PASS Information

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Research question and objectives	The primary objective of this study is to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6-17 years of age relative to a propensity score-matched cohort of stimulant treated patients, using a cohort study design.
Country(-ies) of study	United States
Author	Kristin Joy Meyers, MPH PhD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 Telephone: +1 317 452 5421
Signature of principal investigator	Signature on file/see approval date below

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company
MAH contact person	Kristin Joy Meyers, MPH PhD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 Telephone: +1 317 452 5421

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1. Abstract

Title: The Risk of Dystonia among Children and Adolescents Treated with Atomoxetine within the Truven MarketScan Database: B4Z MC-B031.

Keywords: Atomoxetine, ADHD, Dystonia

Rationale and background: Dystonia is a known adverse reaction with many medications including antipsychotics, antidepressants, and other psychotropics. However, little is known about whether atomoxetine carries a risk of dystonia. One publication reviewing individual case reports from the VigiBase database suggested a possible signal between dystonia and atomoxetine use (Boyd 2015). However, there are no published case reports or epidemiological studies on atomoxetine and dystonia. Nor are there any publications regarding dystonia among those with attention-deficit/hyperactivity disorder (ADHD).

Research question and objectives: The primary objective of this study was to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6 and 17 years of age, relative to a propensity score-matched cohort of stimulant treated patients. This objective was attained by estimating the hazard ratio (HR) from Cox proportional hazards regression.

Study design: Retrospective cohort study.

Setting: This study included children and adolescents (6 to 17 years of age) who were treated with either atomoxetine or stimulant.

Subjects and study size, including dropouts: Patients needed at least 6 months (180 days) of continuous enrolment in the health plan prior to index date to be eligible for inclusion. After propensity score matching, there were 70,655 patients in each the atomoxetine-treated cohort and the stimulant treated cohort.

Variables: The primary endpoint was incident dystonia, as defined by International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. The first event of dystonia occurring after the initiation of the drug, and within the follow-up period was counted. The primary exposure of interest was atomoxetine. Use of any ADHD medication was not allowed in the 6-month baseline period prior to index date.

Data sources: The present study used a United States- (US-) based administrative healthcare claims database: Truven Health Analytics MarketScan ® (THAM) Database.

Results: The crude incidence rate of dystonia for the atomoxetine-treated cohort was 54.9 per 100,000 person-years (95% confidence interval [CI]: 27.1 to 82.7) compared to a crude incidence rate of 77.9 per 100,000 person-years (95% CI: 49.1 to 106.8) for the stimulant-treated cohort. After review and consideration of the proportional hazard assumptions with model covariates including atomoxetine (yes/no [y/n]), sex, age, and index year, there was no statistically significant increased risk of dystonia in the atomoxetine cohort, compared to the propensity score-matched stimulant cohort (adjusted HR=0.68; 95% CI: 0.36 to 1.28; p=0.23).

Of the dystonia cases identified in the atomoxetine cohort (n=15), the earliest case of dystonia from time of atomoxetine initiation was 2 days (median time to onset=94 days) and no cases of dystonia occurred within 14 days of a dose increase. The patient with dystonia occurring 2 days after initiation of atomoxetine initiated lamotrigine on the same day; which carries a labelled, known risk for dystonia. Therefore, while 60% of dystonia cases in the atomoxetine cohort were coded as due to drugs (ICD-9-CM 333.72), the time-to-onset data is not supportive that atomoxetine was the drug responsible. After excluding patients taking medications with a known risk of dystonia, the crude incidence rate of dystonia for the atomoxetine-treated cohort was 31.7 per 100,000 person-years (95% CI: 6.3 to 57.0) compared to a crude incidence rate of 52.2 per 100,000 person-years (95% CI: 23.8 to 80.5) for the stimulant-treated cohort. The incidence rate decreased in both cohorts after excluding patients taking these medications, compared to the incidence rates in the primary analysis. However, the conclusion of no statistically significant increased risk of dystonia in patients treated with atomoxetine compared to patients treated with stimulants remained the same (adjusted HR=0.60; 95% CI: 0.23 to 1.59; p=0.31).

Discussion: The results of this study did not show a statistically significant difference in the incidence and risk of dystonia among atomoxetine treated patients between 6 to 17 years of age, relative to a propensity score-matched cohort of stimulant treated patients. Furthermore, there was no clinically significant evidence to support an association between atomoxetine and dystonia, based on the time to onset from atomoxetine initiation or dose increase. This study does not suggest dystonia is a potential risk of atomoxetine use, and, therefore, does not impact the benefit-risk balance of atomoxetine.

