

# Factors affecting treatment adherence to atomoxetine in ADHD: a systematic review

Tamás Treuer<sup>1</sup>

Luis Méndez<sup>2</sup>

William Montgomery<sup>3</sup>

Shenghu Wu<sup>4</sup>

<sup>1</sup>Neuroscience Research, Eli Lilly and Company, Budapest, Hungary; <sup>2</sup>Eli Lilly de Mexico, Mexico City, Mexico;

<sup>3</sup>Global Patient Outcomes and Real World Evidence, Eli Lilly Australia Pty Ltd, West Ryde, NSW, Australia;

<sup>4</sup>Neuroscience Research, Eli Lilly Asia, Inc, Shanghai, People's Republic of China

**Abstract:** The purpose of this paper was to systematically review the literature related to research about the factors affecting treatment adherence and discontinuation of atomoxetine in pediatric, adolescent, and adult patients with attention-deficit/hyperactivity disorder (ADHD). Medline was systematically searched using the following prespecified terms: “ADHD”, “Adherence”, “Compliance”, “Discontinuation”, and “Atomoxetine”. We identified 31 articles that met all inclusion and exclusion criteria. The findings from this review indicate that persistence and adherence to atomoxetine treatment were generally high. Factors found to influence adherence and nonadherence to atomoxetine treatment in ADHD in this review include age, sex, the definition of response used, length of treatment, initial dose of treatment, comorbid conditions, and reimbursement. Tolerability was cited as an important reason for treatment discontinuation. More research is needed to understand those factors that can help to identify patients at risk for poor adherence and interventions that could improve treatment adherence early in the stage of this illness to secure a better long-term prognosis.

**Keywords:** atomoxetine, treatment discontinuation, adherence, compliance, ADHD medication, relapse

## Introduction

Lack of information regarding the factors affecting adherence and discontinuation of effective pharmacotherapy for attention-deficit/hyperactivity disorder (ADHD) poses a significant challenge to the children and adolescents who are struggling with the disorder, their families, and the clinicians who treat the disorder. Although it still requires more research, it is speculated that long-term medication adherence is critical to achieving beneficial long-term treatment outcomes, especially with improved longer-term prognosis and reductions in disorder-specific difficulties.<sup>1-3</sup> It is also important to understand the factors that influence treatment adherence, compliance, and discontinuation in these patients. Because most clinical drug trials require strict adherence to study medication regimen, they generally do not allow conclusions regarding medication adherence to be made in patients with ADHD treated in routine, naturalistic clinical settings.<sup>1-3</sup>

Rates of medication use have increased in recent years due to an increase in ADHD awareness, recognition, number of diagnosed patients, and treatment options; increased duration of use; as well as increased use among girls, preschool children, adolescents, and adults.<sup>4</sup> Rates vary by geography, provider type, and patient characteristics, as well as by formulation of pharmacological agent.

In chronic mental disorders, such as ADHD, treatment nonadherence has an important short-term impact, affecting the initial efficacy and tolerability of treatment,

Correspondence: Tamás Treuer  
Neuroscience Research, Eli Lilly  
and Company, H-1075 Budapest,  
Madach I u 13-14, Hungary  
Tel +36 1 328 5127  
Fax +36 1 328 5100  
Email treuer\_tamas@lilly.com



and a longer-term impact, associated with poorer medical outcomes and a higher economic burden of disease.<sup>5,6</sup> Nonadherence was associated with poorer response and less improvement in clinical severity.<sup>7</sup> For children, adolescents, and adults with ADHD, treatment adherence has been shown to be especially poor, regardless of the treatment options chosen, ie, stimulant or nonstimulant, pharmacologic or nonpharmacologic. Reported levels of nonadherence in children and adults range between 15% and 87%.<sup>8</sup> It could also be hypothesized that the sooner ADHD is treated effectively by clinicians, the more likely patients have a favorable long-term outcome and prognosis.<sup>9</sup> This could be especially important in chronic conditions, such as ADHD, that develop in patients at a younger age.<sup>9</sup> Effective treatment can work only if patients adhere to it, and physicians usually assume that patients and caregivers may usually adhere to treatment if they find it effective.

Nonadherence to ADHD medications has been noted as a barrier to positive treatment outcomes, such as improvements in intellectual or cognitive functionality and academic achievement and reductions in social difficulties, family dysfunction, unintentional injury, and risk of future substance abuse,<sup>10</sup> and has been associated with poorer response and less improvement in clinical severity.<sup>7</sup> As treatment adherence should be regarded as a shared agreement between the patient or patient's family and the clinician, these data might reflect an underlying poor alliance in the decision-making process that needs to be explored. Nonadherence may also result, in part, from a lack of understanding of the importance of medication adherence during the treatment initiation and maintenance phases of treatment in achieving and maintaining the desired outcomes. In addition, the World Health Organization defines treatment adherence as the extent to which a person's behavior – for example, taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider.<sup>11</sup> Nonadherence can take many forms. It may be a patient taking a lower dose than prescribed or making any other change to the doctor's recommendations and not just stopping the treatment. In short, adherence to pharmacologic treatment means following exactly what the doctor recommended with respect to the dose to be taken and the frequency and duration of treatment.<sup>12</sup>

The following definition for medication adherence as described by Cramer et al<sup>13</sup> was used in this review. Medication adherence (synonym: compliance) was defined as “the degree or extent of conformity to the recommendations

about day-to-day treatment by the provider with respect to the timing, dosage, and frequency” and “the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen”.<sup>13</sup> Persistence was not included as a search term as it refers to the continuation of a treatment for the prescribed duration,<sup>13</sup> whereas the intent of the review was to focus on treatment adherence in general terms. However, articles that were included in this review that also discussed persistence were indicated.

There is an increasing recognition that “treatment engagement” may have a positive influence on treatment adherence/compliance and continuation and lead to better outcomes.<sup>14</sup> Whereas compliance refers to how well an individual obeys the directives of health care providers, engagement refers to the involvement of the patient in decision making and coordinating their own needs with professional advice and available information.<sup>15</sup> As the concept of engagement is relatively novel and not often reported as an outcome measure in clinical studies,<sup>16</sup> this factor was not included in the present search. The Center for Advancing Health has compiled a list of measurable actions to aid in assigning treatment engagement.<sup>15</sup>

Atomoxetine is a selective norepinephrine reuptake inhibitor and is a nonstimulant that has been approved for the treatment of ADHD symptoms in pediatric, adolescent, and adult patients in several countries.<sup>17–19</sup> It has favorable adverse effect and safety profiles and no demonstrable abuse liabilities and has been cited as having a better than expected maintenance of response against ADHD symptoms.<sup>20</sup> Consequently, atomoxetine is beneficial in short- and long-term treatment options for ADHD.<sup>17</sup>

In this paper, the authors reviewed the available literature with the following objectives: 1) to determine the levels of medication adherence/compliance and of discontinuation in atomoxetine-treated patients described in the literature; 2) to explore factors affecting treatment adherence and nonadherence in ADHD; 3) to examine the potential relationship between treatment adherence/nonadherence and long-term outcomes, functionality, and cost-effectiveness; and 4) to investigate potential links regarding the differences in remission with atomoxetine in long-term treatment vs discontinuation, in maintenance of response.

