CNS Neuroscience & Therapeutics

ORIGINAL ARTICLE

CNS Neuroscience & Therapeutics

Real-World Dosing Patterns of Atomoxetine in Adults with Attention-Deficit/Hyperactivity Disorder

Samaneh Kabul,[1] Carlos Alatorre,[1] Leslie B. Montejano,[2] Amanda M. Farr[2] & David B. Clemow[1]

1 Eli Lilly and Company, Indianapolis, IN, USA
2 Truven Health Analytics, Cambridge, MA, USA

Keywords
Adult; Atomoxetine; Attention-deficit disorder with hyperactivity; Dose–response relationship; Drug; Medication adherence.

Correspondence
Carlos I. Alatorre, M.B.A., Ph.D., Director, US Health Outcomes Research, Global Patient Outcomes and Real World Evidence, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA.
Tel.: +1-317-4417870;
E-mail: alatorre_c@lilly.com
Received 15 April 2015; revision 15 July 2015; accepted 15 July 2015

doi: 10.1111/cns.12442

SUMMARY

Aims: The aim was to investigate the dosing patterns of atomoxetine monotherapy in adult patients with attention-deficit/hyperactivity disorder (ADHD) in a retrospective analysis. **Methods:** Adult (≥18 years) patients with ADHD newly initiated on atomoxetine with ≥1 outpatient pharmacy claim for atomoxetine between January 2006 and December 2011 were selected from the Truven Health MarketScan® Commercial database. After a 30-day titration period, dosing patterns of atomoxetine monotherapy were analyzed in the 12 months following initiation. In addition, patient demographic and clinical characteristics were compared to identify characteristics associated with suboptimal versus recommended dosing. **Results:** Of the 12,412 adult patients with ADHD newly initiated on atomoxetine, 4548 (36.6%) were suboptimally dosed, whereas 3323 (26.7%) were treated at recommended dose. Overall, study patients were treated at a mean (standard deviation [SD]) dose of 68.5 (44.9) mg/day. The suboptimal dosing cohort included significantly more females (54% vs. 44%, $P < 0.001$) and had fewer patients with pre-index use of other ADHD medications (17% vs. 20%, $P < 0.001$) compared with the recommended dosing cohort. **Conclusions:** Adult patients with ADHD receiving atomoxetine therapy in a real-world setting are often dosed suboptimally. Increasing the awareness on optimal dosing strategy among clinicians and patients is warranted to maximize the therapeutic benefits of atomoxetine among adult patients with ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by persistent inattentiveness, impulsivity, and hyperactivity, is a chronic psychiatric condition [1]. ADHD occurs in childhood; however, approximately 30–60% of diagnosed cases experience continuity into adulthood [2–5]. The National Comorbidity Study Replication estimated that approximately 4.4% of the working adult population in the United States has ADHD, with higher prevalence rates reported in males [6]. Adult ADHD carries a significant economic and healthcare resource utilization burden in the United States [7].

Pharmacotherapy has been widely accepted as a treatment option for ADHD [8]. Several stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, and mixed amphetamine salts) or nonstimulants (atomoxetine) are indicated for use in clinical practice for treating adults with ADHD [8,9]. Although stimulants are the most common treatment for reducing ADHD symptoms, some patients do not respond [10], have intolerable side effects [11], or have concerns with abuse potential or exacerbation of anxiety [12]. Atomoxetine is a nonstimulant alternative, with once-a-day oral dosing, approved in the United States for the treatment of ADHD [13]. While numerous randomized and open-label clinical studies have demonstrated the therapeutic efficacy of atomoxetine in adults with ADHD [14–18], data suggest that treatment using an adequate dose of atomoxetine for sufficient time duration is important for symptom improvement in adults with ADHD [18,19].