Marketing Authorisation Holder(s): Eli Lilly and Company

Name(s) and affiliation(s) of principal investigator(s):

Kristin Joy Meyers, MPH PhD

Global Patient Safety Epidemiologist

Eli Lilly and Company

893 S. Delaware Street

Indianapolis, IN 46225 USA

Telephone: +1 317 452 5421

Email: meyers_kristin_joy@lilly.com

2. List of Abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
CI	confidence interval
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICSR	individual case safety report
MAH	Marketing Authorisation Holder
PAS	post-authorisation study
PASS	post-authorisation safety study
THAM	Truven Health Analytics MarketScan®
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US	United States
USA	United States of America
WHO	World Health Organization
y/n	yes/no

3. Investigators

The principal investigator for this observational study was:

Kristin Joy Meyers, MPH PhD

Global Patient Safety Epidemiologist

Eli Lilly and Company

893 S. Delaware Street

Indianapolis, IN 46225 USA

Telephone: +1 317 452 5421

Email: meyers_kristin_joy@lilly.com

4. Other Responsible Parties

Not applicable.

5. Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data collection	11 January 2016	06 January 2016	
End of data collection	01 April 2016	06 May 2016	
Registration in the EU PAS register	01 November 2015	29 March 2016	
Final report of study results	Version 1.0: 30 June 2016 Version 2.0: 31 March 2017	Version 1.0: 30 June 2016 Version 2.0: 03 March 2017	

Abbreviations: EU = European Union; PAS = post-authorisation safety.

6. Rationale and Background

6.1. Background for Conducting a Retrospective Database Study

Dystonia is a known adverse reaction with many medications including antipsychotics, antidepressants, and other psychotropics. However, little is known about the relationship, if any, between atomoxetine and dystonia.

The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring (also called Uppsala Monitoring Centre [UMC]) published a "possible signal" between atomoxetine and dystonia in children and adolescents in August 2015 (Boyd 2015). This signal was based on disproportionality analyses through data mining and review of individual case safety reports (ICSRs) in VigiBase, a method described in Caster et al. 2014. Outside of this report from WHO, there are no published case reports or epidemiological studies on atomoxetine and dystonia, nor are there any publications regarding dystonia among children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Information on dystonia in the ADHD population is limited primarily to case reports of dystonia after administration of drugs other than atomoxetine, rather than from observational studies (Chong et al. 1999; Senecky et al. 2002; Benjamin and Salek 2005; Keshen and Carandang 2007; McLaren et al. 2010; Yilmaz et al. 2013).

This retrospective, observational study was conducted to evaluate whether there is an increased risk of dystonia among children and adolescents treated with atomoxetine, compared to a propensity score-matched cohort of patients treated with a stimulant.

Feasibility for conducting this observational study was considered in both a United States- (US-) based electronic claims database (Truven Health Analytics MarketScan® [THAM]), as well as the United Kingdom- (UK-) based Clinical Practice Research Datalink (CPRD) (Annex 7 of B4Z-MC-B031 Study Protocol [see Annex 2 of this document]). MarketScan is larger, with nearly 370,000 atomoxetine exposed children and adolescents. Whereas fewer than 3,000 children and adolescents of the same age were identified as exposed to atomoxetine within CPRD, only 1 of which was subsequently diagnosed with dystonia following atomoxetine treatment. Therefore, in the interest of sample size and study power, this study used the Truven MarketScan® data.

6.2. Atomoxetine and ADHD

Attention-deficit/hyperactivity disorder is a common neurodevelopment disorder of childhood, which often persists into adulthood. Attention-deficit/hyperactivity disorder is characterised by developmentally inappropriate levels of inattention, hyperactivity, or a combination of these, which impair functioning in multiple settings. The prevalence of ADHD ranges between 2% and 18% in community samples (Rowland et al. 2002). There was a 42% increase in parent-report of health care provider diagnosed ADHD from 2003 to 2011 in the US (Visser et al. 2014).
In addition to increased prevalence of diagnoses, the prevalence of medication for ADHD treatment has increased, with more than two-thirds of those with current ADHD taking

medication in 2011 (Visser et al. 2014). The increased use of ADHD medications may enable the detection of rare safety issues which were previously undetected.

Medications to treat ADHD are classified as either stimulants or non-stimulants. Stimulant medication options include methylphenidate (e.g., Ritalin®), amphetamine (e.g., Adderall®), dextroamphetamine (e.g., Dexedrine®), and dexmethylphenidate (e.g., Focalin®).

Atomoxetine (Strattera®) was the first non-stimulant option when it was approved in the US in 2002. Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter, and has a minimal effect on other noradrenergic receptors, other neurotransmitter receptors, or transporters. It is also a weak inhibitor of dopamine uptake. Atomoxetine is indicated for the treatment of ADHD in children 6 years of age and older, adolescents, and adults. Eight years later, 2 other non-stimulant monotherapies, both alpha-2-adrenergic agonists, were approved by the Food and Drug Administration (FDA) for ADHD: guanfacine (Intuniv®) and clonidine (Catapres®). The European Medicines Agency (EMA) also approved Intuniv in 2015.