## Materials and methods

### Database search strategy

This review follows guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group.<sup>21</sup> No review protocol was registered for

this study. To find eligible studies, abstracts were screened and selected from an accepted scientific database based on the following inclusion and exclusion criteria.

## Inclusion criteria

Criteria for inclusion in this systematic review were the following: 1) full-text primary publications of real-world studies; 2) ADHD treatment guidelines for the USA, Canada, the UK, Germany, France, Spain, Italy, Sweden, and the Netherlands, as well as any general European guidelines; 3) observational studies based on real-world data; 4) Phase IV clinical trials, in which at least 80% of study population (children, adolescents, or adults) have ADHD as the primary disorder; 5) utilized atomoxetine as a drug treatment; 6) reported discontinuation/switching results or reported reasons for discontinuation/switching and/or adherence/compliance of ADHD drug treatment; 7) published in English; and 8) published from January 2003 through February 2015.

## Exclusion criteria

Exclusion criteria consisted of the following: 1) nonprimary publications of real-world studies; 2) conference abstracts or posters, congress proceedings, books, chapters, addresses, bibliographies, biographies/lectures, case reports, author commentaries, or letters; 3) reviews/meta-analyses; 4) pre-clinical studies; 5) Phase I–III clinical trials; 6) prognostic studies; 7) genetic studies; 8) nonhuman subjects; 9) patients without ADHD; 10) 80% of study population without ADHD as the primary disorder; 11) no drug treatment; 12) drug treatment not listed in the inclusion criteria; 13) did not report discontinuation/continuation results or compliance or adherence rates specific to atomoxetine treatment, 14) publication was not in English; and 15) published before January 2003 and after February 2015.

Literature was retrieved after searching MEDLINE on February 20, 2015, with the following search terms: ADHD AND Adherence AND Atomoxetine; ADHD AND Compliance AND Atomoxetine; and ADHD AND Discontinuation AND Atomoxetine. All retrieved abstracts were initially screened, and studies that clearly met the exclusion criteria were excluded. The remaining studies were rescreened, and only articles meeting the aforementioned inclusion/exclusion criteria were included. The search terms and the inclusion/exclusion criteria were established by all the authors, all of who reviewed and agreed upon the final terms. The data extraction was performed by an external consultant enlisted for this purpose.

## Results

### Literature search results

A total of 114 unique potentially relevant articles were retrieved with the search strategies described earlier. Of those, 31 articles were included in the current review. Table 1 displays a summary of studies included in this review. A total of 83 retrieved references were excluded because the reference was a review or meta-analysis ( $n=29$ ), was not in English ( $n=5$ ), was a case report ( $n=3$ ), was an author commentary ( $n=2$ ), was published before January 2003 ( $n=1$ ), did not contain discontinuation/continuation results or compliance/adherence rates specific to atomoxetine ( $n=12$ ), included study results of patient population  $\leq 10$  ( $n=1$ ), and was duplicated (required manual removal,  $n=30$ ) (Figure 1).

### Medication treatment adherence/compliance

The topic of treatment adherence or compliance in pediatric, adolescent, and adult patients with ADHD was specifically addressed by 13 of the 31 articles included in the present review (Table 1). There was considerable variation in the way treatment adherence (or compliance) was defined and quantified, and considerable variation in the manner the studies were conducted. In a 1-year study of children and adolescents with ADHD, treatment adherence was determined with the Pediatric Compliance Self-Rating (PCSR) instrument and items 1–4 of the Medication Adherence Rating Scale (MARS) and gave an adherence rate for atomoxetine was 67.5% at 1 year, and it declined over time.<sup>22</sup> In a post hoc analysis of data obtained from the Strattera Support Service, treatment adherence was defined as the proportion of patients who reported taking atomoxetine at week 12, regardless of any previous interruptions in treatment.<sup>23</sup> That study reported an adherence of 90.5% for atomoxetine.<sup>23</sup> In Norway, a follow-up questionnaire was sent to adult patients with ADHD receiving pharmacologic treatment for a mean of 4.5 years.<sup>24</sup> Treatment adherence, defined by patients self-reporting not missing a single dose within the past week, was 50% for atomoxetine.<sup>24</sup> In a randomized, clinical trial (RCT), treatment adherence was determined by direct questioning and a review of returned medications.<sup>25</sup> Only three of the 49 patients randomized to atomoxetine were found noncompliant at week 10.<sup>25</sup>

Most of the remaining studies addressing treatment adherence were performed by a post hoc review of prescription claims, the primary care database (UK), or treatment and hospitalization records.<sup>6,26–31,32</sup> In those studies, treatment adherence was estimated by determining the proportion of days covered by medication divided by the total number of

Table 1 Included references

Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
Wehmeier et al <sup>22</sup>	Prospective, 12-month, observational, open-label study	Children and adolescents 6–17 years of age Met ICD-10 or DSM-IV criteria for current ADHD Patients had to be treatment naïve to previous ADHD medication and were newly initiated on a medication approved for the treatment of ADHD at baseline Adherence evaluated over 1 year ATX (N=252) Stimulants (N=247) ATX and stimulants (N=5)	After 1 year, adherence rates were as follows: ATX: 67.5%; psychostimulant: 74.2%, as measured by a Pediatric Compliance Self-Rating score $\geq 5$ Medication adherence deteriorated in both treatment groups over time, with Medication Adherence Rating Scale scores declining from the beginning of the study to the end of the study (ATX: from 3.7 to 2.9; psychostimulant: from 3.6 to 3.1), although the decline was not statistically significant between groups No statistically significant difference in medication adherence between the two different treatment groups				
Savill et al <sup>23</sup>	Post hoc analysis of data from 12-week nursing support program (Strattera Support Service)	Patients had to have initiated ATX between January 1, 2009 and March 31, 2010 $\leq 18$ years of age ATX (N=346)	Adherence Measured as the number of patients in the Strattera Support Service who were taking ATX at week 12 At 12 weeks, 33 (9.5%) patients had discontinued ATX, giving a non-continuous compliance rate of 90.5% with continuation rates similar, regardless of age and sex				

Treuer et al <sup>33</sup>	Post hoc analysis of 12-month, prospective, observational study	6–17 years of age Met DSM-IV criteria for current ADHD, as diagnosed by clinical interview	Factors affecting adherence/nonadherence Greater rates of remission for ATX-treated patients were associated with age (older), country (United Arab Emirates), and sex (female) (all $P < 0.05$ ) CART analysis confirmed older age and lack of specific phobias were associated with greater remission rates
Setyawan et al <sup>26</sup>	US administrative claims database (Truven Health Analytics MarketScan) study	Patients with ADHD who initiated a new FDA-approved ADHD treatment between 2007 and 2009 Based on age prior to the treatment initiation date, patients were classified into two populations, children/adolescents (6–17 years old) and adults ( $\geq 18$ years old), and into four cohorts based on ADHD treatment status: 1) treatment-naïve children and adolescents (N=52,686), 2) previously treated children and adolescents (N=48,930), 3) treatment-naïve adults (N=32,937), and 4) previously treated adults (N=20,737)	In children and adolescents, LDX-treated patients were more likely to be adherent than patients in each of the other treatment groups, except in treatment-naïve patients where LDX-treated patients had a similar likelihood of adhering to treatment compared to ATX-treated patients ( $P=0.6925$ ) and were less likely to adhere to treatment compared to OROS MPH-treated patients ( $P=0.0004$ ) In adults, the LDX treatment group was also more likely to be adherent compared to each of the other treatment groups, except when compared to AMPH/dextroamphetamine long-acting, where no statistically significant differences were observed