Adult patients with ADHD are recommended to be initiated with atomoxetine at a daily dose of 40 mg (for a minimum of 3 days) followed by dose escalation to a target daily dose of 80 mg. After an additional 2–4 weeks, the dose may be increased to a maximum of 100 mg in patients not achieving an optimal response [13]. Despite the recommended target dosage (80 mg/day), adults with ADHD may be treated and maintained with suboptimal doses of atomoxetine, resulting in poor patient outcomes [20]. Few studies assessing real-world utilization and dosing patterns of atomoxetine in adult ADHD populations have been conducted to date. Therefore, this retrospective study aimed to investigate the dosing patterns of atomoxetine monotherapy in adults with ADHD and assess whether the average daily dose in real-world conditions is consistent with the recommended daily dose.

Materials and Methods

Data Source

This retrospective analysis was conducted using administrative medical and pharmacy claims data from the Truven Health MarketScan® Commercial Claims and Encounters (Commercial) Database for the period January 2006 to December 2011. This database contains complete longitudinal records of inpatient and outpatient services, and prescription drug claims of more than 45 million employees and their dependents, covered under a variety of fee for service, fully capitated, and partially capitated health plans across all geographic regions of the United States. In capitated plans, like health maintenance organizations, physicians are paid a set price per capita regardless of services provided, as opposed to fee-for-service plans where physicians are reimbursed for each service provided. All study data are de-identified and fully compliant with Health Insurance Portability and Accountability Act (HIPAA) of 1996. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board approval to conduct this study was not necessary.

Study Population

Adult patients (aged 18 years and above) newly initiated on atomoxetine (i.e., no atomoxetine use in the prior 6 months) with at least one outpatient pharmacy claim for atomoxetine between January 1, 2006 and December 31, 2011 were identified. The date of the most recent atomoxetine treatment episode was set as the index date. All patients were required to have at least one inpatient or outpatient medical claim with an International Classification of Diseases, Clinical Modification, Ninth Revision (ICD-9-CM) diagnosis code for ADHD (314.0x) and be continuously enrolled with medical and pharmacy benefits in the 6 months pre-index and 12 months postindex. Additionally, patients were required to have ≥31-day supply of atomoxetine over the initial 60 days postindex (to allow for an initial titration period) and be treated with atomoxetine monotherapy during the 12 months postindex (not having ≥15 continuous days of overlap with another ADHD medication). The study period spanned from July 1, 2005 through December 31, 2012 with a 6-month pre-index and 12-month postindex or follow-up period.

Dosing

Atomoxetine dosing was determined from pill strength based on the National Drug Code (NDC) and quantity dispensed and days' supply information on pharmacy claims for atomoxetine. The first 30 days of therapy was excluded when calculating dose to allow for upward titration during this period. The average daily dose while on therapy for days 31–365 was calculated by summing the dose for each day a patient had drug on hand and dividing by the number of days with drug on hand.

Based on atomoxetine daily dose (after allowing for titration during the first month of medication supply), eligible patients were stratified into four cohorts: *suboptimal*, *recommended*, *above-recommended*, and *fluctuating* dosing cohorts. In the primary analysis, patients who received an average daily dose of <80 mg on all postindex prescriptions were identified as *suboptimal dosing* cohort; those receiving an average daily dose of 80–100 mg, inclusive, on all postindex prescriptions were grouped into *recommended dosing* cohort; patients with average daily dose >100 mg on all postindex prescriptions were classified into *above-recommended dosing* cohort, and those who could not be categorized into any of the dose cohorts above owing to the postindex dose changes after the titration period were grouped into *fluctuating dosing* cohort. The patients who received fluctuating doses of atomoxetine were excluded from further analysis. Dosing distributions for the overall sample, and by cohort, were captured. Persistence to atomoxetine during the postindex period was also measured. Persistence was defined as the time continuously on atomoxetine before a gap of >30 days without drug (a discontinuation).

