

# Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: An integrated analysis of the complete database of multicenter placebo-controlled trials

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## Abstract

Persistence of attention deficit hyperactivity disorder (ADHD) into adulthood can be disabling or lead to substantial impairment. Several clinical trials of atomoxetine (ATX) in adults with ADHD have been reported following the National Institute for Health and Clinical Excellence (NICE) guidelines issued in 2008. We performed an integrated analysis of all Eli Lilly-sponsored, randomized, double-blind, placebo-controlled studies of ATX in adults with ADHD completed as of May 2012. Individual patient data were pooled from six short-term (10–16 week) studies (1961 patients) and three longer-term (six-month) studies (1413 patients). In the short-term analysis, ATX patients achieved a significantly greater mean reduction in ADHD symptoms than placebo patients ( $-12.2$  vs  $-8.1$ ; Conners' Adult ADHD Rating Scale–Investigator-Rated: Screening Version (CAARS-Inv: SV);  $p < 0.001$ ). In the longer-term analysis, respective improvements after six months were  $-13.2$  vs  $-9.7$  ( $p < 0.001$ ). Response rates at study endpoints for ATX vs placebo, based on CAARS-Inv: SV improvement  $\geq 30\%$  and Clinical Global Impressions of ADHD–Severity (CGI-ADHD-S)  $\leq 3$  were  $34.8\%$  vs  $22.3\%$  in the short-term and  $43.4\%$  vs  $28.0\%$  after six months, and CAARS-Inv: SV improvements  $\geq 40\%$  were  $41.3\%$  vs  $25.3\%$  in the short-term and  $44.0\%$  vs  $31.4\%$  after six months (all  $p < 0.001$ ). Overall, ATX had a clinically significant effect in adults with ADHD, with reductions in core symptoms and clinically meaningful responder rates.

## Keywords

Attention deficit hyperactivity disorder, adults, atomoxetine, pooled analysis, treatment guidelines

## Background

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder of childhood, with an estimated average prevalence of 5% in different geographical regions (Polanczyk et al., 2010). Follow-up studies of children with ADHD show persistence of ADHD into adulthood in approximately 29% of the cases based on meeting the same diagnostic criteria as ADHD in childhood (Barbarese et al., 2013), or even higher proportions when evaluating the persistence of some of the ADHD symptoms, which still cause significant levels of psychosocial impairment (Faraone et al., 2006). A cross-national study using data collected across the Americas, Europe, and Asia estimated a prevalence in adults of 3.4% based on the Diagnostic Interview Schedule of the *Diagnostic and Statistical Manual of Mental Illness, 4th Edition* (DSM-IV) (Fayyad et al., 2007). These data are consistent with persistence rates estimated from clinical follow-up studies and reported in other surveys and meta-analytic reviews (Kessler et al., 2006; Simon et al., 2009).

Persistence of ADHD into adulthood is associated with a wide range of outcomes and levels of impairment (Asherson et al., 2012). When severe, the condition can be disabling: however, even moderate levels of impairment can be distressing to individuals and cause significant functional impairment in their daily lives. This is due at least in part to the chronicity of ADHD and its

association with the development of comorbid mental health and behavioral problems (Biederman et al., 1993). For example, a Norwegian study found that ADHD in adults was associated with lower educational achievement and levels of employment, resulting in fewer ADHD subjects having employment as their income source; with subsequent consequences for society in general (Gjervan et al., 2012). In addition, ADHD is particularly common among individuals with severe comorbid disorders, including autism, antisocial and borderline personality disorders, addiction disorders, and bipolar disorder (Kooij et al., 2010; Skirrow et al.,

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2012). A recent very large epidemiological survey of ADHD in Sweden found rates of criminal convictions around four times the general population rate, with reductions in convictions linked to prescribing of medical treatments, both stimulant and non-stimulant medications (Lichtenstein et al., 2012).

Access to clinical resources for ADHD in adults remains limited in many countries, in part because of the traditional perspective that ADHD is a problem restricted to childhood and due to the lack of approved treatments in many countries (Kooij et al., 2010). However, awareness of ADHD in adults is growing rapidly and there is now an urgent need to broaden understanding of the condition and to evaluate the effectiveness of available therapeutic interventions.

Based on current evidence, national and international guidelines recommend drug treatments as the first-line of clinical management for ADHD in adults, particularly where the disorder is associated with moderate-to-severe levels of impairment (Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA), 2011; Kooij et al., 2010; National Institute for Health and Clinical Excellence (NICE), 2008; Nutt et al., 2007). In the USA a wide range of pharmacological treatments are approved for use in adults, including atomoxetine (ATX), methylphenidate (MPH), dexamethylphenidate, and various amphetamines (Castells et al., 2011; Fredriksen et al., 2013). ATX was approved in the EU in May 2013 for initiation in adults to treat ADHD. No other medications are approved in Europe to be initiated for treatment of ADHD in adults, except in Germany only, where a long-acting form of MPH is approved since 2011.

ATX has been approved for use in children and adults in the USA since 2002 and for use in children and adolescents, as well as continuation of treatment into adulthood in Europe since 2004. ATX is a non-stimulant selective noradrenalin reuptake inhibitor (Bymaster et al., 2002). The onset of the effects of ATX on ADHD is gradual in children and adolescents and may take up to at least 12 weeks to be fully established (Montoya et al., 2009). Common side effects include typical noradrenergic side effects (nausea, dry mouth, sweating), and possible increases in heart rate and blood pressure. ATX appears to have low abuse-potential. In human laboratory studies, clinical trials and clinical practice, there is no evidence that ATX induces any subjective effects indicative of abuse (Upadhyaya et al., 2013).