Based on a retrospective claims-based analysis conducted between 2003-2007 (prior to the approval of guanfacine and clonidine), it was estimated that 16.7% to 19.7% of medically treated patients with ADHD, aged 6 to 17 years, were prescribed atomoxetine as an index medication, whereas, 42.6% to 51.2% were prescribed methylphenidate and 32.2% to 37.7% amphetamine (Christensen et al. 2010). Since the approval of other non-stimulant medications, the percentage of index medications being atomoxetine has decreased. Issues of persistence, adherence, drug switching, and drug holidays are common among the ADHD-treated population. Barner et al. (2011) estimated the mean persistence (days of continuous therapy without a 30-day gap) for atomoxetine users aged 3 to 18 years of age was 153 days.

6.3. Dystonia

6.3.1. Definitions

Dystonia denotes abnormal movements that are slow or so sustained that they may appear as abnormal postures. Dystonia may involve a single body part (as in torticollis), may involve adjacent body parts, or may be more generalised. The movements are generally absent during sleep, and are exacerbated by emotional stress or voluntary activity (CIOMS 1999).
Drug-induced dystonia is most often early onset (within 1 week of commencement of treatment), but can be late onset (after several weeks, months, or years of treatment) (CIOMS 1999).
Approximately 50% of dystonic reactions, due to either antipsychotics or other dopamine blocking agents, occur within 48 hours of initiation of treatment, and 90% within 5 days (Ayd 2000). Additionally, late, persistent dystonia is usually termed tardive dyskinesia; as described in Section 9.3, tardive dyskinesia was excluded from consideration in the current study.

6.3.2. Risk Factors

Risk factors for dystonia are classified as either medication- or non-medication-related.
Many classes of medications are associated with extrapyramidal symptoms, which includes

dystonia events. The most common drug class associated with dystonia is antipsychotics, such as pimozide, thiothixene, mesoridazine, thioridazine, molindone, perphenazine, loxapine, risperidone, olanzapine, haloperidol, trifluoperazine, chlorpromazine, clozapine, quetiapine, and ziprasidone. The reactions to antipsychotics are common in young males and typically develop within a few days (approximately 7 days) of starting, or raising the dose of, an antipsychotic medication, or after reducing the dose of a medication used to treat extrapyramidal symptoms (APA 2013). Dopamine receptor blockade is considered the most accepted mechanism for antipsychotic drug-induced dystonia.

Other classes (individual medications) associated with extrapyramidal symptoms (involving dystonia) include: antiparkinson drugs (levodopa), antihistamines (promethazine, cetirizine, loratadine, desloratadine), anticonvulsants (phenytoin, carbamazepine), antiemetics (metoclopramide, benzquinamide, thiethylperazine, prochlorperazine, droperidol), antidepressants (amitriptyline, doxepin, amoxapine, nortriptyline, fluoxetine, clomipramine, trazodone, protriptyline, desipramine, imipramine, paroxetine, citalopram), and other psychotropic medications (bupropion, buspirone, alprazolam) (Gill et al. 1997; Aronson 2006).

Non-medication-related factors, which are associated with increased risk of dystonic symptoms, include temporal lobe seizures, viral infections, bacterial infections, trauma, space-occupying lesions in the peripheral nervous system, lesions in the central nervous system, and endocrinopathies (hypoparathyroidism) (APA 2013).

6.3.3. Epidemiology of Dystonia

Epidemiological data on dystonia is difficult to establish (Steeves et al. 2012). Methodologies across studies vary for case definition, ascertainment, as well as the broad range of causes and ages affected. A meta-analysis of studies conducted within largely adult populations estimated a prevalence of primary dystonia of 16.43 per 100,000 (95% confidence interval [CI] 12.09-22.32) (Steeves et al. 2012). Focusing on results for those <29 years of age, the prevalence of various types of dystonia ranged from 0-7.6 per 100,000 (Steeves et al. 2012). No publications were identified estimating the incidence of dystonia in children and adolescents.

7. Research Question and Objectives

The primary objective of this study was to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6-17 years of age, relative to a propensity score-matched cohort of stimulant treated patients.

8. Amendments and Updates

Following Lilly approval of the final study report for B4Z-MC-B031 (version 1.0, approved 23 June 2016), an internal validation project identified inadvertent deviations in the analytic code from the pre-specified statistical methods. Corrections were made to the analytic coding to accurately reflect what was specified in the study protocol. The current final study report (version 2.0) reflects edits to the results (Section 10) and discussion (Section 11) with these corrections made.

9. Research Methods

9.1. Study Design

The study was a retrospective cohort study using secondary data from the THAM database.