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Table 1 (Continued)

Study	Study design	Patient population	Outcome	Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
				(previously treated: $P=0.6471$ , treatment naïve: $P=0.0733$ ) Overall, LDX-treated patients demonstrated better treatment adherence compared to patients initiated on other ADHD medications, except for AMPH LA in adults and OROS MPH and ATX in treatment-naïve children and adolescents				
Hodgkins et al <sup>27</sup>	Observational, retrospective analysis using data from PHARMO medical record linkage system	Patients aged 6–17 years who filled at least one prescription for immediate-release or long-acting MPH (alone or in combination), dexamphetamine (immediate-release AMPH), ATX, or for treatment of ADHD between January 2000 and December 2007 Patients treated with various ADHD medications ( $N=4,909$ )	The proportion of patients within each treatment group who were classified as fully adherent (ie, those with $MPR \geq 80\%$ ) after the first year of follow-up was 57% in the ATX group, and the mean MPR was 67% for patients starting on ATX over the first 12 months of follow-up, with no significant differences between treatment groups seen in the study median per-child prescriptions dispensed were highest in the ATX group and lowest in the immediate-release AMPH group. The proportion of children undergoing a treatment change during the first year of follow-up was highest among users of immediate-release AMPH (92%) and lowest		Majority of children receiving ATX-initiated treatment on a lower daily dose than those receiving immediate-release MPH ( $\leq 0.30$ DDDeq vs $0.31-0.50$ DDDeq, respectively; $P<0.001$ ) For the analyzed group as a whole, the rate of persistence at 365 days of follow-up was 40%; persistence at this time point was lowest among users who had initiated immediate-release AMPH (19%) and highest among patients who had initiated ATX (51%)	Of the patients who temporarily stopped treatment, those treated with ATX had the shortest time until stopping treatment At least half of all patients who stopped taking their initial ADHD medication resumed treatment, with the notable exception of the ATX treatment group, in which only 12% patients restarted treatment		

Barnier et al <sup>6</sup>	Texas Medicaid prescription claims database	3–18 years old ≥2 ADHD prescription claims (July 2002–December 2008) Patients treated with various ADHD medications (N=62,789)	among patients prescribed ATX (62%) Adherence Rates of ADHD treatment adherence measured using the MPR were strongest for children initiating treatment with ATX or long-acting MPH Mean adherence rates were highest for the nonstimulants (52.5%±30.9%) and extended-release stimulants (52.1%±30.2%), with mean adherence of 52.5%±30.9% for ATX 25.8% of patients taking extended-release ATX achieved adherence rate cutoff level Dichotomous (80% cutoff) was lower for short-acting vs long-acting medications (9.8% vs 21.1%–25.8%, respectively)	Nonstimulant users persisted on treatment for ~5 months (153.3±124.3), followed by extended-release stimulant users who persisted for 4.8 months (143.7±120.8) and prodrug (LDX dimesylate) stimulant users who persisted for 3.8 months (113.3±100.5) Immediate-release, extended-release, and prodrug-stimulant users ( $P<0.0001$ ) were significantly less likely to be persistent on treatment than nonstimulant users	Medication costs Higher for long-acting medications compared to short-acting Lower for short-acting (US\$1.24) vs long-acting (US\$3.42–US\$4.04) medications
Lachaine et al <sup>28</sup>	Cross-sectional, retrospective prescription claims analysis using a Quebec database (RAMQ)	Patients of all ages with confirmed diagnosis of ADHD, based on ICD-9 diagnostic codes 314.0–314.9 Received ≥1 pharmacological agents approved by Health Canada for treatment of ADHD from July 2004–June 2009 Patients treated with various ADHD medications (N=15,838)	Adherence was higher among patients who were initially prescribed long-acting medications compared with those prescribed short-acting medications Patients treated with long-acting nonstimulant medications had an adherence rate of 60.2%	The proportion of patients persisting on treatment was greater in the long-acting stimulant group (81.1%) vs the short-acting stimulant (59.6%) or long-acting nonstimulant groups (61.7%) at 12 months, as well as 3 and 6 months	Treatment patterns Short-acting medications declined from 72.8% to 26.4% of all claims over the course of the study Proportion of stimulant and nonstimulant long-acting medications increased from 27.2% to 73.6%

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Table 1 (Continued)

Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
McCarthy et al <sup>29</sup>	THIN database GP questionnaire study	Adults $\geq 18$ years of age Patients with a diagnosis of ADHD/HKD and were prescribed MPH, dexamphetamine, or ATX between January 1, 2003 and December 31, 2008 Patients treated with various ADHD medications (N=3,626)	In patients prescribed long-acting nonstimulants, the highest adherence rates were observed in the 10- to 14-year-old age group Teenagers aged 15–19 years and adults aged $\geq 20$ years were observed to be more nonadherent to their treatment compared to other age groups Factors affecting adherence/nonadherence GPs were not aware of the reason for treatment cessation in 43% of cases		Patient choice was most common reason for treatment discontinuation (56%)		
Zetterqvist et al <sup>30</sup>	Swedish PDR prescription drug database study	Patients 6–45 years of age who were alive and registered as residents in Sweden from 2006–2009 Patients treated with various ADHD medications (N=41,700)	The dispensing prevalence increased from 2.93 per 1,000 in 2006 to 6.98 in 2009 (PR ~2.38, 95% CI ~2.34–2.43) The PR was 3.40 for adults 22–45 years old, 2.41 for adolescents 15–21 years old, and 1.90 for children 6–14 years old. The increase was also greater in women than in men (PR ~2.92 vs 2.19)		Patients aged 15–21 were the most likely to discontinue treatment; after 3 years and 11 months, only 27% of those patients who initiated treatment remained under treatment		
Bahmanyar et al <sup>31</sup>	Swedish National Patient Register and PDR study	Received diagnosis of ADHD or treatment for ADHD at $< 19$ years old. In Sweden between January 1, 2006 and December 31, 2007	More than 55% of patients, who could be followed-up for 2 years after treatment initiation, had at least one treatment gap of 6 months				Medication use MPH and ATX were first line of therapy for the majority of patients, and AMPH and