In this manuscript, we report on a systematic review and integrated analysis of all available double-blinded randomized placebo-controlled studies of ATX in adults with ADHD. An integrated efficacy analysis is a patient-level meta-analysis where complete individual level data are combined across study datasets, obviating the need to amalgamate summary results from publications of individual studies, as in standard meta-analyses. In this integrated statistical analysis the complete set of randomized placebo-controlled studies conducted by Eli Lilly and Co. are included. We set out to summarize findings from all studies of ATX in adults with ADHD, including those that were not available when previous guidelines and reviews were published. Randomized double-blinded placebo-controlled studies from other groups have not been published, so we present an analysis of all potential data that could be included in this study at this time. One particular focus is on the results of longer-term studies which lasted for six months.

The systematic review includes all published studies and reports results using an integrated efficacy analysis of all nine randomized, placebo-controlled studies with ATX in adults with ADHD. These studies were submitted and assessed by the

European Union (EU) authorities for demonstration of efficacy and safety. The overall aim was to provide the first integrated analysis of the efficacy of ATX in adults with ADHD based on currently available data, particularly regarding long-term use, including clinically meaningful responder rates and effect size calculations, thus allowing indirect comparisons with other medications. The safety data from a related integrated dataset are reported in a separate publication (Camporeale et al., 2014).

## Methods

An integrated (pooled) analysis was performed. An integrated analysis can be viewed as a meta-analysis of individual patient-level data, as opposed to study-level summary data used in meta-analyses. This allows patient characteristics to be investigated by within-subgroup analyses which were not part of the original study analyses. The present analysis included all multicenter, randomized, double-blind efficacy studies of ATX in adults sponsored by Eli Lilly. Two Eli Lilly-sponsored studies were not included in the integrated analysis: one phase 2 cross-over study with very short treatment periods of three weeks (Spencer et al., 1998) and a maintenance of effect study including a randomized withdrawal period of atomoxetine responders (Upadhyaya et al., 2013) were not included as these had different objectives and study designs. The included studies comprised six short-term (10–16 week) placebo-controlled studies, including two studies of ADHD with comorbid disorders, and three longer-term (six-month) placebo-controlled studies (Table 1). In Table 1, and throughout this paper, each source study is referred to using their alphabetically-assigned Eli Lilly study identifier. New analyses were undertaken to calculate response rates across studies based on common definitions of response.

Data from the nine included studies were pooled to provide more precise estimates of response and responder rates, and effect size, and to increase the power of the analysis relative to the smaller subpopulations in the individual studies. All included studies were similar regarding inclusion criteria based on DSM-IV diagnostic criteria for ADHD and the use of the Connors Adult ADHD Diagnostic Interview from DSM-IV (CAADID) to establish the clinical diagnosis. Table 1 provides an overview of the designs of the included studies.

Regarding the acute studies of adults with ADHD, patients in one study (Eli Lilly study identifier: LYBY) had comorbid alcohol abuse (Wilens et al., 2011) and patients in another study (Eli Lilly study identifier: LYDQ) had comorbid social anxiety disorders (Adler et al., 2009a). Other Axis I comorbidities were excluded from all studies.

The choice of rating scales was not identical in all studies. The use of specific scales in specific studies is shown in Table 1. The following efficacy measures were assessed in the integrated analysis: (a) standard core symptom rating scales for ADHD in adults, based on DSM-IV items; (b) functional outcome measures; and (c) clinical response, defined as a combination of improvements in both core symptoms and functional response.

### Core symptoms

The CAARS-Inv: SV (Connors' Adult ADHD Rating Scale- Investigator Rated: Screening Version) was administered in eight out of the nine studies. The total CAARS score was the primary efficacy measure in seven of the nine studies. The CAARS-Inv: SV

**Table 1.** Design characteristics of placebo-controlled studies of atomoxetine in adult patients with attention deficit hyperactivity disorder (ADHD).

Eli Lilly study identifier	Age (mean), years	Male/female	Duration of double-blind treatment, weeks	ATX doses (mg/day) and sample size	Location of sites	Disorder	Primary measure	Key secondary measure(s)
<b>Short-term studies</b>								
<b>LYAA</b>	<b>≥18 (40.3)</b>	178/102	10	60–120 b.i.d. ATX <i>n</i> =141 Placebo <i>n</i> =139	USA, Canada	ADHD	CAARS-Inv: SV	CGI-ADHD-S
<b>LYAO</b>	<b>≥18 (42.1)</b>	170/86	10	60–120 b.i.d. ATX <i>n</i> =129 Placebo <i>n</i> =127	USA	ADHD	CAARS-Inv: SV	CGI-ADHD-S
<b>LYEE</b>	<b>≥18 (32.3)</b>	185/203	10	40–120 q.d. ATX <i>n</i> =195 Placebo <i>n</i> =196	Japan, South Korea, Taiwan	ADHD	CAARS-Inv: SV	BRIEF-A, EQ-5D, AAQoL, CGI-ADHD-S
<b>LYBY</b>	<b>≥18 (34.6)</b>	125/22	12	25–100 q.d. or b.i.d. ATX <i>n</i> =72 Placebo <i>n</i> =75	USA, Canada	ADHD with alcohol abuse	AISRS, Time to relapse of alcohol abuse	CGI-Overall-S
<b>LYDQ</b>	<b>18–65 (38.0)</b>	237/205	16	40–100 b.i.d. ATX <i>n</i> =224 Placebo <i>n</i> =218	USA	ADHD with social anxiety disorder	CAARS-Inv: SV	LSAS, CGI-Overall-S, AAQoL
<b>LYDZ</b>	<b>18–30 (24.7)</b>	255/190	12	40–100 b.i.d. ATX <i>n</i> =220 Placebo <i>n</i> =225	USA and Puerto Rico	ADHD	CAARS-Inv: SV	CGI-ADHD-S, AAQoL, BRIEF-A
<b>Longer-term studies</b>								
<b>LYCW</b>	<b>≥18 (41.3)</b>	239/263	26	40–100 o.m. ATX <i>n</i> =268 Placebo <i>n</i> =234	USA	ADHD	CAARS-Inv: SV	CGI-ADHD-S, FAM-III
<b>LYBV</b>	<b>18–50 (36.8)</b>	240/170	26	40–100 q.d. (but b.i.d. allowed) ATX <i>n</i> =271 Placebo <i>n</i> =139	USA	ADHD	EWPS	CGI-ADHD-S, CAARS-Inv: SV, AAQoL
<b>LYCU</b>	<b>18–54 (37.6)</b>	254/247	26	25–100 o.m. ATX <i>n</i> =250 Placebo <i>n</i> =251	USA	ADHD	AISRS	CGI-ADHD-S, CAARS-Inv: SV, CAARS-0: SV-evening; ASRS Symptom Checklist Evening, Brown ADD, STAI, D-KEFS, AAQoL