To address the primary objective, 2 cohorts were generated:

1) **Atomoxetine-treated cohort:** 6- to 17-year-old patients initiating atomoxetine use.
2) **Stimulant-treated cohort:** 6- to 17-year-old patients initiating a stimulant medication.

The null hypothesis was that there is no increased risk of dystonia among paediatric and adolescent users of atomoxetine, relative to a propensity score-matched population of stimulant users. This null hypothesis was formally tested using Cox proportional hazards regression.

Children are increasingly being treated simultaneously with ADHD and psychotropic medications (Safer et al. 2003). A study conducted between 2002 and 2008 estimated that among 3- to 18-year-old patients prescribed ADHD medication, 14.8% were concomitantly using an antidepressant and 12.3% were concomitantly using an antipsychotic (Barner et al. 2011). Many psychotropic medications carry a known risk for dystonia (as described in Section 6.3.2). Therefore, it is important to ensure a similar distribution of common comorbidities and concomitant medication use between the atomoxetine and comparator cohort. Selecting a comparator, which is using a medication to treat the same indication as atomoxetine, will reduce bias due to these confounding factors. Furthermore, propensity score matching will be used to achieve balance of numerous characteristics across groups, including demographics, medical diagnoses, concomitant medications, and healthcare utilisation.

Sensitivity analysis (See Sections 9.8.2 and 10.5) was conducted to assess whether, after propensity score matching, there was residual confounding by concomitant medication use.

9.2. Setting

9.2.1. Study Population

The source population consisted of children and adolescents (6 to 17 years of age) with at least 6 months (180 days) of continuous enrolment in the health plan prior to index date. For the purpose of this study, continuous enrolment was defined as no enrolment gap greater than 31 consecutive days during the baseline period. This ensured at least 6 months of data proceeding cohort entry to characterise baseline variables for study subjects. Two cohorts were created from this source population (described below) for primary analysis. Baseline patient characteristics were compared across the exposed cohort of interest and comparator cohort prior to, and after, propensity score matching. These included demographics, comorbidities, concomitant medication use, and resource utilisation (i.e., healthcare cost). The detailed list of variables compared is listed in (Annex 3 of B4Z-MC-B031 Study Protocol [see Annex 2 of this document]).

Inclusion criteria:

- 6 to 17 years of age.
- Continuous enrolment in the health plan for a minimum of 6 months prior to index date. Continuous enrolment will be defined as no enrolment gap exceeding 31 consecutive days, at any given time, in the course of the study.
- Treatment with either atomoxetine or stimulant.

Exclusion criteria:

- Diagnosis of dystonia (as defined in Table 9.1) during the baseline period prior to index.

9.2.2. Atomoxetine-Treated Cohort

All patients with at least 1 prescription of atomoxetine were identified. The date of the first atomoxetine prescription served as the index date, and the 6 months prior provided baseline data (Figure 9.1). No use of other ADHD medications was allowed during the 6 month baseline period. A diagnosis of ADHD was not required.

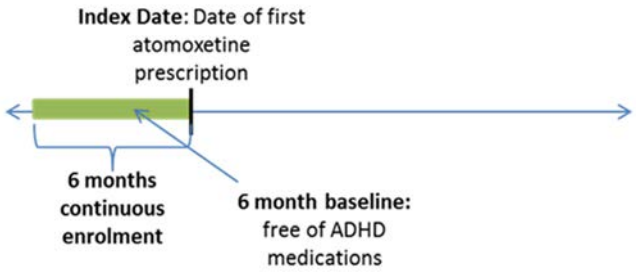


Figure 9.1. Depiction of atomoxetine cohort identification, including baseline period and index date.

9.2.3. Stimulant-Treated Comparator Cohort

A comparator cohort of children and adolescents receiving a stimulant medication was also identified from the source population. Stimulants include amphetamines (N06BA01, N06BA02, N06BA03, N06BA12) or methylphenidates (N06BA04, N06BA11). The date of first stimulant prescription served as the index date, and the 6 months immediately prior to the index date provided baseline data (Figure 9.2). From this pool of stimulant initiators, the comparator cohort was generated by propensity score matching to the atomoxetine users. The propensity score was based on variables specified *a priori* as predictors of atomoxetine use and/or dystonia. To better capture unknown, measured confounders, and increase comparability between the atomoxetine and stimulant cohorts, comorbid conditions present in at least 100 atomoxetine users which demonstrate different distributions across the atomoxetine and stimulant cohorts were additionally considered for inclusion in the propensity score. The goal of the propensity score-matching process is to identify a cohort of individuals who were using stimulants, but had a similar distribution in the propensity to be prescribed atomoxetine.

