the nonresponders to atomoxetine during the double-blind studies, those that subsequently responded to atomoxetine in the open-label study continued to improve in their response for 36 weeks [22].

Atomoxetine's incremental efficacy over long time periods for the treatment of ADHD symptoms may be distinct, as there is no apparent evidence of a similar response pattern with stimulant ADHD medications [28]. While the mechanism to explain atomoxetine's incremental efficacy over time is unknown, it has been postulated that neuroadaptational changes may be involved with atomoxetine treatment [29–32] that may not be occurring with stimulant treatment [33].

In a recent analysis, pooling data from 4273 adult ADHD patients from 13 atomoxetine studies (24-weeks data, n = 1443; 12-week data, n = 2830), based upon CAARS total scores, patients were observed to have distinct atomoxetine response trajectories [34]. Five trajectory clusters were identified, with 4 of 5 clusters (representing 95% of completer patients, those who completed 24 and/or 12 weeks atomoxetine treatment) showing continued positive growth response trajectories throughout the 24-week studied time period. Although limited because these analyses were post hoc in a completer cohort, the data suggest that a patient's likelihood for atomoxetine treatment response increases over time on medication. These data suggest that patients treated with atomoxetine generally show a response that is gradual over at least several weeks for those patients that do respond, although variable trajectories of response may include early rapid response in some patients. While atomoxetine efficacy may not be maximal until 12–24 weeks or greater, additional long-term randomized, controlled trials are needed for more definitive conclusions regarding response plateau [10].

A key clinical point ascertained from these data is that healthcare providers might consider waiting at least 4–6 weeks at target dose before assessing atomoxetine efficacy. In particular, for patients showing some efficacy during the first 6 weeks, it may be beneficial to make subsequent decisions on whether to continue, add to, switch, or stop atomoxetine treatment based on efficacy at 12–24 weeks. It is also important to set expectations with patients that symptom improvement will be gradual and will take time. This is particularly important for patients who are not naive to stimulant medications, as amphetamine- and methylphenidate-based stimulant treatments tend to provide their maximal benefit quickly in those patients that respond [10].

Those atomoxetine patients that respond within the first 2 weeks of treatment are likely to be maximal responders over time, as early response has been shown in children to be a strong predictor of a greater subsequent response [11,35]. Patients that do not show clinically meaningful symptom reduction within the first 4–6 weeks at target dose may simply not be responders to atomoxetine treatment. Approximately 50% of adults responded to atomoxetine treatment in the two adult atomoxetine 10-week registration studies, based on a $\geq$ 25% reduction in the CAARS total score [5]. However, a clinically relevant percentage of patients will have a slower response profile such that those patients showing some symptom reduction by 6 weeks may have a clinically meaningful response by 12 weeks or longer [34].

Atomoxetine Dosing

Despite the recommended 80–100 mg/day target dose for adults, data suggest that healthcare providers prescribe atomoxetine at approximately 60–70 mg/day [13]. In one claims database dosing study of over 12,000 patients, only 27% of patients were dosed throughout the entire follow-up per prescribing information, and the average atomoxetine dose across all patients was only 68 mg/day [17]; patients never reaching 80 mg/day dosing had an average daily dose of 43 mg, which was about one-third of the patients. There are no data to suggest that adult daily doses less than 80 mg are generally effective. Thus, understanding the impact of dosing on patient outcomes is an important clinical question.

When discussing the efficacy results by dose over time, it is important to remember that based upon the investigators discretion, patients could have their atomoxetine increased to a maximum dose of 100 mg/day depending upon their atomoxetine treatment response and tolerability. Based upon the much larger number of patients in the 100 compared to 80 mg/day group, it appears that investigators tended to increase the atomoxetine

Table 6 Treatment-emergent adverse events in ≥5% of patients by dose titration strategy