Patient Characteristics

Characteristics of the suboptimal and recommended dosing cohorts were compared to identify characteristics associated with suboptimal vs. recommended dosing in the primary analysis. Demographic characteristics measured at index included age, gender, insurance plan type, US Census geographic region, and presence of any capitated claims. Clinical characteristics were measured in the pre-index period and included ADHD subtype and selected comorbid psychiatric disorders based on the presence of ≥1 medical claim with relevant ICD-9-CM diagnosis codes in any position. Clinician/physician specialty from the office visit prior to index and prior ADHD medication use based on pharmacy claims with relevant NDC codes were also captured.

Sensitivity Analyses

Two sensitivity analyses were conducted to assess the robustness of the dosing cohort assignment in the primary analysis using alternative dosing definitions. In the first sensitivity analysis, patients were categorized based on the patient's dose on day 31, rather than across all subsequent postindex claims. For the second sensitivity analysis, dosing cohorts were created using a titration period of 60 days, among patients with at least 61-day supply of atomoxetine over the initial 90 days of the postindex period.

Statistical Analysis

All study variables including demographic and clinical characteristics for the overall sample and by dosing cohort were summarized descriptively. Statistical tests of significance for differences between the recommended and suboptimal dosing cohorts were performed. Chi-square tests were used to evaluate the statistical significance of differences for categorical variables. To evaluate the statistical significance of differences for normally distributed continuous variables, *t*-tests were used. An *a priori* *P*-value <0.05 was set as the threshold for statistical significance.

Results

Sample Size

Out of an initial sample of 256,836 patients with at least one claim for atomoxetine in the Commercial database between January 1,

2006 and December 31, 2011, a total of 12,412 adult patients with ADHD newly initiated on atomoxetine monotherapy met all of the study inclusion criteria. Of these, 4548 (36.6%) patients were treated at suboptimal dose, 3323 (26.8%) received treatment at recommended dose, and 213 (1.7%) were treated at above-recommended dose across all postindex prescriptions in the primary analysis (total N = 8084). Due to variation in dose across postindex prescriptions, 4328 (34.9%) patients could not be classified into any of the above dosing cohorts, and hence, they were grouped into fluctuating dosing cohort (Figure 1).

Dosing and Persistence

Overall, the average daily dose of atomoxetine during the study period was 68.5 mg (SD 44.9) across all study-eligible patients with ADHD. Patients in the suboptimal dosing cohort were treated with 42.9 mg/day on average (SD 15.9), while those in the recommended dosing cohort were treated at a mean dose of 83.1 (6.9) mg/day (Table 1). More than 90% of patients discontinued atomoxetine within the 12-month postindex period. The recommended dosing cohort persisted on atomoxetine for an average of 131 days (SD 91), while the suboptimal dosing cohort persisted for an average of 129 days (SD 93).