Lensing et al <sup>24</sup>	Survey study (November 2008 to April 2009)	Adults who met ICD-10/DSM-IV criteria for ADHD Lived in southeastern Norway and approved for pharmacotherapy 2003–2005 Patients treated with various ADHD medications (N=1,096)	Older age at diagnosis, lower number of hospitalizations, and comorbidity with other mental disorders increased risks of gaps in medication	dexamphetamine were rarely used Of 6,649 patients with ADHD and receiving drug treatment, 302 (4.5%) had received at least two drugs, and ATX was most common drug in combination therapy Long-term outcomes Psychiatric comorbidity at baseline predicted poorer outcome than did no comorbid illness
	Retrospective claims database analysis	≥ 1 claim with diagnosis code for ADHD (ICD-9-CM 314.00; 314.01; 314.1; 314.2; 314.8; or 314.9) in primary or secondary position from January 1, 2004, through September 30, 2006 (identification period) ≥ 6 years of age Filled prescription for an ADHD medication during the identification period (fill date on first appearing qualifying claim was defined as index date) No more than one ADHD medication filled on index date Continuous health plan eligibility with medical and pharmacy benefits for 182 days prior to and 365 days following the index date No evidence of filled prescriptions for ADHD-related medications in preindex period (index date minus 182 days	Among patients taking ATX (n=13), 50% reported not having missed a single dose during the last week	Treatment patterns Changes to the dose of the index drug were least likely among individuals taking nonstimulants (vs stimulants), MPHs (vs AMPHs), or intermediate-acting drugs (vs short- and long-acting drugs; all $P<0.0001$ ) Medication switches were more frequent among those on nonstimulants, MPHs, or short-acting drugs (all $P<0.0001$ ) Subjects taking long-acting medications were less likely to augment treatment with a drug with a different duration of action than those
Christensen et al <sup>32</sup>				

(Continued)

Table 1 (Continued)

Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
Svanborg et al <sup>25</sup>	Swedish, multicenter, randomized, double-blind, PBO-controlled clinical study	through index date minus 1 day). Data from July 1, 2003, to September 30, 2007, used Patients treated with various ADHD medications (N=60,010) 7–15 years of age Met DSM-IV criteria for current ADHD, as diagnosed by clinical interview and examination by investigator and confirmed by the K-SADS-PL Had a severity threshold of 1.5 SDs above the US age and sex norms for their diagnostic subtype on the ADHDRS-IV-P; <sup>1</sup> ATX (N=49) PBO (N=50)	Three patients were not compliant with the dosing regimen (one ATX-treated patient at week 10, one PBO-treated patient at weeks 3 through 10, and another PBO-treated patient at week 10)		ATX treatment was not associated with any premature discontinuations		taking intermediate- or short-acting medication ( $P<0.0001$ )
Setyawan et al <sup>68</sup>	US administrative claims database (Truven Health Analytics MarketScan) study	Patients with ADHD who initiated a new FDA-approved ADHD treatment between 2007 and 2009 Based on age and ADHD treatment status prior to the treatment initiation date, patients were classified into two populations, children/adolescents (6–17 years old) and adults ( $\geq 18$ years old), and into four cohorts: 1) treatment-naïve children and adolescents (N=52,686), 2) previously treated children and adolescents (N=48,930), 3) treatment-naïve adults (N=32,937), and 4) previously treated adults (N=20,737) Patients treated with various ADHD medications		Among children and adolescents, LDX patients had a significantly lower discontinuation rate compared to other treatment groups (range HRs: 1.04–2.26; all $P<0.05$ ), except when compared to treatment-naïve patients on ATX and OROS MPH, where no statistically significant differences were found and where LDX had a higher risk of discontinuation, respectively Among adults, patients with LDX had a significantly lower discontinuation rate			

(N=149,189 who met all selection criteria)	<p>compared to patients in other treatment groups (range HR: 1.14–1.86; all <math>P&lt;0.05</math>), except for the comparison with AMPH LA patients, where the differences were not statistically significant</p> <p>LDX-treated patients demonstrated a higher rate of persistence compared to patients initiated on other ADHD medications, except for the comparisons with OROS MPH and ATX-treated patients in treatment-naïve children and adolescents and AMPH LA-treated patients in adults</p>	
Durell et al <sup>39</sup>	<p>African-American and Caucasian outpatients aged 6 to &lt;18 years with diagnosis of ADHD as defined by criteria in the <i>DSM-IV-TR</i></p> <p>Diagnosis corroborated using K-SADS-PL</p> <p>Score on ADHDRS-IV-P:I that was –1.0 SD above age and sex norms and normal intelligence (IQ ~80)</p> <p>ATX (N=1,173)</p>	<p>Overall rates of discontinuation measured in African-American and Caucasian patients were similar (20.5% vs 20.7%, respectively)</p> <p>Discontinuation rates due to adverse events were 2.4% of African-Americans vs 3.0% of Caucasians, perceived lack of efficacy (8.4% vs 10.1%), loss to follow-up (2.4% vs 1.5%), patient decision (4.8% vs 3.2%), physician decision (1.2% vs 0.6%), and other reasons (1.2% vs 2.3%)</p> <p>No significant differences were seen in the completion</p>
Greenhill et al <sup>67</sup>	<p>Post hoc analysis of five randomized, double-blind, studies included children and combination of children and adolescents, aged 6–17</p>	

(Continued)

Table 1 (Continued)

Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
	PBO-controlled, acute-phase studies	Met DSM-IV criteria for ADHD, as diagnosed by clinical interview and examination by investigator and confirmed by the K-SADS-PL. Subjects scores on the ADHDRS-IV- P; to be at least 1.5 SDs above the age and sex ADHD symptom score norm for diagnostic subtype or for the total score for the combined subtype (if DSM-IV criteria were met for the combined subtype), using published norms for the ADHDRS-IV-P; ATX (fast/once daily; N=234) ATX (slow/twice daily; N=213)			rates or reasons for discontinuation using either once-daily dosing and fast titration or twice-daily dosing and slow titration		
Kratochvil et al <sup>69</sup>	Double-blind, clinical study	Children and adolescents aged 7–17 with DSM-IV–defined ADHD (any subtype) and comorbid depressive or anxiety symptoms that met minimum severity criteria ATX + FLU (N=127) ATX + PBO (N=46)			Completion rates for the two groups were similar; as were discontinuation rates for adverse events		
Torres et al <sup>36</sup>	Retrospective medical record analysis	Patients who received treatment in a tertiary care pediatric psychopharmacology practice for patients with epilepsy who were treated with ATX ≤ 18 years of age ATX (N=27)			Seventeen patients (63%) discontinued ATX due to inadequate response (n=7, 26%), worsening behavior such as increased irritability/ activation (n=7, 26%), nonadherence (n=1, 4%), emerging psychotic-like symptoms (n=1, 4%), and appetite decrease and tremor (n=1, 4%) ATX dose, epilepsy etiology, seizure type, and		