AAQoL: Adult ADHD Quality-of-Life Scale; ADHD: attention deficit hyperactivity disorder; AISRS: Adult ADHD Investigator Symptoms Rating Scale; ASRS: Adult ADHD Self-Report Scale Symptom Checklist; ATX: atomoxetine; b.i.d.: twice daily; BRIEF-A: Behavior Rating Inventory of Executive Functioning-Adult version; Brown ADD: Brown Attention Deficit Disorder Scale; CAARS-Inv: SV: Conners' Adult ADHD Rating Scale-Investigator-Rated; CAARS-0: SV: CAARS-Observer-Rated; CAARS-S: SV: CAARS-Self-Rated; CGI-ADHD-S: Clinical Global Impressions of ADHD-Severity; CGI-Overall-S: Clinical Global Impressions Overall-Severity; DB: double-blind; D-KEFS: Delis-Kaplan Executive Functioning System; DSM-IV: *Diagnostic and Statistical Manual of Mental Illness, 4th Edition*; EQ-5D: EuroQol: 5 Dimensions Questionnaire; EWPS: Endicott Work Productivity Scale; FAM-III: Dyadic Relationship Scale of the Family Assessment Measure, version 3; LSAS: Liebowitz Social Anxiety Scale; *n*: number of patients; o.m.: every morning; q.d.: every day; STAI: State Trait Anxiety Inventory.

(Conners et al., 1999) is a 30-item scale containing three subscales: inattention, hyperactivity-impulsivity, and the ADHD index.

The AISRS (Adult ADHD Investigator Symptoms Rating Scale) was administered as the primary efficacy measure in two studies (LYBY, LYCU). It is an 18-item scale that captures the 18 DSM-IV symptoms of ADHD (Spencer et al., 2010).

### Functional outcome measures

CGI-ADHD-S (Clinical Global Impression-Severity) or CGI overall. The CGI scale is a standardized assessment measure. It provides a general rating of a patient's overall impairment or overall improvement (Guy, 1976). The versions used in the studies reported were the CGI-ADHD-S, which consists of a single-item rating of the clinician's assessment of the severity of ADHD symptoms in relation to the clinician's total experience with

ADHD patients and the CGI-Overall-S, which is a modified version of the CGI used in the studies that included patients with ADHD and comorbid disorders (LYBY and LYDQ).

The Adult ADHD Quality-of-Life Scale (AAQoL) is a 29-item patient-reported outcome measure used to examine disease-specific functional impairments relevant to adults with ADHD (Brod et al., 2006). The five AAQoL subscales cover life productivity, psychological health, life outlook, and relationships. The AAQoL was administered in five of the nine studies.

### Response measures

Response measures based on the CAARS and CGI were primary or secondary endpoints in five of the nine adult studies using either a priori defined response criteria at certain time points (four studies) or a time to response analysis (two longer-term

studies). In this integrated analysis we used three response definitions based on CAARS and CGI. Symptomatic response was assessed by CAARS-Inv: SV Total score improvement with three different levels of decrease,  $\geq 30\%$ ,  $\geq 40\%$ , and  $\geq 50\%$  from baseline to endpoints. A combined symptomatological and functional response definition evaluated responses based on functional improvement only; specifically a CGI-ADHD-S score improved to less than or equal to three (i.e. at most mildly ill) at study endpoint. In addition response regarding quality of life was assessed by an AAQoL improvement of  $\geq 1$  SD at baseline. Responder rates were calculated separately for the short-term and the longer-term studies.

### Statistical methods for integrated analysis

For the analysis of continuous measures, an analysis of variance (ANOVA) model which contained the main effects of treatment and trial was used for demographics analysis. An analysis of covariance (ANCOVA) model was used with the terms in the ANOVA with baseline added as a covariate. The last observation carried forward (LOCF) method was used for missing data in the efficacy analyses.

For subgroup analysis of the CAARS-Inv-SV, an ANCOVA model which contained baseline, trial, treatment, subgroup and the treatment-by-subgroup interaction was used. For categorical data, the significance of overall treatment group differences was assessed using Fisher's exact test for demographics analysis, and Cochran-Mantel-Haenszel statistic stratified by study for efficacy analysis.

## Results

### Individual studies

The main efficacy results from six short-term and three longer-term (six-month) placebo-controlled studies, which were included in the integrated analyses, are summarized in Tables 2(a) and 2(b), respectively.

### Integrated analyses of baseline characteristics

In total, 1961 patients (from the six short-term studies) and 1413 patients (from the three longer-term studies) were included in the integrated efficacy analyses. All patients were adults who had a diagnosis of ADHD according to DSM-IV criteria and did not have concomitant depression or bipolar disorder. Table 3 presents an overview of the patient demographics and baseline characteristics by treatment. In the short and longer-term integrated analyses, no statistically significant differences were observed between ATX and placebo treatment groups with age, sex or ethnicity. In all nine studies combined, 55.8% of the patients were male, 73.5% Caucasian, and most (~90%) were recruited in the US and Canada.