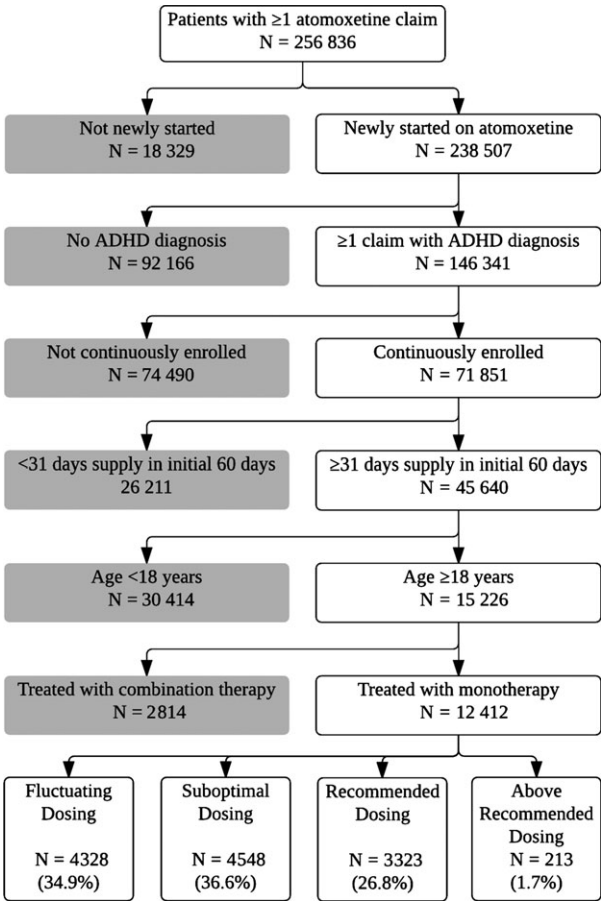

Figure 1 Sample selection and dosing cohort stratification. Patients with ≥1 atomoxetine claim who met all study inclusion and exclusion criteria were stratified into dosing cohorts based on average daily dose while on therapy, after a 30-day titration period.

Patient Characteristics by Dosing Cohorts

Patient characteristics stratified by suboptimal vs. recommended dosing are presented in Table 2. The suboptimal and recommended dosing cohorts had similar demographic and clinical characteristics with few exceptions. Among ADHD adults who received atomoxetine monotherapy, a significantly higher proportion of patients were in the 25–44 years age group in the recommended dosing cohort compared to the suboptimal dosing cohort (45.3% vs. 40.6%; $P < 0.001$). Patients in the suboptimal dosing cohort had a greater proportion of females (53.5% vs. 44%, $P < 0.001$) and had fewer patients with pre-index use of other ADHD medications (16.8% vs. 20%, $P < 0.001$). Depression, anxiety disorder, and bipolar disorder were the most prominent psychiatric comorbidities across both cohorts with no significant difference between the two cohorts.

Sensitivity Analyses

In the primary analysis, 8084 patients could be categorized as being treated with suboptimal, recommended, or above-recommended dose. In the sensitivity analyses, the absolute number of patients who could be categorized differed but the proportion of patients falling into each dosing category was consistent with the primary analysis (Figure 2).

Discussion

The current retrospective study determined the real-world dosing patterns of atomoxetine monotherapy and patient characteristics of adult patients with ADHD receiving atomoxetine in a large commercially insured United States population. The results showed that suboptimal dosing of atomoxetine in adults with ADHD is not uncommon in the study population. Clinical trials have indicated that doses within the recommended range are optimal for achieving symptom reduction and favorable outcomes [20,21].

In general, eligible patients in the current analysis were similar to those included in previous studies of patients treated with atomoxetine using administrative claims data [22,23]. Mean age was similar to that reported by Wu and colleagues [23], but the proportion of patients aged 25–44 was larger than that reported by van Brunt et al. [22]. The proportion of females was greater in this analysis, and the proportion of patients with pre-index depression/anxiety was slightly lower compared to other analyses [22,23]. In addition, a majority of the patients included in this analysis were from a working population, which is similar to the population reported by the National Comorbidity Survey Replication study (72%) [6]. This suggests the patients included in the present analysis were representative of the adult ADHD population as demonstrated by similar real-world studies.

The results from the current analysis revealed that over one-third of the adult patients with ADHD initiated on atomoxetine monotherapy were suboptimally dosed after titration, receiving an average dose of 42.9 mg/day. The percentage of suboptimally

Table 1 Mean daily dose of atomoxetine while on therapy, by dosing cohort

	All patients (N = 12,412)	Fluctuating dosing (N = 4328)	Suboptimal dosing (N = 4548)	Recommended dosing (N = 3323)	Above-recommended dosing (N = 213)
Mean (SD) dose, mg/day	68.5 (44.9)	76.2 (25.2)	42.9 (15.9)	83.1 (6.9)	230.2 (232.7)
Quartiles					
75% Q3	80.0	87.5	60.0	80.0	160.0
50% Median	71.7	77.9	40.0	80.0	120.4
25% Q1	43.9	61.3	32.8	80.0	120.0

Dose calculations exclude the 30-day titration period.

dosed patients is conservative, as many of the large number of patients categorized as having fluctuating dosing are being underdosed. Even when patients are dosed within the recommended 80–100 mg/day target, the 75th quartile mean dose for these patients was only 80 mg/day, indicating that few of these patients increased their dose to 100 mg/day, as recommended in the atomoxetine labeling if patients have not achieved an optimal response [13]. Results from both the sensitivity analyses showed that irrespective of the dosing definitions employed in the current study, the proportion of patients treated at suboptimal and recommended doses of atomoxetine was consistent to those obtained in the primary analysis.