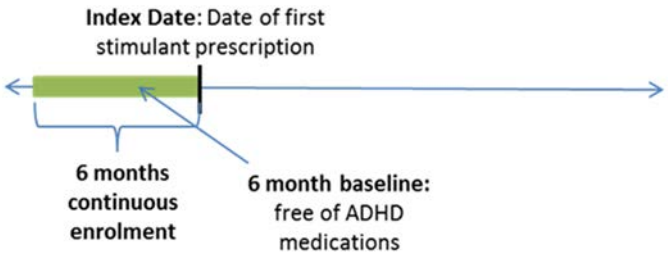


Figure 9.2. **Depiction of stimulant cohort identification, including baseline period and index date.**

9.2.4. Study Period

Medication and outcome data were available from Truven beginning 01 January 2006 through 31 December 2014. Given the 6-month baseline period, this study included atomoxetine prescriptions which were initiated on or after 01 July 2006. The index date for each cohort was described above. Follow-up time was defined using an as-treated design. This means that exposed individuals only contributed person-time during an active study prescription for the drug which they were originally identified.

After index, patients were followed until the first of the following censoring events:

- The end of the prescription period, defined as last day's supply plus 30 day grace period
- First event of dystonia (as defined by ICD-9-CM codes listed in Table 9.1)
- Switch to other ADHD drug (atomoxetine user switching to stimulant or alpha-2-adrenergic agonist, stimulant user switching to atomoxetine or alpha-2-adrenergic agonist; see Table 9.2 for listing of ADHD medications)
- Gap in health plan enrolment greater than 31 days
- End of study period, 31 December 2014

9.3. Variables

The **primary endpoint** was incident dystonia, as defined by the ICD-9-CM codes in Table 9.1. Codes specific to dyskinesia or genetic/familial forms of dystonia were excluded. The primary analysis considered diagnosis for any of the outlined dystonia codes. Only the first event of dystonia occurring after the initiation of the drug, and within the follow-up period, was counted.

Table 9.1. **ICD-9-CM Codes Used to Define Dystonia in Present Study**

ICD-9-CM Code	Code Description
333.7	Acquired torsion dystonia
333.72	Acute dystonia due to drugs
333.79	Other acquired torsion dystonia (idiopathic, non-familial dystonia)
333.81	Blepharospasm
333.83	Spasmodic torticollis
333.84	Organic writer's cramp (hand dystonia)
333.89	Other fragments of torsion dystonia

Abbreviations: ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

The **primary exposure of interest** was atomoxetine (N06BA09). Dose information for atomoxetine was also queried. Attention-deficit/hyperactivity disorder medications are outlined in Table 9.2. Use of the ADHD medication was not allowed in the 6-month baseline period prior to index date. Modafinil is not currently approved in the US for the treatment of ADHD, but is sometimes used off-label for this indication.

Table 9.2. ATC Codes for ADHD Medications

ATC Code	Name	Drug Class
N06BA09	atomoxetine	Norepinephrine reuptake inhibitor
N06BA01	amphetamine (includes mixed salt amphetamine)	Stimulant
N06BA02	dexamphetamine	Stimulant
N06BA03	dextromethamphetamine	Stimulant
N06BA04	methylphenidate	Stimulant
N06BA11	dexmethylphenidate	Stimulant
N06BA12	lisdexamfetamine	Stimulant
N06BA07	modafinil	Stimulant
C02AC01	clonidine	Alpha-2-adrenergic agonist
C02AC02	guanfacine	Alpha-2-adrenergic agonist

Abbreviations: ATC = Anatomical Therapeutic Chemical classification.

Baseline characteristics assessed are outlined below in Annex 3 of the B4Z-MC-B031 Study Protocol (see Annex 2 of this document) and include demographics, measures of resource utilisation, comorbidities, and concomitant medication use. Of particular interest for inclusion were baseline characteristics which are also risk factors for dystonia (Section 6.3.2), including: use of drugs with known adverse reaction of dystonia (antipsychotics, antihistamines, anticonvulsants, antiemetics, antidepressants, psychotropics), seizure disorders, infections, trauma, and disorders of the nervous system.

9.4. Data Sources

The present study used the US-based electronic claim database, Truven Health Analytics MarketScan®. MarketScan contains individual-level de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Since its creation in the early 1990s, the MarketScan database has grown into one of the largest collections of de-identified patient-level data in the nation. This database reflects real world treatment patterns and costs by tracking millions of patients as they travel through the healthcare system, offering detailed information about numerous aspects of care. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilisation and cost record connections at the patient level. Used primarily for research, this database is fully Health Insurance Portability and Accountability Act (HIPAA) compliant. Research using MarketScan data has been widely published in peer-reviewed journals. In the most recent full-data year, the MarketScan claim databases contains data on 50 million lives. Its sample size is large enough to allow creation of nationally representative data sample of Americans with employer provided health insurance or Medicaid.