### Integrated analyses

As described below, in the pooled analyses ATX demonstrated statistically significantly greater mean improvements than

placebo in measures of ADHD symptomatology, functioning and responder rates (Tables 4 and 5).

**Short-term studies.** In the pooled analyses, based on the five out of six short-term studies that used the CAARS-Inv: SV Total score, ATX-treated patients achieved statistically significantly greater mean reduction in ADHD symptoms compared with placebo-treated patients ( $-12.4$  vs  $-8.4$ ) and, as presented in Table 4, in the CAARS-Inv: SV inattention and hyperactivity-impulsivity subscales ( $-6.9$  vs  $-4.7$  and  $-5.5$  vs  $-3.7$ , respectively), with  $p < 0.001$  for all three measures. The CGI-ADHD-S, the key functional outcome measure in four of the studies, showed statistically significantly greater mean improvement in ATX-treated compared with placebo-treated patients ( $-1.0$  vs  $-0.6$ ;  $p < 0.001$ ; Table 4). The average effect size for ATX compared with placebo at 10 weeks (based on CAARS-Inv: SV Total score) was 0.41 for the integrated short-term analysis.

In the responder analyses, based on CAARS and CGI-ADHD-S, five response definitions were analyzed and are presented in Table 5. ATX-treated patients had statistically significantly higher response rates compared with placebo-treated patients for all three cutoffs ( $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ) in the symptomatic response definition based on the CAARS-Inv: SV Total score, as well as in the combined response criterion based on CAARS-Inv: SV Total score and the CGI-ADHD-S.

As an additional functional outcome measure analysis, the AAQoL total score and subscores were available in three of the studies. ATX-treated patients achieved statistically significantly greater mean improvement than placebo-treated patients in the AAQoL total score ( $13.7$  vs  $9.7$ ;  $p < 0.001$ ) and all of the subscores (life productivity,  $p < 0.001$ ; psychological health,  $p = 0.001$ ; life outlook,  $p = 0.003$ ; and relationships,  $p < 0.001$ ; Table 4). A response based on quality of life measurements showed a statistically significant difference between ATX and placebo-treated patients at the endpoints of the short-term studies ( $p = 0.002$ ; Table 5).

To determine differential effects, a subgroup analysis based on the mean change from baseline to endpoint on the CAARS-Inv: SV Total score was performed using data from the short-term studies integrated analysis. Subgroups analyzed were age group, ethnicity, sex, CYP2D6 status, prior stimulant use, baseline ADHD severity, baseline quality-of-life, and ADHD subtype. Of these, the only analysis that demonstrated a statistically significant treatment-by-subgroup interaction was ethnicity ( $p = 0.027$ ). This result was driven by much higher placebo responses in the small ( $n = 235$ , 7.0%) group of Hispanics relative to other groups.

**Longer-term studies.** In the longer-term pooled analysis, ATX-treated patients achieved statistically significantly greater mean reductions in ADHD symptoms compared with placebo-treated patients in the CAARS-Inv: SV Total score ( $-13.2$  vs  $-9.7$ ) and the Inattention and Hyperactivity-Impulsivity subscales ( $-5.4$  vs  $-5.7$  vs  $-4.3$ , respectively), with  $p < 0.001$  for all three measures (Table 4).

ATX-treated patients also achieved statistically significantly greater mean improvement than placebo-treated patients in CGI-ADHD-S ( $-1.1$  vs  $-0.8$ ;  $p < 0.001$ ; Table 4). The average effect size for ATX compared with placebo after six months was 0.31 for the integrated longer-term analysis.

**Table 2(a).** Efficacy data from individual short-term (10–16 weeks), placebo-controlled studies: changes by treatment group from baseline.

Eli Lilly study identifier	LYAA		LYAO		LYEE		LYBY		LYDQ		LYDZ	
	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)	Placebo vs ATX (p-value)
Number of patients	134 vs 133	124 vs 124	195 vs 191	75 vs 72	158 vs 171	198 vs 192						
Completion rates (%)	72.3 vs 77.0	63.6 vs 70.1	80.5 vs 87.2	44.4 vs 64.0	56.7 vs 62.8	52.5 vs 57.8						
CAARS-Inv: SV, mean change from baseline <sup>a</sup>	-6.0 vs -9.5 (0.006)	-6.7 vs -10.5 (0.002)	-8.8 vs -14.3 (<0.001)	Scale not used <sup>b</sup>	-5.6 vs -8.7 (<0.001)	-7.2 vs -10.7 (<0.001)						
Total score												
Inattention subscore	-3.1 vs -5.0 (0.010)	-3.5 vs -5.8 (0.001)	-5.1 vs -8.2 (<0.001)		-3.6 vs -4.8 (0.001)	-4.3 vs -5.7 (<0.001)						
Hyperactive/impulsive subscore	-2.9 vs -4.5 (0.017)	-3.2 vs -4.7 (0.012)	-3.7 vs -6.1 (<0.001)		-2.0 vs -3.9 (<0.001)	-2.9 vs -5.0 (<0.001)						
AAQoL, total score	Scale not used	Scale not used	8.2 vs 12.8 (<0.001)	Scale not used <sup>b</sup>	11.1 vs 14.9 (0.030)	11.0 vs 15.8 (0.005)						
CGI-ADHD-S or CGI-Overall-S, mean change from baseline <sup>c</sup>	-0.4 vs -0.8 (0.011)	-0.5 vs -0.9 (0.002)	-0.8 vs -1.3 (<0.001)	-0.7 vs -1.0 (0.048)	-0.6 vs -0.8 (0.022)	-0.7 vs -1.1 (<0.001)						
Response rate (%) <sup>d</sup>	20.9 vs 27.8 (0.188)	22.0 vs 29.8 (0.103)	23.6 vs 34.8 (<0.001)	Not analyzed	Not analyzed	22.1 vs 34.4 (0.002)						
Reference	Marchant et al., 2011	Marchant et al., 2011	Goto et al., 2013	Wiliens et al., 2011	Adler et al., 2009a	Durell et al., 2013						

AAQoL: Adult ADHD Quality-of-Life scale; ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; CAARS-Inv: SV: Connors' Adult ADHD Rating Scale, Investigator Rated; CGI-ADHD-S: Clinical Global Impression of Severity for ADHD; CGI-Overall-S: Clinical Global Impressions Overall-Severity.