These findings are consistent with pharmaceutical dispensing data which showed that despite the recommended treatment at the target dose of 80 mg/day, adult patients with ADHD often receive subtherapeutic doses of atomoxetine in real-world clinical settings [20]. Although reasons for suboptimal treatment could not be thoroughly investigated in the current study due to limitations of claims data, market research data suggest a lack of awareness regarding recommended target dosing among physicians as being the primary reason for underdosing: When asked what the adult target dose of atomoxetine is, 65% of primary care physicians (n = 101) and 48% of adult psychiatrists (n = 50) responded with answers of ≤60 mg/day [20].

To attempt to understand the characteristics associated with suboptimal versus recommended dosing, the demographic and clinical characteristics of patients across both the cohorts were compared. Although the suboptimal and recommended dosing cohorts were similar in terms of most of the baseline characteristics, statistically significant differences existed between the cohorts with regard to a few parameters. For example, over half of the patients in the suboptimal dosing cohort were females as opposed to over half were males in the recommended dosing cohort. Fewer patients in the suboptimal dosing cohort than in the recommended dosing cohort had pre-index use of other ADHD medications. More underdosing of atomoxetine among adult females compared to males could be due to multiple factors including more inattentive and less disruptive hyperactive/impulsive symptoms and better coping strategies (that mask symptoms) than males, resulting in a less aggressive treatment approach by the clinician [24]. Among the patients treated with recommended or suboptimal doses of atomoxetine in the study, 53.9% of men and 58.6% of women had a diagnosis for inattentive subtype. Of note is the statistically significantly lower percentage of patients with previous ADHD treatment in the suboptimal cohort compared with recommended dosing group. Clinicians may be more apt to use higher doses of atomoxetine if the patient has a lack of optimal efficacy with previous pharmacological treatments, particularly if their tolerability profile is known.

Comorbidities, including depression and anxiety, do not appear to affect dosing, which is surprising to the authors considering that these patients may be perceived as more challenging in achieving treatment success. There was a small but statistically significant difference in age groups between cohorts, which may not be clinically meaningful; however, healthcare providers may be more comfortable with higher doses in older patients. There was no cohort difference in prevalence of ADHD subtype, although there were more inattentive patients than combined plus hyperactive/impulsive patients, which is in contrast to what might be expected (more patients in the combined plus hyperactive/impulsive cohort). While significant differences were noted, these differences may or may not be clinically meaningful. This study had no clear demographic or clinical characteristic drivers of suboptimal, suggesting underdosing was due to a lack of awareness of recommended dosing rather than clinical need.

The adult patients with ADHD included in this analysis were persistent to atomoxetine for just over 4 months, which is consistent with previous research involving this medication [16,18]. Many other analyses have reported poor persistence to ADHD medications in general, with discontinuation rates and days persistent varying by medication class, but also by the definitions used to capture these variables [25]. Potential explanations for poor persistence among patients with ADHD include adverse effects; both lack of symptom control and adequate symptom control, the latter related to patient tendency to stop treatment once they feel better; and drug holidays [25,26]. The specific reasons for discontinuation could not be measured in the claims data used for this analysis so can be hypothesized, but not compared between the recommended and suboptimal dosing cohorts. Although persistence to atomoxetine was similar between the two cohorts, reasons for discontinuation may not be. For example, patients in the suboptimal group may have continued therapy despite minimal efficacy, because the low dose was tolerable and had few, if any, adverse effects. It is also possible patients in the suboptimal dosing group experienced a placebo-type effect, which led to similar persistence as observed in the recommended dosing group. Previous research found treatment persistence in adult patients assigned to active treatment with atomoxetine and placebo to be similar (136 days vs. 142 days) [16]. Additionally, in patient selection, there were a sizeable number of patients