Adler et al <sup>70</sup>	Retrospective safety analysis of atomoxetine in adult patients with ADHD with or without comorbid alcohol abuse and dependence	Adults who met the DSM-IV-TR criteria for ADHD (inattention, hyperactivity/impulsivity, and combined subtypes), determined by clinical interview and confirmed by the Adult ADHD Clinician Diagnostic Scale An ADHD symptom severity score of $\geq 20$ on the AISRS was required for comorbid alcohol use disorder study Patients from the alcohol use disorder study also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence)	comorbid psychiatric disorders did not predict discontinuation No significant differences in discontinuation rates due to adverse events or lack of efficacy between heavy drinkers, nonheavy drinkers, and those without alcohol-use disorder
Adler et al <sup>71</sup>	Randomized, double-blind, PBO-controlled, clinical study	18–65 years of age Met DSM-IV-TR diagnoses for both ADHD and social anxiety disorder	No significant differences in discontinuation rates due to adverse events or lack of efficacy
Lee et al <sup>35</sup>	Post hoc double-blind, PBO-controlled clinical study	Korean adults $\geq 18$ years of age Met DSM-IV criteria for current ADHD and had a historical diagnosis of ADHD during childhood, as assessed by the CAADID	Discontinuation rate of ATX-treated patients was significantly higher than that of PBO-treated patients (40.5% vs 16.2%; $P \leq 0.05$ )
Takahashi et al <sup>37</sup>	Open-label, dose escalation safety/tolerability study	ATX (N=37) PBO (N=37) Japanese adults $\geq 18$ years of age Met DSM-IV criteria for current ADHD and had a historical diagnosis of ADHD during childhood, as assessed by the CAADID	ATX was well tolerated, with 6.7% of patients discontinuing due to nausea, malaise, or anorexia
Takahashi et al <sup>38</sup>	Open-label, dose-escalation safety/tolerability study	ATX (N=45) Korean, Chinese, and Taiwanese adults $\geq 18$ years of age	ATX was well tolerated with a low discontinuation rate of

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Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
Young et al <sup>14</sup>	Randomized, double-blind, PBO-controlled clinical study	Met DSM-IV criteria for current ADHD and had a historical diagnosis of ADHD during childhood, as assessed by the CAADID	2.3% due to adverse events				
		ATX (N=44) Adults $\geq 18$ years of age Met DSM-IV-TR criteria for current ADHD and have historical diagnosis of ADHD during childhood, as confirmed by CAADID ATX (N=268) PBO (N=234)	Discontinuation due to an adverse event was greater for on-label vs slow titration, although the rate of patients experiencing adverse events was comparable				
Pottg�rd et al <sup>14</sup>	Danish National Prescription Registry database study	Patients who filled $\geq 1$ MPH or ATX for the first time from January 1, 2000 through December 31, 2012 No age restrictions MPH and ATX first-time users with at least 6 months of follow-up time (N=59,116)	Comparable proportions of early discontinuation were observed: 11.3% (MPH extended-release), 12.7% (MPH immediate-release), and 13.7% (ATX) in 2012				
Wernicke et al <sup>72</sup>	Post hoc analysis of four (two pediatric and two adult) double-blind, PBO-controlled clinical studies in which discontinuation of ATX was assessed in children and adults with ADHD following 9–10 weeks of continuous therapy	Pediatric Children 7–12 years of age Met DSM-IV criteria for current ADHD ATX (N=102) PBO (N=92) Adult Met DSM-IV criteria for current ADHD, as diagnosed by clinical interview and confirmed by CAAR-D ATX (abrupt discontinuation [N=90]) ATX (tapered discontinuation [N=94]) PBO (N=196)	Incidence of discontinuation-emergent adverse events was low, and there were no statistically significant differences between the patients abruptly discontinuing from ATX and those continuing on PBO Discontinuation of ATX did not result in the development of an acute discontinuation syndrome and was well tolerated				

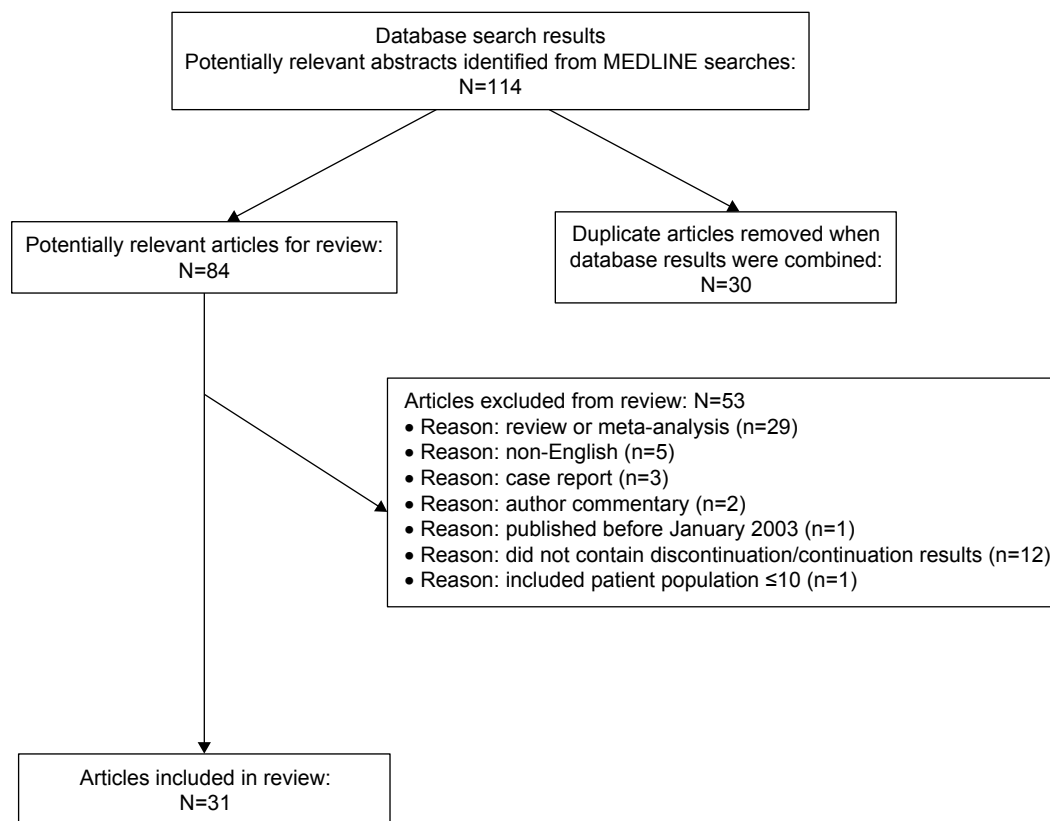
Buitelaar et al <sup>41</sup>	Double-blind, multicenter, clinical study Subjects who maintained a response to ATX acutely and had completed 1 year of double-blind ATX treatment randomized to either continue ATX or switch to PBO for further 6 months	6–15-year-olds who met DSM-IV criteria for ADHD as assessed by clinical history and confirmed by K-SADS-PL and whose symptom severity was at least 1.5 SDs above US age and sex norms on ADHD-RS ATX (N=81) PBO (N=82)	Among those assigned to discontinuation (switched to PBO), the magnitude of symptom return was generally less severe than that observed at study entry	ATX was superior to PBO in preventing relapse and in maintaining symptom response (ADHD-RS score, $P<0.001$ )
Garbe et al <sup>43</sup>	German health insurance database study	Cohort of children and adolescents 3–17 years of age First diagnosis of ADHD in 2005 Followed until discontinuation of insurance, death, or December 31, 2008 Patients treated with various ADHD medications (N=6,210)	In subjects beginning treatment with ATX, 45% continued and 25.2% discontinued ATX treatment during first year	Switches to ATX in 1.5% of initial immediate-release MPH users and 2.7% of modified-release MPH users switching to ATX Switches to MPH occurred in 26.8% of ATX initiators Adverse events ATX-treated patients: greater increases in heart rate and decreases in body weight, and rates of treatment-emergent decreased appetite and nausea also higher medication use patterns Of the 47.0% of children who progressed to a second medication trial, 88.7% tried a stimulant from a second class. In total, 19.7% tried ATX, which was typically used as a third-stage choice (ie, after two different stimulant exposures) Remission
Allen et al <sup>73</sup>	Double-blind, clinical study	7–17 years old Met DSM-IV criteria for ADHD Had concurrent Tourette syndrome or chronic motor tic disorder PBO (N=72) ATX (N=76)	Discontinuation rates PBO (26.4%) vs ATX (34.2%); $P=0.372$	
Wagner et al <sup>45</sup>	CD-MAS study	5–14 years old Referral from the COPE program Admission and discharge (or dropout) from CD-MAS March 1, 2007, to December 31, 2012. Patients treated with various ADHD medications (N=132)		