9.5. Bias

As the cohorts were not formed by randomisation, but were observed based on usual care, comparisons between cohorts may have been confounded by selection bias. The new-user design is a reasonable strategy to reduce bias when healthcare databases are used (Johnson et al. 2013). To adjust for measured confounders, comparisons between cohorts were performed using propensity score matching. The aim of propensity score matching was to create groups where treatment is unrelated to any baseline characteristics, similar to the balance achieved through randomisation in clinical trials (Rosenbaum and Rubin 1983).

9.6. Study Size

A feasibility assessment within MarketScan was conducted to determine the anticipated sample size (see Annex 7 of the B4Z-MC-B031 Study Protocol [in Annex 2 of this document] for details).

Between 01 January 2006 and 31 December 2014, there were 369,690 unique users of atomoxetine identified in MarketScan, 280,985 of which did not use any other ADHD medications in the 6 months prior to first atomoxetine prescription (index date). Assuming we were able to find a 1:1 match for 60% of the atomoxetine cohort, it was estimated there would be 168,591 patients in each the atomoxetine cohort and comparator cohort. The expected background incidence rate of dystonia was not known because no epidemiological studies of dystonia incidence among children and adolescents were identified. Power was estimated using the software nQuery + nTerim 3.0 (Statistical Solutions 2014) for a log-rank test of survival in two groups for fixed time, constant HR. Power was estimated for 3 different baseline incidence rates (ranging from 5 to 15 per 100,000).

The power to detect an HR ranging from 1.5 to 3 under the 3 baseline dystonia rates are depicted in Table 9.3.

Table 9.3. Power to Detect Various HR under 3 Scenarios for Incidence Rate of Dystonia in Reference Group

HR	5 per 100 000	10 per 100,000	15 per 100,000
3	82%	98%	99%
2.5	64%	90%	98%
2.0	38%	65%	82%
1.5	14%	25%	35%
Assumptions: two-sided, α=0.05, 168,591 patients in each group followed for average of 1 year.			

Abbreviation: HR = hazard ratio.

9.7. Data Transformation

Data management and statistical analysis were done using SAS® Proprietary Software, version 9.2. Datasets and analytic programs were kept on a secure server and archived per Lilly record retention procedures.

9.8. Statistical Methods

The primary analysis was a comparison of the risk of dystonia in patients initiating atomoxetine relative to a propensity score-matched cohort of individuals initiating a stimulant. This comparison was carried out using Cox proportional hazards regression. Overview of the analysis strategy is outlined below, followed by the detailed methods for each analysis step:

- Estimated the propensity for atomoxetine initiation for each patient in the atomoxetine cohort and the stimulant comparator cohort
- Used Greedy 1:1 matching algorithm to form propensity score-matched samples
- Assessed balance between cohorts across all baseline covariates using standardised differences
- Revised and finalised propensity score, as needed
- Estimated the hazard ratio (HR) (with 95% CI) of dystonia associated with atomoxetine, compared to simulant users, using a Cox proportional hazards regression model
- Performed sensitivity analyses
- Assessed generalisability by summarising population characteristics and outcomes for patients included and excluded by matching process.

9.8.1. Main Statistical Methods

9.8.1.1. Propensity Score Estimation

The propensity score for each patient in the atomoxetine and stimulant cohorts was estimated using logistic regression, with atomoxetine use as the dependent (i.e., outcome) variable. Independent (i.e., predictor) variables for the propensity score model include those listed in Annex 3 of the B4Z-MC-B031 Study Protocol (see Annex 2 of this document), drawn from the 6-month baseline period. These measures were selected based on literature and expert opinion as potentially moderately related to both treatment status and dystonia, or strongly related to either.

To consider potential confounders not specified *a priori*, we tabulated the most frequently occurring diagnoses, procedures, or drugs dispensed in the baseline period among the 2 cohorts. Any characteristics present in at least 100 atomoxetine users and which differed substantially between atomoxetine and stimulant cohort (based on univariate statistical significance, α=0.05) were included in the propensity score model. While the potential exists for unmeasured confounders, risk factors for dystonia are largely medication related, and, therefore, captured in the MarketScan database. Furthermore, because atomoxetine only has 1 approved indication (ADHD), we are confident the diagnoses included in the propensity score (which include ADHD, as well as common comorbid psychiatric and development disorders) are appropriately representing possible confounders.

9.8.1.2. Propensity Score Matching

A greedy 1:1 matching algorithm (D'Agostino 1998) was used to match each atomoxetine initiator with a stimulant initiator control patient. The algorithm used a ranked-based Mahalanobis distance with a calliper of 0.2 standard deviations of the logit of the propensity score (Austin 2010; Rosenbaum 2011).