	Study LYCU[†]			Study LYCW[†]				
Adverse event	PLA (N = 248) n (%)	ATX lower/slower titration[‡] (N = 243) n (%)	*P*-value versus PLA	PLA (N = 234) n (%)	ATX on–label titration[§] (N = 146) n (%)	*P*-value versus PLA	ATX slower titration[¶] (N = 120) n (%)	*P* -value versus PLA
Patients with ≥1 TEAE	150 (60.5)	191 (78.6)	<0.001	137 (58.5)	123 (84.2)	<0.001	98 (81.7)	<0.001
Dry mouth	13 (5.2)	61 (25.1)	<0.001	10 (4.3)	32 (21.9)	<0.001	28 (23.3)	<0.001
Nausea	16 (6.5)	52 (21.4)	<0.001	7 (3.0)	32 (21.9)	<0.001	37 (30.8)	<0.001
Headache	27 (10.9)	28 (11.5)	NS	32 (13.7)	18 (12.3)	NS	12 (10.0)	NS
Decreased appetite	7 (2.8)	26 (10.7)	<0.001	8 (3.4)	24 (16.4)	<0.001	24 (20.0)**	<0.001
Fatigue	12 (4.8)	24 (9.9)	0.038	12 (5.1)	11 (7.5)	NS	12 (10.0)	NS
Erectile dysfunction[††]	3 (2.3)	10 (8.5)	0.044	0 (0.0)	2 (2.6)	0.017	4 (6.8)	NS
Insomnia	15 (6.0)	15 (6.2)	NS	5 (2.1)	12 (8.2)	0.020	9 (7.5)	NS
Dizziness	11 (4.4)	13 (5.3)	NS	8 (3.4)	10 (6.8)	0.015	12 (10.0)	NS
Irritability	7 (2.8)	13 (5.3)	NS	10 (4.3)	4 (2.7)	NS	7 (5.8)	NS
Somnolence	8 (3.2)	12 (4.9)	NS	9 (3.8)	6 (4.1)	0.030	12 (10.0)	NS
Hyperhidrosis	1 (0.4)	8 (3.3)	0.019	0 (0.0)	8 (5.5)	NS	2 (1.7)	NS
Paresthesia	0 (0.0)	8 (3.3)	0.003	2 (0.9)	11 (7.5)	0.020	6 (5.0)	NS
Sleep disorder	4 (1.6)	6 (2.5)	NS	3 (1.3)	2 (1.4)	NS	6 (5.0)	NS
Ejaculation disorder[††]	0 (0.0)	2 (1.7)	NS	0 (0.0)	4 (5.2)	0.048	3 (5.1)	NS

ATX, atomoxetine; NS, nonsignificant; PLA, placebo; TEAE, treatment-emergent adverse event. [†]N is based upon all randomized patients who took at least one dose of study drug. [‡]ATX lower/slower titration: 25 mg/day for ≥7 days, then 40 mg/day for ≥7 days followed by 80 mg/day. [§]ATX on-label titration: 40 mg/day for 3 days followed by 80 mg/day. [¶]ATX slower titration: 40 mg/day for 7 days followed by 80 mg/day. [**]*P* = 0.023; ATX slower titration versus ATX lower/slower titration. [††]Denominator based on males only (LYCU: ATX lower/slower titration n = 118, Placebo n = 128 and LYCW: ATX on-label titration n = 77, ATX slower titration n = 59, Placebo: n = 102).

dose, perhaps thinking additional efficacy could be gained. The data also suggest that a large number of patients who had their atomoxetine dose increased to 100 mg/day were able to tolerate the dose.

The result that atomoxetine did not show a dose–response was not totally unexpected as patients were not randomized by dose, but were rather titrated up in dose based upon individual patient's needs. Symptom severity, based upon CAARS or AISRS baseline scores, did not appear to drive increased dosing. Patients less responsive to atomoxetine treatment could have had their dose increased up to 100 mg/day, thereby skewing the data in favor of the 80 mg/day group.

Effect size increased over 1–22 weeks in the 80 mg/day group, which also had the greatest endpoint effect size. Otherwise, effect size did not generally appear to increase after 6 weeks. While speculative and possibly chance findings, these data do suggest that the following: (1) getting to 80 mg/day may be important to optimize efficacy in responders, (2) good responders on average will continue to have increased response over time up through 22 weeks, and (3) patients not responding optimally at 80 mg/day on average also may not further respond at 100 mg/day. A few patients responded well at doses lower than the 80 mg/day recommended target dose. This did not appear to be based upon metabolizer status. Those patients dosed at 100 mg/day on average did not tend to do better, but it could be that those patients would have responded even less if kept at a lower dose.