<sup>a</sup>Mean changes in CAARS-Inv: SV were calculated using the last observation carried forward (LOCF) method.

<sup>b</sup>Study LYBY used the Adult ADHD Investigator Symptom Rating Scale (AISRS) instead of CAARS. With AISRS, total scores (placebo vs ATX) were -8.3 vs -13.6 ( $p=0.007$ ), inattention scores were -4.4 vs -7.2 ( $p=0.013$ ) and hyperactivity/impulsive scores were -3.9 vs -6.5 ( $p=0.009$ ).

<sup>c</sup>The CGI Overall-S scale was administered in Studies LYBY and LYDQ. CGI Overall evaluated the severity of both ADHD and a secondary condition.

<sup>d</sup>Response in Studies LYAA, LYAO, LYEE, and LYDZ was defined as a decrease of  $\geq 30\%$  (from baseline through final observation point) in CAARS-Inv: SV total ADHD symptom score and a CGI-ADHD-S  $\leq 3$  at endpoint.

**Table 2(b).** Efficacy data from individual longer-term (six-month), placebo-controlled studies: changes by treatment group from baseline.

Eli Lilly study identifier	LYBV	LYCU	LYCW
	Placebo vs ATX ( <i>p</i> -value)	Placebo vs ATX ( <i>p</i> -value)	Placebo vs ATX ( <i>p</i> -value)
Number of patients	109 vs 185	216 vs 214	234 vs 268
Completion rates (%)	38.4 vs 48.9	37.6 vs 44.6	44.4 vs 57.3
CAARS-Inv: SV, mean change from baseline <sup>a</sup>	-11.5 vs -11.6 (0.412) <sup>b</sup>	-10.2 vs -13.2 (0.005) <sup>c</sup>	-8.3 vs -14.3 (<0.001) <sup>d</sup>
Total score			
Inattention subscore	-6.7 vs -6.9 (0.406)	-5.7 vs -7.4 (0.013)	-4.4 vs -8.1 (<0.001)
Hyperactive/impulsive subscore	-4.8 vs -4.7 (0.538)	-4.6 vs -5.8 (0.006)	-3.9 vs -6.2 (<0.001)
AAQoL, total score	11.18 vs 13.90 (0.045)	8.62 vs 13.14 (0.004)	Scale not used
CGI-ADHD-S, mean change from baseline	-0.9 vs -1.0 (0.173)	-0.9 vs -1.2 (0.001)	-0.7 vs -1.2 (<0.001)
Response rate (%) <sup>e</sup>	33.9 vs 41.1 (0.165)	29.2 vs 41.6 (0.006)	24.2 vs 46.6 (<0.001)
Mean time to response (days)	Not analyzed	84 vs 53 (<0.001)	61 vs 40 (<0.001)
Remission rate (CGI-S 1 or 2)	Not analyzed	Not analyzed	12.1 vs 20.8 (0.011)
Mean time to remission (days)	Not analyzed	142 vs 165 (0.001)	144 vs 125 (<0.001)
Reference	Adler et al., 2008	Adler et al., 2009b	Young et al., 2011

AAQoL: Adult ADHD Quality-of-Life scale; ATX: atomoxetine; CAARS: Connors Adult ADHD Rating Scale; CGI-ADHD-S: Clinical Global Impression of Severity for ADHD.

<sup>a</sup>Mean changes in CAARS-Inv: SV were calculated using the LOCF method.

<sup>b</sup>The primary measure for Study LYBV was Endicott Work Productivity Scale (EWPS), used to evaluate work productivity.

<sup>c</sup>The primary measure for Study LYCU was a repeated measures analysis of the Adult ADHD Investigator Symptom Rating Scale (AISRS), which showed similar results (-11.7 for placebo vs -16.2 for ATX; *p*=0.001) to the CAARS-Inv: SV.

<sup>d</sup>The primary analysis for Study LYCW was a repeated measures analysis, which showed similar results (-8.7 for placebo vs -16.4 for ATX; *p*<0.001) to the CAARS-Inv: SV.

<sup>e</sup>Response was defined as a ≥30% CAARS-Inv: SV improvement and CGI-ADHD-S ≤3.

In the responder analyses based on CAARS and CGI, five response definitions were analyzed in a similar way as in the short-term pooled analysis (Table 5). ATX patients had statistically significantly higher response rates compared with placebo patients for all three cutoffs (≥30%, ≥40%, ≥50%) in the symptomatic response definition based on the CAARS-Inv: SV Total score. In a stringent combined symptomatological and functional response criterion using a definition of ≥30% reduction in CAARS-Inv: SV total score and a CGI-ADHD-S score ≤3, the proportion of ATX responders at six months was significantly larger than for placebo (43.4% vs 28.0%; *p*<0.001, Table 5).

The AAQoL was used to assess quality-of-life and additional functional outcomes in two of the three longer-term studies (LYBV and LYCU). In the pooled analysis of AAQoL total and subscores for these two studies, ATX-treated patients achieved statistically significantly greater mean improvement than placebo-treated patients in AAQoL total score (13.5 vs 9.6; *p*=0.001) and three of the four subscores (life productivity, *p*=0.001; psychological health, *p*=0.021; and life outlook, *p*=0.003; Table 4). An analysis based on the AAQoL showed a statistically significant higher quality of life responder rate for ATX compared to placebo-treated patients at the endpoint of the longer-term studies (see Table 5).