(Continued)

Table 1 (Continued)

Study	Study design	Patient population	Outcome Adherence (compliance)	Persistence	Discontinuation	Relapse/remission	Other
Pottegård et al <sup>12</sup>	Danish RMPS prescription drug database study	Patients who filled $\geq 1$ MPH or ATX prescription from January 1995 through September 2011 No age restrictions MPH, ATX, and modafinil users (N=54,024)					Symptomatic remission at the end of treatment achieved by 70.4% (parent ratings) and 82.4% (teacher ratings) for those with outcome data and who completed treatment with any medication Treatment pattern The percentage of users only receiving one prescription varied from 6% to 14%, with a higher dropout in age categories where treatment was off-label The drop-out rate was 6%–7% in the 6–17-year-old group and 14% in the 18–49-year-old group Concomitant treatment with MPH and ATX was rare, as only 2% of MPH treatment overlapped with ATX treatment

**Abbreviations:** ADHD, attention deficit/hyperactivity disorder; ADHD-RS, ADHD rating scale IV; ADHDRS-IV-P, ADHD rating scale-IV-parent version; Investigator Administered and Score; AISRS, ADHD investigator symptom rating scale; AMPH, amphetamine; AMPH LA, amphetamine long-acting; ATX, atomoxetine; CAADID, Conners' Adult ADHD Diagnostic Interview for DSM-IV; CAAR-D, Conners' Adult ADHD Diagnostic Interview for DSM-IV; CART, classification and regression tree analysis; CD-MAS, child development-medication assessment service; CI, confidence interval; COPE, community outreach of pediatrics and psychiatry in education; DDDeg, defined daily dose equivalents; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*; FDA, Food and Drug Administration; FLU, fluoxetine; GP, general practitioner; HR, hazard ratio; HKD, hyperkinetic disorder; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10, International Statistical Classification of Diseases, 10th revision; IQ, intelligence quotient; LDX, lisdexamfetamine; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-aged Children-Parent and Lifetime Version; MPH, methylphenidate; MPR, medication possession ratio; OROS, osmotic release oral system; PBO, placebo; PDR, prescribed drug register; PHARMO, PHARMacoMorbidity; PR, prevalence ratio; RAMQ, Régie de l'assurance maladie du Québec; RMPS, Registry of Medicinal Product Statistics; SD, standard deviation; THIN, The Health Improvement Network.



**Figure 1** PRISMA diagram of the literature selection criteria.

**Abbreviation:** PRISMA, preferred reporting items for systematic reviews and meta-analyses.

days in the study period. In those studies, treatment adherence was indicated by a ratio of  $\geq 80\%$ <sup>6,26–30,32</sup> or by a 6-month gap in treatment.<sup>31</sup> In a post hoc analyses of a 12-month prospective study of atomoxetine, the degree of treatment adherence was not determined, but the factors associated with treatment adherence were examined.<sup>33</sup> Adherence to a treatment plan for chronic conditions, which includes ADHD, and where multiple doses are required, tends to be poor.<sup>33</sup> Consistent with these points, patients taking long-acting drugs tend to show better treatment adherence than those taking shorter-acting formulations,<sup>28</sup> and adherence to an atomoxetine regimen deteriorates over time.<sup>22,27</sup> For example, the adherence rates for atomoxetine ranged from 64% at 3 months to 44% at 1 year.<sup>27</sup> A factor that may influence treatment adherence rates reported in school-age children is a tendency of some parents to provide medication only on school days, resulting in treatment gaps corresponding to weekends, holidays, and summer vacation.<sup>6,31</sup> Females show significantly better treatment adherence than males.<sup>6</sup>

## Medication persistence

Persistence is defined as the period of time during which a patient continues taking a treatment.<sup>13</sup> It differs from

adherence in that adherence refers to how well a patient conforms to the entire treatment requirements in terms of dose, frequency, and timing within a prescribed period of time.<sup>13</sup> Pediatric patients taking atomoxetine persisted for 5 months in one study<sup>6</sup> and showed a 51% rate of persistence over 1 year and were more likely to persist than patients taking stimulants.<sup>27</sup> When adult and pediatric patients were considered, the persistence rate at 1 year was similar between atomoxetine (62%) and short-acting stimulants (60%) and less than long-acting stimulants (81%).<sup>28</sup> A retrospective claims analysis of pediatric and adult patients reported a significantly ( $P < 0.0001$ ) greater persistence for patients on stimulants when compared to nonstimulants.<sup>32</sup> Overall, persistence is low among nonstimulant and stimulant ADHD treatments in children and adults and tends to be lower in treatment-naïve patients.<sup>26</sup>

## Medication discontinuation

Of the articles included in the present review, 18 included a discussion of drug discontinuance. It differs from persistence in that this includes patients who discontinue outside of a prescribed period within a study and includes patients who would resume the treatment after a period of time. Overall,

the rate of discontinuance to atomoxetine for any reason was fairly high, ranging from 13.7%<sup>34</sup> to 40.5%.<sup>35</sup> One RCT reported that no patients discontinued atomoxetine prematurely,<sup>25</sup> whereas a retrospective review of medical records of 27 patients reported that 17 (63%) discontinued atomoxetine.<sup>36</sup> In general, the rate of discontinuation of atomoxetine due to adverse effects was low. In the other studies where reason for discontinuation was given, discontinuation due to adverse effects ranged from 2.3%<sup>37</sup> to 6.7%.<sup>38</sup> In contrast, discontinuation for perceived lack of efficacy ranged from 8.4%<sup>39</sup> to 26%.<sup>36</sup> Patient choice, other than due to lack of efficacy or adverse effects, accounted for 56% of discontinuations in one study.<sup>29</sup> Patients in the 15–21-year-old age group were most likely to discontinue treatment, with only 27% still being treated after 3 years and 11 months, whereas the overall rate of continuation for this period was 42%.<sup>30</sup> This finding is consistent with a general unwillingness to continue chronic medications as an individual transitions from childhood to young adult.<sup>30,40</sup>

One RCT in which patients were randomized to discontinue atomoxetine found that symptoms remained less severe than they were at study entry, and response was maintained after termination of atomoxetine.<sup>41</sup>

## Additional considerations

Utilization patterns for medications used to treat ADHD (methylphenidate, atomoxetine, and modafinil) were examined from a “patient’s perspective”.<sup>42</sup> The percentage of users who dropped out after only one prescription varied from 6% to 14%, with a higher dropout in those age categories where treatment was off-label.<sup>42</sup>