9.8.1.3. Evaluation of Quality of Propensity Score Matching

The quality of the propensity score matching for achieving balance of baseline characteristics between groups was assessed prior to initiating outcome analysis. Balance was assessed via 2 measures. The first was t-tests or chi-square tests (as appropriate) to assess differences between the cohorts across all measured baseline covariates before and after matching. Second, the standardised difference, defined as the difference in means between the 2 groups divided by a measure of the standard deviation of the variable, was computed in the matched subsets.

The standardised difference provides a metric for assessing variables with larger residual imbalance after propensity score matching. As a rule of thumb, standardised differences greater than 0.10 indicated imbalance and would require further adjustment in outcome models (Austin and Mamdani 2006). Baseline characteristics of the matched cohorts were presented, in table and graphical form, both pre- and post-matching.

The 1:1 matching was selected to optimise control of selection bias, although it can result in a larger subset of patients excluded from the primary analysis. Baseline characteristics and outcomes of patients excluded from the analysis were summarised relative to the set of patients included in the analysis. This allowed for more appropriate interpretation regarding the generalisability of results. See Annex 6 of the B4Z-MC-B031 Study Protocol (in Annex 2 of this document) for a table shell which outlines how the differences between the cohorts were presented, pre-match, after-match, and how those who do not find a match are, therefore, excluded.

9.8.1.4. Outcomes Analysis

The primary comparison of dystonia incidence between patients treated with atomoxetine and patients treated with a stimulant was assessed by a propensity score-matching analysis and Cox proportional hazard regression. Only patients matched on propensity score were included in the analysis. The index date for start of follow-up was the date of first study prescription. The end of follow-up was the end of the at-risk period (as defined in Section 9.2.4) or last date of enrolment, whichever came first. Variables in the regression model included treatment (atomoxetine or stimulant), gender, age at index, index year, and any propensity-score variable which did not reach balance between the 2 arms after matching.

The incidence rate of dystonia was reported as the number of events per 100,000 person years for each cohort. The HR was estimated, comparing incidence in atomoxetine users compared to stimulant users. A 2-sided 95% CI was computed for the HR and a p-value <0.05 was considered as evidence for rejecting the null hypothesis of no difference in dystonia incidence. Diagnostics to assess the proportionality assumption for the Cox regression were conducted.

9.8.2. Sensitivity Analysis

There were 2 sensitivity analyses pre-specified in the protocol. First, a sensitivity analysis was performed to assess the robustness of the pre-specified analysis to potential confounding by concomitant medication use. The primary analysis was subset to include only those with no use of any medications, at any time (baseline or follow-up), with known risk of dystonia (medications as listed in Section 6.3.2).

There was a second, optional analysis to assess sensitivity of the primary analysis to the choice of comparator group. It was to be conducted only if the primary analysis identified a significantly elevated risk of dystonia with atomoxetine use compared to stimulants. In this optional sensitivity analysis, the incidence of dystonia within the atomoxetine cohort from the primary analysis would be compared to the incidence of dystonia in an untreated ADHD population, still using the propensity score matching.

9.8.3. Other Analyses

To further assist in understanding and interpreting the primary analysis, the following summary statistics were produced for patients identified with dystonia from the atomoxetine cohort: dose (mg) of atomoxetine at time of dystonia, time (in days) between initiation of atomoxetine and dystonia, time (in days) between increasing dose of atomoxetine and dystonia, number (percentage) of cases with dystonia occurring within 14 days of dose increase, time (in days) between initiation of any other medication known to cause dystonia (as listed in Section 6.3.2) and onset of dystonia, and number (percentage) of cases with dystonia occurring within 14 days of initiating one of these other medications. Drug-induced dystonia, as seen in antipsychotic and other dopamine blocking agent-induced dystonia, typically occurs within one week of drug initiation (CIOMS 1999; Ayd 2000). However, 14 days was chosen as a classifier in the present study to be conservative and acknowledge the limitation that claims data do not necessarily reflect the day medication was taken.

9.8.4. Amendments to the Statistical Analysis Plan

None.

9.9. Quality Control

The study used an existing database, which was used primarily for research and is fully HIPAA compliant. To ensure their functionality and accuracy, data management and statistical analysis programs that were developed for this study were validated by internal personnel who were familiar with the study, but were not directly involved in the creation/development of these programs.

- Access to the data was limited to Lilly Research project team members who needed to work with those data for the purposes outlined in this report.
- The study's principal investigator reviewed data for accuracy and completeness.
- Results included in this report's text, tables, and/or figures were verified against source documentation by internal personnel who were familiar with the study, but were not directly involved in the development of the report.
- The electronic data were stored at Lilly on a networked computer that is password protected and is protected from access outside of the network by a firewall.