## Discussion

In this integrated analysis, we were able to assess not only core ADHD symptom change but also functional and clinically meaningful responder rates, based on all nine placebo-controlled ATX trials undertaken in adults by Eli Lilly. There are currently no published direct comparative trials of ATX with stimulants or other targeted treatments for adults with ADHD. Hence, the response rates and effect sizes that we calculated in this

integrated analysis only allowed indirect comparisons with data available for other treatments. Nevertheless, our findings may have relevance for clinicians, guideline development and future trial design.

In both the short-term and longer-term analyses, ATX demonstrated clinical efficacy versus placebo in all variables including response rates and effect size.

Across all six short-term studies and in the short-term integrated analysis, ATX demonstrated significantly greater mean improvement than placebo on core measures of ADHD symptoms, quality-of-life and functional impairment. In a majority of the analyses of clinically meaningful response, as defined using measures of symptoms, measures of functional impairment, or a combination of both, there were significantly higher proportions of ATX-treated patients achieving a positive outcome compared with placebo. The consistency of these results across all six short-term studies demonstrates that ATX has a robust effect improving ADHD symptomatology and functional outcomes in the short-term treatment of adult patients with ADHD.

Although no head-to-head comparative studies of ATX and stimulants are available, results were recently reported in a study which used ATX and MPH as active comparators vs placebo and bupropion, a histamine H3 receptor agonist (Weisler et al., 2012). ATX and long-acting MPH were both statistically significantly superior to placebo after six weeks of treatment and showed comparable mean improvements based on the ADHD-RS scale from baseline of -15.3 for ATX and -15.7 for long-acting MPH (Weisler et al., 2012). Overall our results suggest that effect sizes are more similar to those of stimulants than previously thought, with recent meta-analyses of MPH in adults with ADHD giving average effect sizes around 0.5 (Castells et al., 2011; Koesters et al., 2009).

As ADHD in adults is usually treated over long periods, longer-term studies evaluating efficacy are of particular value. Regarding the use of ATX in children, there is evidence that the

**Table 3.** Demographics and baseline characteristics of patients in the short-term and longer-term studies (integrated analyses).

Parameter	Short-term studies integrated analysis			Longer-term studies integrated analysis		
	Placebo	ATX	<i>p</i> -value	Placebo	ATX	<i>p</i> -value
Age (years), <i>N</i>	980	981		624	789	
Mean±SD	34.2±11.1	34.8±11.3	0.39	38.6±9.0	38.7±8.8	0.48
Sex, <i>N</i>	980	981		624	789	
Male, <i>n</i> (%)	575 (58.7)	575 (58.6)	1.00	320 (51.3)	413 (52.3)	0.71
Female	405 (41.3)	406 (41.4)		304 (48.7)	376 (47.7)	
Ethnic origin, <i>N</i>	980	981		624	789	
White, <i>n</i> (%)	632 (64.5)	646 (65.9)	0.61	531 (85.0)	671 (85.0)	0.90
Black	53 (5.4)	46 (4.7)		32 (5.1)	37 (4.7)	
Asian	214 (21.8)	216 (22.0)		6 (1.0)	9 (1.1)	
Hispanic	69 (7.0)	67 (6.8)		45 (7.2)	54 (6.8)	
Other	12 (1.2)	6 (0.6)		10 (1.6)	18 (2.3)	
ADHD subtype, <i>N</i>	980	979		623	789	
Inattentive, <i>n</i> (%)	331 (33.8)	325 (33.2)	0.73	177 (28.4)	239 (30.3)	0.72
Hyperactive/impulsive	18 (1.8)	14 (1.4)		5 (0.8)	5 (0.6)	
Combined	631 (64.4)	640 (65.4)		441 (70.8)	545 (69.1)	
CAARS-Inv: SV scores, <i>N</i>	905	909		623	786	
Mean±SD	35.3±8.1	35.1±8.2	0.55	35.8 ±8.3	35.0±8.2	0.11
CGI-ADHD-S scores, <i>N</i>	687	685		624	789	
Mean±SD	4.7±0.7	4.8±0.7	0.30	4.6±0.6	4.6±0.7	0.42
<4, <i>n</i> (%)	0 (0.0)	0 (0.0)	0.18	0 (0.0)	1 (0.1)	0.26
4–5	591 (86.0)	571 (83.4)		579 (92.8)	717 (90.9)	
>5	96 (14.0)	114 (16.6)		45 (7.2)	71 (9.0)	

ATX: atomoxetine; CAARS-Inv: SV: Conners' Adult ADHD Rating Scale–Investigator-Rated; CGI-ADHD-S: Clinical Global Impressions of ADHD–Severity; *N*: number of randomized patients per parameter; *n*: number of patients per sub-parameter; SD: standard deviation.

Studies LYBY and LYDQ are excluded from CGI-ADHD-S descriptive statistics because they were conducted in comorbid populations. Similarly, Study LYBY did not collect CAARS-Inv: SV, therefore the numbers of patients included in the analyses are lower than the numbers randomized, *p*-values for categorical data are from Fisher's exact test; *p*-values for ethnicity are from the chi-square test; *p*-values for continuous data are from the Type III sums of squares analysis of variance (ANOVA) model with terms for treatment and study.

response of ADHD symptoms increases with time on medication, with results suggesting further improvement in effect size up to 12 weeks (Bushe and Savill, 2011). A similar result was seen in Study LYCU, with maximum effect size around 10 weeks, followed by a stable effect up to six months (Adler et al., 2009b). In the other positive long-term study, further enhancement of the effect size was seen beyond 12 weeks, with effect size increasing from 0.41 at 12 weeks to 0.57 at six months (Young et al., 2011). These two studies show statistically significant but not maximal treatment effects at 2–4 weeks, which was also seen in other ATX studies (Durell et al., 2013; Michelson et al., 2003).