An examination of treatment patterns of children and adolescents with ADHD in Germany found that few patients switched to atomoxetine (1.5% of initial immediate-release methylphenidate users and 2.7% of modified-release methylphenidate users), whereas switches to methylphenidate occurred in 26.8% of atomoxetine initiators.<sup>43</sup>

It was observed that medication costs were higher for long-acting medications compared to short-acting ones and were highest for the nonstimulants.<sup>6</sup> However, treatment adherence (dichotomous: 80% cutoff) was also lower for the short-acting vs long-acting medications (9.8% vs 21.1%–25.8%, respectively).<sup>6</sup> It was suggested that the increased benefit in terms of better treatment adherence may outweigh the increased cost of long-acting preparations.<sup>6</sup>

The efficacy of different dosing regimens of atomoxetine was compared in adults with ADHD.<sup>44</sup> On-label treatment (40 mg once daily for 3 days, then 80 mg daily) was

associated with a greater discontinuation due to an adverse event that was slow titration (40 mg once daily for 7 days, then 80 mg daily), although the rate of patients experiencing adverse events was comparable.<sup>44</sup>

In a study of long-term outcomes via a questionnaire survey, it was found that 50% of patients taking atomoxetine (n=13) reported not having missed a single dose during the previous week.<sup>24</sup> Further, comorbidity at baseline predicted poorer outcome than did no comorbid illness.<sup>24</sup>

We identified one publication that reported on the differences in remission and treatment adherence with stimulants and atomoxetine in long-term treatment. Wagner et al<sup>45</sup> examined service patterns and treatment outcomes from an ADHD medication service that implemented a Children’s Medication Algorithm Project approach. Of the 47.0% of children who progressed to a second medication trial, 88.7% tried a stimulant from a second class. In total, 19.7% tried atomoxetine, which was typically used as a third-stage choice (ie, after two different stimulant exposures). Stage 4–6 medications were rarely used; rather, stimulants were retried after atomoxetine and/or medication combinations were tried. Symptomatic remission at the end of treatment was achieved by 70.4% and 82.4% of children, according to parents and teachers, respectively, for those with outcome data and who completed treatment with any medication.

## Discussion

Overall, relatively little data about the factors influencing adherence to atomoxetine treatment in patients with ADHD in comparison to other chronic mental disorders are available in the literature. The findings from this review indicate that persistence and adherence to atomoxetine treatment were generally high. Factors found to influence adherence and nonadherence to atomoxetine treatment in ADHD in this review include age, sex, the definition of response used, length of treatment, initial dose of treatment, comorbidities, and reimbursement. Tolerability was cited as an important reason for treatment discontinuation.

Poor medication adherence at the pediatric level may stem from the parents’ initial hesitancy to have their child with ADHD treated with medication.<sup>46</sup> ADHD is often perceived as a social, emotional, or psychological problem and related to willpower; thus, many patients and/or their caregivers inherently believe that pharmacological treatment is not necessary. Once the child has tried the medication, clear symptom benefit with few adverse effects and a simplified dosing schedule encourage families to continue its use. In the case of treatment with atomoxetine, in which

a benefit may not be perceived immediately, the experience during the initial treatment period may greatly influence a parent's/caregiver's decision to continue or stop treatment. Other factors that may influence adherence include complexity of medication regimen (eg, number of daily doses, number of concurrent medications); treatment that requires mastery of certain techniques (eg, injections, inhalers); duration of therapy; frequent changes in medication regimen; medications with social stigma attached to their use; actual or perceived unpleasant side effects; and treatment that interferes with lifestyle or requires significant behavioral changes.<sup>47</sup>

When making decisions about medication, adolescents and adults with ADHD balance the positives and negatives, a behavior described by the health beliefs model.<sup>48</sup> Participants reported the positives of medication in improving the core symptoms of ADHD, helping with school/college/work, and improving social relationships, along with the negatives of medication, which included physical side effects, effects on sense of self, loss of personality, stigma associated with medication use, and inconvenience of taking medication, especially when short-acting stimulants were used at school or at work.

## Medication adherence and discontinuation

Among studies of adolescents, patients frequently expressed a desire for more autonomy and control over their conditions, prompting them to make decisions about medication treatment (reviewed in McCarthy<sup>40</sup>). When patients stopped taking medication, typically during adolescence, the decision was one that they often made themselves. Reasons included not wanting to take medication indefinitely, not perceiving a need for medication, believing that the medication does not work, and feeling that other negatives associated with medication use outweighed the positives. Stopping treatment may take the form of unplanned "drug holidays" or complete treatment cessation. Moreover, parents usually assume that their children are compliant.

Medication adherence is an area of considerable concern across varied chronic medical conditions (eg, asthma, diabetes, cardiovascular disorders).<sup>47</sup> Depending on the chronic condition in question, medication adherence rates among pediatric populations can be as low as 11%.<sup>49</sup> Regarding chronic illnesses in particular, parents often discontinue medications upon perceived resolution of symptoms, lack of effectiveness, or experience of adverse effects.<sup>50</sup> Clinicians need to consider that ADHD often is perceived as a "noncritical" illness with no physical pain or

discomfort associated, thus perception of a treatment need may be low.

Although treatment compliance and adherence are important issues in the management of all chronic medical and psychiatric conditions, ADHD shares many of the impediments to adequate compliance that are common to any lifelong condition. However, it also includes features and therapeutic responses that seem to be unique to individuals with ADHD (eg, a recent analysis showed that current methods of improving medication adherence for chronic health problems are mostly complex and not very effective, so the full benefits of treatment cannot be realized<sup>51</sup>). In addition, research in this field needs advances, including improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements in patient-important clinical outcomes. To address this important clinical challenge, the effectiveness of treatment adherence programs and related interventions, the role of guidelines, treatment modalities (such as formulation), and treatment strategies (such as dosage regimen simplification) must be scrutinized.

Although patient engagement in their treatment was not addressed in the present review, or in most of the articles included in this review, it appears that perhaps a greater degree of engagement may enhance adherence. In one survey, most general practitioners were unaware of the reason that many children and adolescents stopped taking atomoxetine as they progressed to adulthood.<sup>29</sup> This age range is associated with poor adherence and may be attributed to a desire of the individual to take control of their condition and to not feel the need to continue medication.<sup>29,30,40</sup> It is likely that a deeper level of engagement, where the patient is seen more as a partner in planning their health care program, may lead to better treatment adherence overall.

In 2009, Dopheide detailed how the implementation of initiatives promoting medication adherence, such as patient/parent education, provider follow-up, and adverse effect management, are critical to ensure treatment success.<sup>52</sup> Although available evidence is limited and some findings may be difficult to interpret, the positive role of psychoeducation and other educational interventions in children and adolescents with ADHD regarding several outcome measures and treatment adherence is supported by most of the literature.<sup>53</sup>

## Factors affecting treatment adherence/nonadherence

It can often be difficult for health care professionals to understand the reasons for nonadherence among patients because

the causes of nonadherence are often multidimensional. Treatment adherence is influenced by many factors: the health care team and system-related factors, condition-related factors, characteristics of therapies, and patient-related factors.<sup>11</sup> These factors alone or in combination can lead a patient to become nonadherent.<sup>40</sup> Because poor treatment adherence and discontinuation of therapy can result in symptom deterioration, providers should identify patients who do not adhere to medication schedules and their reason for nonadherence (eg, forgetfulness, side effects, parental support, parent, or child opposition) and provide strategies to overcome any barriers.