Table 2 Demographic and clinical characteristics of patients with attention-deficit/hyperactivity disorder (ADHD) treated with suboptimal vs. recommended doses of atomoxetine

	Recommended dosing (N = 3323)	Suboptimal dosing (N = 4548)	*P*-value
Mean (SD) age at index	34.2 (12.3)	34.1 (12.9)	0.953
Age group, N (%)			<0.001
18–24	1047 (31.5)	1546 (34.0)	
25–44	1504 (45.3)	1846 (40.6)	
45+	772 (23.2)	1156 (25.4)	
Gender, N (%)			<0.001
Male	1860 (56.0)	2115 (46.5)	
Female	1463 (44.0)	2433 (53.5)	
Capitated services, N (%)			<0.001
No	3039 (91.5)	4005 (88.1)	
Yes	263 (7.9)	521 (11.5)	
Unknown	21 (0.6)	22 (0.5)	
Predominant ADHD subtype[a], N (%)			0.141
Inattentive	1837 (55.3)	2590 (56.9)	
Hyperactive impulsive or combined	1486 (44.7)	1958 (43.1)	
Proxied prescriber specialty[b], N (%)			0.255
Primary care	1826 (55.0)	2495 (54.9)	
Psychiatry	22 (0.7)	29 (0.6)	
Neurology	48 (1.4)	80 (1.8)	
Other	1074 (32.3)	1521 (33.4)	
Unknown	353 (10.6)	423 (9.3)	
Pre-index ADHD medication use[c], N (%)	663 (20.0)	763 (16.8)	<0.001
Long-acting stimulants	397 (11.9)	432 (9.5)	0.001
Intermediate-acting stimulants	190 (5.7)	230 (5.1)	0.198
Short-acting stimulants	88 (2.6)	120 (2.6)	0.979
Pro-drug stimulants	91 (2.7)	101 (2.2)	0.141
Alpha-2 adrenergic agonists	28 (0.8)	19 (0.4)	0.016
Pre-index comorbidities[d], N (%)			
Depression	538 (16.2)	795 (17.5)	0.132
Anxiety disorder	425 (12.8)	614 (13.5)	0.358
Hypertension	319 (9.6)	365 (8.0)	0.014
Gastrointestinal disorders	254 (7.6)	368 (8.1)	0.467
Sleep disorders	235 (7.1)	295 (6.5)	0.306
Substance abuse/dependence	214 (6.4)	253 (5.6)	0.104
Bipolar disorder/mania	140 (4.2)	181 (4.0)	0.605
Diabetes	89 (2.7)	100 (2.2)	0.170

[a]Inattentive defined as ≥1 claims with ICD-9 314.00 without any claims with ICD-9 314.01; hyperactive/impulsive or combined defined as ≥1 claim with ICD-9 314.01.

[b]Prescription claims do not list provider specialty; proxied from provider specialty on the office visit on index or in the 6 months pre-index that fell closest to index.

[c]Patients could have used more than one ADHD medication class in the 6 months pre-index.

[d]Comorbidities affecting <1% of patients not shown (conduct disturbance, eating disorders, oppositional defiance disorders, personality disorders, pervasive developmental disorders, psychotic disorders).

excluded for not having at least 31 days of atomoxetine treatment. This may indicate that healthcare providers are not setting appropriate expectations for patients about the time period over which patients need to take atomoxetine to experience symptom reduction [19].