Despite the finding in the Young et al. study (2011) of a maximal effect at six months, an enhanced effect size developing beyond three months is not seen in the overall findings from the integrated analysis; comparing the average effect size of the short-term studies (0.41) to the longer-term studies (0.31). However, there are limitations to drawing firm conclusions based on these three studies. Study LYBV involved a different pattern of findings that could be explained by the study design. Unlike the other two studies, Study LYBV included only patients who were in paid employment, and measured work productivity as the primary outcome. Furthermore, there was a high drop-out rate in this study, potentially influencing the results, and overall a negative result for improvement in ADHD symptoms not consistent

with the findings from the other adult ATX studies. Further evidence for possible enhanced effects over longer periods of time comes from a separate long-term open-label follow-up study, which found that some individual patients who failed to respond during a randomized trial phase of the study responded at a later time point (Marchant et al., 2011). Overall, these findings suggest that in most cases a significant response will be seen within four weeks, with further improvements in effect size expected up to 12 weeks.

To evaluate the generalizability of the result of the acute integrated analysis, we performed subgroup analyses by age group, ethnicity, sex, CYP2D6 status, prior stimulant use, baseline ADHD severity, baseline quality-of-life, and ADHD subtype. These analyses did not show any clinically relevant differences in the efficacy of ATX for any of these subgroups, apart from small but statistically significant differences seen in the ethnicity analyses. This should assure good generalizability of the efficacy data to clinical practice (Surman et al., 2010), although it does not take account of common comorbidities seen in adults with ADHD. Two of the studies suggest that ATX is effective in adult cases of ADHD with comorbid social anxiety and alcohol abuse disorders (Adler et al., 2009a; Wilens et al., 2011).

While both of these integrated analyses of ATX are solely based on the nine Eli Lilly-sponsored studies, for which complete

**Table 4.** Efficacy data (CAARS-INV: SV, CGI-ADHD-S, AAQoL scores) from the short-term and longer-term studies (integrated analyses).

Parameter	Short-term studies integrated analysis			Longer-term studies integrated analysis		
	Placebo	ATX	ATX vs placebo, <i>p</i> -value	Placebo	ATX	ATX vs placebo, <i>p</i> -value
CAARS-Inv: SV total score, <i>n</i>	863	849		557	663	
Baseline, mean±SD	35.2±8.1	35.0±8.2		35.6±8.2	34.8±8.2	
Endpoint, mean±SD	26.8±11.2	22.6±11.4		25.9±11.9	21.7±11.6	
Change to endpoint, mean±SD	-8.4±10.0	-12.4±10.9		-9.7±11.8	-13.2±12.1	
ATX vs placebo, LS mean (95% CI)	-4.1 (-5.0- -3.2)		<0.001	-3.9 (-5.2- -2.7)		<0.001
CAARS-Inv: SV, inattentive score, <i>n</i>	863	849		557	665	
Baseline, mean±SD	20.4±4.1	20.2±4.2		20.2±4.1	20.0±4.3	
Endpoint, mean±SD	15.6±6.3	13.3±6.5		14.9±6.9	12.6±6.7	
Change to endpoint, mean±SD	-4.7±5.9	-6.9±6.3		-5.4±6.9	-7.5±7.0	
ATX vs placebo, LS mean (95% CI)	-2.2 (-2.8- -1.7)		<0.001	-2.2 (-2.9- -1.4)		<0.001
CAARS-Inv: SV, hyperactive/ impulsive score, <i>n</i>	863	849		557	664	
Baseline, mean±SD	14.8±5.8	14.8±5.8		15.4±5.8	14.8±5.8	
Endpoint, mean±SD	11.2±6.3	9.3±6.1		11.1±6.2	9.1±5.9	
Change to endpoint, mean±SD	-3.7±5.1	-5.5±5.5		-4.3±5.9	-5.7±6.1	
ATX vs placebo, LS mean (95% CI)	-1.9 (-2.3- -1.4)		<0.001	-1.7 (-2.3- -1.1)		<0.001
CGI-ADHD-S score, <i>n</i>	652	640		611	758	
Baseline, mean±SD	4.7±0.7	4.8±0.7		4.6±0.6	4.6±0.7	
Endpoint, mean±SD	4.1±1.1	3.7±1.1		3.8±1.1	3.5±1.2	
Change to endpoint, mean±SD	-0.6±1.0	-1.0±1.2		-0.8±1.1	-1.1±1.2	
ATX vs placebo, LS mean (95% CI)	-0.4 (-0.5- -0.3)		<0.001	-0.35 (-0.5- -0.2)		<0.001
AAQoL total score, <i>n</i>	561	538		344	440	
Baseline, mean±SD	45.1±14.3	45.0±14.8		47.4±13.1	47.2±13.2	
Endpoint, mean±SD	54.8±16.4	58.7±17.9		57.0±17.3	60.7±17.2	
Change to endpoint, mean±SD	9.7±14.8	13.7±16.5		9.6±15.8	13.5±16.2	
ATX vs placebo, LS mean (95% CI)	4.0 (2.2-5.7)		<0.001	3.6 (1.5-5.8)		0.001
AAQoL subscore for life productivity measurement, <i>n</i>	561	538		342	440	
Baseline, mean±SD	40.7±19.3	40.5±19.2		41.4±16.9	41.8±16.6	
Endpoint, mean±SD	52.4±21.3	57.2±22.7		53.8±21.0	58.9±20.6	
Change to endpoint, mean±SD	11.7±19.8	16.8±21.7		12.4±21.3	17.1±20.7	
ATX vs placebo, LS mean (95% CI)	4.9 (2.7-7.2)		<0.001	4.5 (1.8-7.3)		0.001
AAQoL subscore for psychological health measurement, <i>n</i>	560	539		343	441	
Baseline, mean±SD	46.1±20.1	45.8±21.0		51.2±19.4	49.0±19.8	
Endpoint, mean±SD	56.0±21.0	59.5±22.6		59.3±21.5	61.4±21.2	
Change to endpoint, mean±SD	9.9±20.5	13.6±21.5		8.1±19.9	12.5±21.0	
ATX vs placebo, LS mean (95% CI)	3.7 (1.4-5.9)		0.001	3.1 (0.5-5.7)		0.021
AAQoL subscore for life outlook measurement, <i>n</i>	558	538		343	440	
Baseline, mean±SD	47.0±16.0	47.8±16.8		49.9±14.0	50.7±14.8	
Endpoint, mean±SD	53.2±17.8	56.4±19.3		56.4±17.5	60.3±17.6	
Change to endpoint, mean±SD	6.2±15.6	8.7±18.1		6.5±16.0	9.7±16.6	
ATX vs placebo, LS mean (95% CI)	2.8 (0.9-4.6)		0.003	3.3 (1.1-5.5)		0.003
AAQoL subscore for relationships measurement, <i>n</i>	561	539		343	440	
Baseline, mean±SD	51.1±20.8	50.6±20.7	<0.001	52.6±18.8	52.4±18.7	0.053
Endpoint, mean±SD	60.8±21.1	64.4±21.1		62.2±20.3	64.7±20.1	
Change to endpoint, mean±SD	9.7±20.3	13.8±21.1		9.5±19.5	12.3±19.7	
ATX vs placebo, LS mean (95% CI)	3.9 (1.7-6.0)			2.5 (0.0-5.0)		