Nonadherence can also be categorized as unintentional (caused by poor memory and dexterity, or cost of medicines and lack of supervision) and intentional (caused by patients' own beliefs and decision-making abilities). In chronic disorders, a patient's belief about his or her treatment can be a significant predictor of adherence to that treatment.<sup>54</sup> The decision to take a medication is complex, and there may be instances in which unintentional and intentional nonadherence interact.

Long-acting medications are associated with better treatment adherence and persistence compared with short-acting medications (both stimulants and nonstimulants). Further, higher doses of medication increase the likelihood of poor treatment adherence due to higher rates of side effects.<sup>55</sup> Patients with intellectual difficulties are more likely to exhibit poorer treatment adherence.<sup>56</sup> The presence of comorbidities and associated medications<sup>56,57</sup> increases the treatment adherence. In addition, children who live in foster care<sup>57</sup> or with separated parents<sup>56</sup> demonstrate increased treatment adherence. Factors associated with decreased treatment adherence and persistence include a family history of ADHD (especially paternal) and higher level of parental education.<sup>55</sup>

Nonadherence to treatment regimens has been shown to be associated with increased hospital visits, unnecessary hospitalizations, increased symptoms of the disease, morbidity, and mortality.<sup>58,59</sup> Adherence to treatment regimens has been shown to be related to improved psychological functioning and overall quality of health in youth and improvements in quality of life.<sup>60–63</sup>

## Remission with long-term treatment and maintenance of response

Until recently, little information was available on relapse rates following treatment discontinuation. Atomoxetine has demonstrated maintenance of response in pediatric

patients.<sup>41,64</sup> In one RCT where children and adolescents responded during an initial 12-week, open-label period of treatment with atomoxetine, response was maintained in patients randomized to continue on atomoxetine for an additional 9 months.<sup>64</sup> Maintenance of response with atomoxetine treatment was analyzed in adults with ADHD during a 25-week, double-blind, placebo-controlled, randomized withdrawal period.<sup>65</sup> Only adults who previously responded to atomoxetine during a 12-week, open-label treatment period and maintained that response during a 12-week, double-blind maintenance period were included in the study. Relapse was defined as a return to  $\geq 80\%$  of baseline Conners' Adult ADHD Rating Scale: Investigator-Rated: Screening Version total score after visit 11 (week 24) and two consecutive visits with a CGI-S score of  $\geq 4$  points. More atomoxetine- than placebo-treated patients maintained a satisfactory response postrandomization (64.3% vs 50.0%;  $P < 0.001$ ). Further, time-to-relapse was significantly longer for atomoxetine than placebo ( $P = 0.004$ ). In addition, relapse rates after discontinuation of treatment with atomoxetine seem to be lower compared to those seen after discontinuation of stimulants, and the differences in relapse rates may be due to differences in the mechanism of action.<sup>66</sup> However, this difference is also probably due to responders on atomoxetine (after long-term maintenance) being able to maintain response after discontinuation much longer, and this may result in increased treatment adherence.

## Sex differences and outcomes

With the exception of two articles, the studies included in this review reported that a majority of subjects were male, ranging from a low of 56%<sup>24</sup> to a high of 90%.<sup>41</sup> Both studies reporting a greater proportion of female subjects, 62%<sup>35</sup> and 52%,<sup>44</sup> were performed with adult patients. This is consistent with reports that, over time, more females are diagnosed with ADHD, reducing the prevalence ratios.<sup>27</sup> For example, Zetterqvist et al<sup>30</sup> reported that the male-to-female prevalence ratio in children was 3.86 and dropped to 1.21 in adults. Most of the studies did not report on any interaction on outcome by sex. One study reported that males had a lower discontinuation rate than females (18% vs 22%, respectively),<sup>43</sup> whereas others indicated that females were more likely to show better adherence<sup>6,27</sup> and greater persistence.<sup>6</sup> Another study reported that females were more likely to show atomoxetine remission than males, whereas males showed poorer adherence.<sup>33</sup> No significant influence of sex on outcome was reported in five studies.<sup>22,31,34,41,67</sup> The interactions of sex on outcome may be influenced by the generally greater preponderance of

male patients within the studies and require more balanced studies to be performed.

## Limitations of the study

One of the potential limitations of this review is that adherence is measured by many different parameters, making comparisons across studies difficult.<sup>6</sup> In the present investigation, adherence was determined by post hoc examination of medical records, questionnaires, direct questioning, or review of returned medications in an RCT. Consequently, the heterogeneous methods, trial design, and outcome measures that were considered likely limited the strength of the evidence included in this review. In spite of a comprehensive literature search and the inclusion of publications from different databases, it is still possible that we may have inadvertently excluded relevant publications. The patient numbers in some of the included articles were low (ie, <100), and of all the articles included, only five were of RCTs. Moreover, in cohort studies (including both prospective and retrospective designs, cross-sectional studies, and case-control studies), and in controlled trials, adherence and persistence are limited to compliance and discontinuation to treatment patients are taking in a controlled setting, thus the inclusion of real-world observational trials in this review may provide a better understanding of treatment adherence in a naturalistic setting.

In summary, although we are limited in our ability to draw robust conclusions from the available data, we recommend further research examining medication adherence, compliance, and discontinuation in atomoxetine-treated patients with ADHD. It is important to gain a clearer understanding of the factors that impact the treatment and management of ADHD and to address the unmet needs in clinical practice to make well-informed treatment decisions for this patient population and in order to better predict treatment adherence and prognosis. A more thorough understanding of treatment adherence can help clinicians individualize ADHD treatments and assess various factors upon initiation of treatment to improve education of patients and caregivers regarding treatment goals, course prediction, and proper dosing. In addition, we may further investigate the subsequent consequences of nonadherence/adherence after atomoxetine treatment on clinical outcomes, such as quality of life, long-term outcomes, functioning, and impact on comorbidity.

## Conclusion

The findings from this review indicate that persistence and adherence to atomoxetine treatment were generally high. Factors found to influence treatment adherence and

nonadherence to atomoxetine treatment in ADHD in this review include age, sex, the definition of response used, length of treatment, initial dose of treatment, comorbidities, and reimbursement. Tolerability was cited as an important reason for treatment discontinuation. A more thorough understanding of treatment adherence can help clinicians to individualize ADHD treatments and assess various factors upon initiation of treatment to improve education of patients and caregivers regarding treatment goals, course prediction, and proper dosing. More research is needed to understand those factors that can help identify patients at risk for poor treatment adherence and identify interventions that could improve treatment adherence early in the stage of this illness to secure a better long-term prognosis.

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## Disclosure

Drs Treuer, Mendéz, and Wu and Mr Montgomery are full-time employees of Eli Lilly and Company, LLC, and minor stockholders of Eli Lilly and Company. The authors report no other conflicts of interest in this work.

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