There was a relatively high response rate across dose groups (about 70–85%), which was greater than in some previous studies where a 50% response rate in adults was observed based upon a 25% reduction in CAARS total score [10]. Assuming a 25% decrease is the minimal level of change needed for symptom reduction to be considered clinically relevant [11], then the levels of clinically relevant response in this study did not improve after about 6 weeks of atomoxetine treatment. This finding is consistent with the idea that most patients who will respond meaningfully to atomoxetine will do so by 4–6 weeks [36]. Across dose groups, the percentage of patients reaching a level of 50% improvement was about 40–70%. As particularly evident in the 80 mg/day group, the response rate based upon 50% improvement continued to increase over the course of 1–26 weeks. While about 70% of patients had a 25% symptom reduction at Week 4, only 40% reached a 50% reduction. However, by Week 20, 70% of patients had reached a 50% symptom reduction. This observation is consistent with the idea that patients who do respond to atomoxetine treatment will continue to have greater symptom improvement over time [10,34].

A key clinical point that can be derived from data to date is that physicians, at their discretion, working to optimize efficacy with tolerability in adults under clinical investigational circumstances, tend to increase the dose to above 80 mg/day. In the currently two pooled studies, the average final prescribed daily dose was 84 mg and 90 mg. Similarly, in the 2 adult 10-week registration studies, patients were titrated based upon tolerability and clinical response in a range of 60–120 mg/day [5]. The mean final dose was approximately 95 mg/day, suggesting the importance of dosing between 80 and 100 mg/day to reach optimal efficacy [15]. To maximize efficacy in some patients, higher doses might be necessary. Cytochrome P450 2D6 (CYP2D6) ultrarapid metabolizers (1.5% in US Caucasians, 2.0% African American) and possibly CYP2D6 extensive metabolizers with at least 2 active alleles (36.4% in US Caucasians and 18.3% African American) might benefit from higher atomoxetine doses, although further studies are needed to establish this theory [37]. The current data lacks pharmacogenetic information and did not provide doses over 100 mg/day, so it is unknown if the nonresponders were comprised of rapid metabolizers or could have benefited from higher doses.

While titrating more slowly or at lower doses than recommended could be advantageous for an individual patient, on average, these titration schemes provided no additional benefit over recommended dosing in the current pooled analysis. Moreover, slow titration in adults has been shown to lead to a greater incidence of decreased appetite, vomiting, and urinary hesitation, as well as longer duration of nausea [38]. Changing the atomoxetine dosing scheme from once daily to twice daily [38,39] or to taking with food is an alternative to improve the tolerability, without adjusting the recommended total daily dose [13].

An advantage of recommended dosing patterns is that patients can reach target dose faster, better allowing for time at target dose before efficacy assessments are made. This is relevant since staying on target dose for at least 4–6 weeks before judging efficacy is warranted. Because atomoxetine can lead to gradual symptom improvement, measurement-based care can be important to detect the symptom changes and avoid missing potential patient treatment response [40].

Conclusions

Long-term atomoxetine treatment in adults with ADHD, on average, resulted in initial (1–2 weeks) small decreases in ADHD symptoms, clinically meaningful improvements by 4–6 weeks, followed by further incremental symptom improvements and response rates over 10–26 weeks. Based upon this pooled dataset, an effect size of 0.45 was evident by 4 weeks and was persistent throughout subsequent time points; by 26 weeks, a moderate effect size of 0.52 was achieved. For patients responding well at the 80 mg/day target dose, the observation of increased symptom improvement over time was most pronounced, with a large effect size of 0.82 at 26 weeks in this subset of patients.

In adults with ADHD, atomoxetine should be initiated at a daily dose of 40 mg/day for a minimum of 3 days prior to upward dose titration to a target daily dose of 80 mg/day. After an additional 2–4 weeks, the dose may be increased to a maximum of 100 mg/day in patients not yet achieving an optimal response. Slow or low dose and slow titration schemes in adults did not provide tolerability advantages over on-label dosing.

The present data, in alignment with other studies, support the need for 10–26 weeks of atomoxetine treatment at target dosing in adults to observe optimal efficacy. It is important for healthcare providers to be aware of the time necessary for patients to be treated with atomoxetine at target dose prior to assessing efficacy outcome for making discontinuation, switching, or augmentation decisions. Additionally, it is important for healthcare providers to set patient expectations that although initial improvements are generally observed within the first few weeks of treatment, optimal outcomes for symptom reduction might take 3–6 months.

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Conflict of Interest

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