AAQoL: Adult ADHD Quality-of-Life; ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; CAARS-Inv: SV: Conners' Adult ADHD Rating Scale- Investigator-Rated; CGI-ADHD-S: Clinical Global Impressions of ADHD-Severity; CI: confidence interval (two-sided); LS: least square; *n*: number of randomized patients with baseline and post-baseline result(s).

Studies LYBY and LYDQ are excluded from CGI-ADHD-S descriptive statistics because they were conducted in comorbid populations. Similarly, Study LYBY did not collect CAARS-Inv: SV data, and Studies LYAA, LYAO and LYBY did not collect AAQoL data, *p*-values for mean CGI-ADHD-S, CAARS-Inv: SV and AAQoL scores are from the Type III sums of squares analysis of variance (ANOVA) model: change: treatment + study + baseline value; *p*-values for response rates are from the Cochran Mantel-Haenszel method.



**Table 5.** Response rates of atomoxetine and placebo in short-term and longer-term studies (integrated analyses).

Response parameters	Short-term studies integrated analysis			Longer-term studies integrated analysis		
	Placebo	ATX	<i>p</i> -value	Placebo	ATX	<i>p</i> -value
CAARS improved by <i>N</i>	851	841		557	663	
≥30%, <i>n</i> (%)	299 (35.1)	444 (52.8)	<0.001	224 (40.2)	373 (56.3)	<0.001
≥40%, <i>n</i> (%)	215 (25.3)	347 (41.3)	<0.001	175 (31.4)	292 (44.0)	<0.001
≥50%, <i>n</i> (%)	136 (16.0)	259 (30.8)	<0.001	140 (25.1)	237 (35.8)	<0.001
CAARS improved ≥30% and CGI-ADHD-S ≤3	651	640		557	663	
<i>n</i> (%)	145 (22.3)	223 (34.8)	<0.001	156 (28.0)	288(43.4)	<0.001
AAQoL improved by ≥1 SD, <i>N</i> :	555	537		344	440	
<i>n</i> (%)	174 (31.4)	213 (39.7)	0.002	100 (29.1)	168 (38.2)	0.007

AAQoL: Adult ADHD Quality-of-Life; ADHD: attention deficit hyperactivity disorder; ATX: atomoxetine; CAARS-Inv: SV: Conners' Adult ADHD Rating Scale- Investigator-Rated; CGI-ADHD-S: Clinical Global Impressions of ADHD-Severity; *N*: number of randomized patients per parameter; *n*: number of patients per sub-parameter; SD: standard deviation.

individual data are available, it is notable that the efficacy of ATX has also been investigated in five controlled studies that were not sponsored by Eli Lilly (Bain et al., 2013; McRae-Clark et al., 2010; Sobanski et al., 2012, 2013; Sutherland et al., 2012; Weisler et al., 2012). We did not include these non-Eli Lilly-sponsored studies in the current analyses because individual data of these were not available. In addition, the design of these studies was difficult to compare (e.g. crossover; Bain et al., 2013), they were not completely blinded or not placebo-controlled (Sobanski et al., 2012, 2013), or had a very high drop-out rate (McRae-Clark et al., 2010). Nevertheless, ATX was shown to be effective in all five of these placebo-controlled studies. For example in the first period of the crossover study by Bain et al. (2013), the effect size for ATX vs placebo was 0.57.

## Conclusions

In summary, these data show that ATX has a statistically significant and clinically relevant response in adults with ADHD, which is maintained over six months. Indirect comparison of the results of these integrated analyses of ATX studies with those from studies of stimulants in adults with ADHD suggests that the effect size may be more similar than previously thought. Not all adult patients are likely to respond or are able to tolerate stimulants, and there are additional advantages of ATX in some cases. The low abuse and diversion potential of ATX, possibility of once or twice daily dosing with enduring efficacy, stable effect throughout the day, and demonstrated effectiveness in reducing ADHD symptoms in patients with comorbid social anxiety and alcohol use disorders, make ATX an important medication to consider when treating adult patients with ADHD.

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