There are several limitations to the study which merit consideration. The MarketScan® Commercial database relies on administrative claims data for clinical detail. Clinical outcomes, such as a reduction in ADHD symptoms, cannot be measured adequately in claims databases, so while controlled trials suggest symptom control would be better in the recommended dosing group compared to the suboptimal dosing group [18,19,23], it was not possible to assess the association between dosing cohort and symptom control in this analysis. As with any other claims database, outcomes were assessed from medication prescribed and filled rather than actual patient-level adherence. It is not known whether or not patients took the medications as intended or why patients discontinued or remained on atomoxetine. Misclassification of dose may have occurred due to erroneous doses listed on pharmacy claims; use of medication not resulting in a drug claim

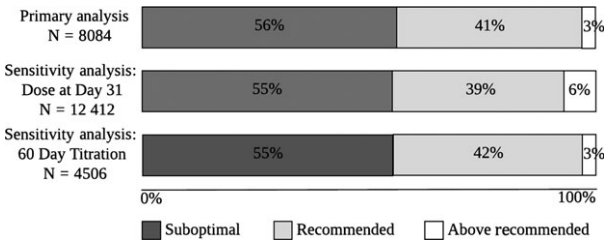

Figure 2 Proportion of patients categorized as suboptimal, recommended, and above-recommended dosing, primary and sensitivity analyses definitions. Fluctuating cohort excluded from this figure to show impact of dosing definitions on stable-dose cohorts.

(e.g., samples, paying with cash); dosing schedules other than daily dosing (e.g., weekend drug holidays); and dosing adjustments with medication on hand rather than the issuance of a new prescription. Atomoxetine may have been used off-label by some patients in this analysis as diagnoses are not present on outpatient pharmacy records. However, requiring at least one medical claim with an ADHD diagnosis increased the probability that these patients were prescribed atomoxetine to treat ADHD. In patient selection, just over 90,000 potential patients were excluded based on this criterion. This excluded patient group may consist of off-label users but also patients who were enrolled in their insurance plans for a short amount of time, during which they never had a medical claim with an ADHD diagnosis. Finally, the analysis was limited to only those individuals with commercial health insurance; therefore, results of this analysis may not be generalizable to ADHD patients with other types of insurance or who lack coverage.

Despite these limitations, this study has several strengths. It is the first study to evaluate a large sample of patients from an administrative database and provide a contemporary estimate on dosing patterns of atomoxetine for the treatment of adult ADHD in a geographically diverse US population. In addition, as the Commercial database includes adult patients with ADHD treated by clinicians across all US geographic regions and covered under various health plans, the findings of this study reflect the dosing patterns of atomoxetine in real-world clinical practice.

Conclusion

The results suggest that a considerable proportion of adult patients with ADHD are often treated with suboptimal doses of atomoxetine monotherapy even after a 30-day titration period in a real-world setting. This finding is relevant for clinicians and patients since treatment at the recommended daily dose is generally important to achieve optimal therapeutic benefit.

Acknowledgments

Truven Health Analytics employees who assisted with the work described in this article include Rob Fowler (programming support), Greg Lenhart (statistical support), and Santosh Tiwari (writing support). Doug Kelsey from Lilly provided medical consultation.

Disclosures

This study was funded by Eli Lilly and Company. Drs. Kabul, Alatorre, and Clemow are employees of Eli Lilly and Company. Truven Health Analytics received funding from Eli Lilly and Company to conduct this analysis. Ms. Montejano and Ms. Farr are employees of Truven Health Analytics.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005;**366**:237–248.
2. Weiss G, Hechtman L. *Hyperactive children grown up: ADHD in children, adolescents, and adults*. New York, NY: Guilford Press, 1993.
3. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. *Am J Psychiatry* 2000;**157**:816–818.
4. Rasmussen P, Gillberg C. Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. *J Am Acad Child Adolesc Psychiatry* 2000;**39**: 1424–1431.
5. Kessler RC, Adler LA, Barkley R, et al. Patterns and predictors of ADHD persistence into adulthood: Results from the National Comorbidity Survey Replication. *Biol Psychiatry* 2005;**57**:1442–1451.
6. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry* 2006;**163**:716–723.
7. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry* 2012;**51**:990–1002.
8. Wilens TE, Morrison NR, Prince J. An update on the pharmacotherapy of attention-deficit/hyperactivity disorder in adults. *Expert Rev Neurother* 2011;**11**:1443–1465.
9. Kolar D, Keller A, Golfinopoulos M, Cumyn L, Syer C, Hechtman L. Treatment of adults with attention-deficit/ hyperactivity disorder. *Neuropsychiatr Dis Treat* 2008;**4**:389–403.
10. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: Acute comparison and differential response. *Am J Psychiatry* 2008;**165**:721–730.
11. Fredriksen M, Dahl AA, Martinsen EW, Klungsoyr O, Haavik J, Peleikis DE. Effectiveness of one-year pharmacological treatment of adult attention-deficit/ hyperactivity disorder (ADHD): An open-label prospective study of time in treatment, dose, side-effects and comorbidity. *Eur Neuropsychopharmacol* 2014;**24**:1873–1884.
12. Clemow DB, Walker DJ. The potential for misuse and abuse of medications in ADHD: A review. *Postgrad Med* 2014;**126**:64–81.
13. Eli Lilly and Company. Strattera package insert. Available from: http://pi.lilly.com/us/strattera-pi.pdf (revised 01/ 2015; cited 2015 Feb 13).
14. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: Two randomized, placebo-controlled studies. *Biol Psychiatry* 2003;**53**:112–120.
15. Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: Final report of a 4-year study. *J Atten Disord* 2008;**12**:248–253.
16. Adler LA, Spencer T, Brown TE, et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: A 6-month, double-blind trial. *J Clin Psychopharmacol* 2009;**29**:44–50.
17. Marchant BK, Reimherr FW, Halls C, et al. Long-term open-label response to atomoxetine in adult ADHD: Influence of sex, emotional dysregulation, and double-blind response to atomoxetine. *Atten Defic Hyperact Disord* 2011;**3**:237–244.
18. Young JL, Sarkis E, Qiao M, Wietecha L. Once-daily treatment with atomoxetine in adults with attention-deficit/hyperactivity disorder: A 24-week, randomized, double-blind, placebo-controlled trial. *Clin Neuropharmacol* 2011;**34**:51–60.
19. Bushe CJ, Savill NC. Systematic review of atomoxetine data in childhood and adolescent attention-deficit hyperactivity disorder 2009-2011: Focus on clinical efficacy and safety. *J Psychopharmacol* 2014;**28**:204–211.

20. Clemow DB. Suboptimal dosing of Strattera (atomoxetine) for ADHD patients. *Postgrad Med* 2014;**126**:196–198.
21. Michelson D, Adler L, Spencer T, et al. Atomoxetine in adults with ADHD: Two randomized, placebo-controlled studies. *Biol Psychiatry* 2003;**15**:112–120.
22. Van Brunt DL, Johnston JA, Ye W, Pohl GM, O'Hara NN. Factors associated with initiation with atomoxetineversus stimulants in the treatment of adults with ADHD: Retrospective analysis of administrative claims data. *J Manag Care Pharm* 2006;**12**:230–238.
23. Wu EQ, Birnbaum HG, Zhang HF, Ivanova JI, Yang E, Mallet D. Health care costs of adults treated for attention-deficit/hyperactivity disorder who received alternative drug therapies. *J Manag Care Pharm* 2007;**13**:561–569.
24. Quinn PO, Madhoo M. A review of attention-deficit/hyperactivity disorder in women and girls: Uncovering this hidden diagnosis. *Prim Care Companion CNS Disord* 2014;**16**: doi: 10.4088/PCC.13r01596.
25. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder – a systematic literature review. *Neuropsychiratr Dis Treat* 2014;**10**:1543–1569.
26. Faraone SV, Spencer TJ, Montano CB, Biederman J. Attention-deficit/hyperactivity disorder in adults: A survey of current practice in psychiatry and primary care. *Arch Intern Med* 2004;**164**:1221–1226.