10. Results

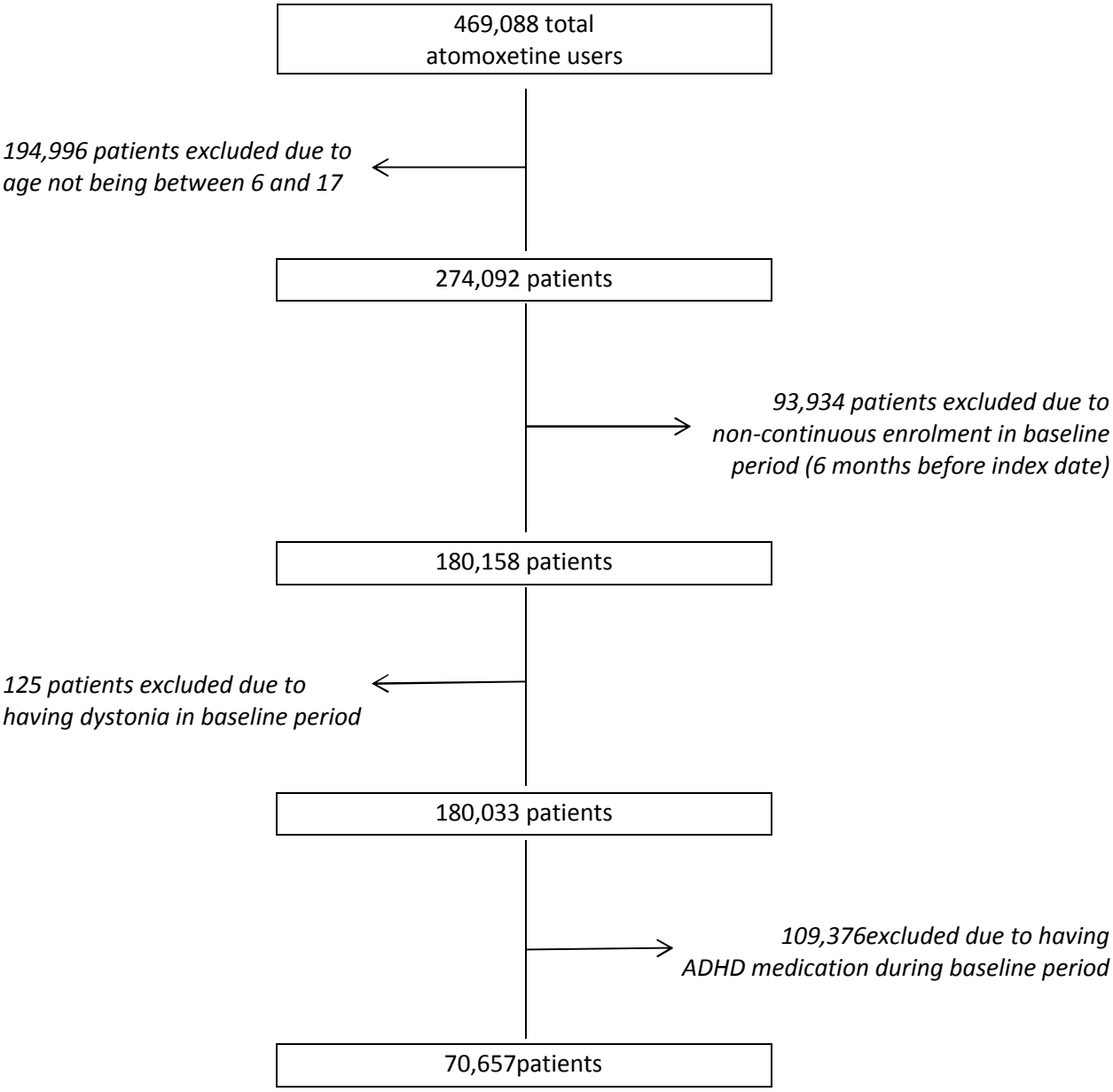
10.1. Participants

10.1.1. Patient Count for Atomoxetine-Treated Patient Population

Figure 10.1 presents a flow diagram of the atomoxetine-treated patients screened for inclusion, the number of patients excluded for each exclusion criterion, and the total number of patients eligible for inclusion. Of the 469,088 atomoxetine users identified, patients were excluded via the following sequence of operations:

- 194,996 patients were excluded due to age not being between 6 and 17 years
- 93,934 patients were excluded due to non-continuous enrolment in baseline period (6 months before index date)
- 125 patients were excluded due to having dystonia in baseline period
- 109,376patients were excluded due to having ADHD medication during baseline period

After application of the inclusion/exclusion criteria, 70,657atomoxetine-treated patients were eligible for propensity score estimation. After propensity score matching, the number of atomoxetine-treated patients was 70,655, which represented 99.99% of the atomoxetine patients eligible for propensity score estimation.



Abbreviations: ADHD = attention-deficit/hyperactivity disorder.

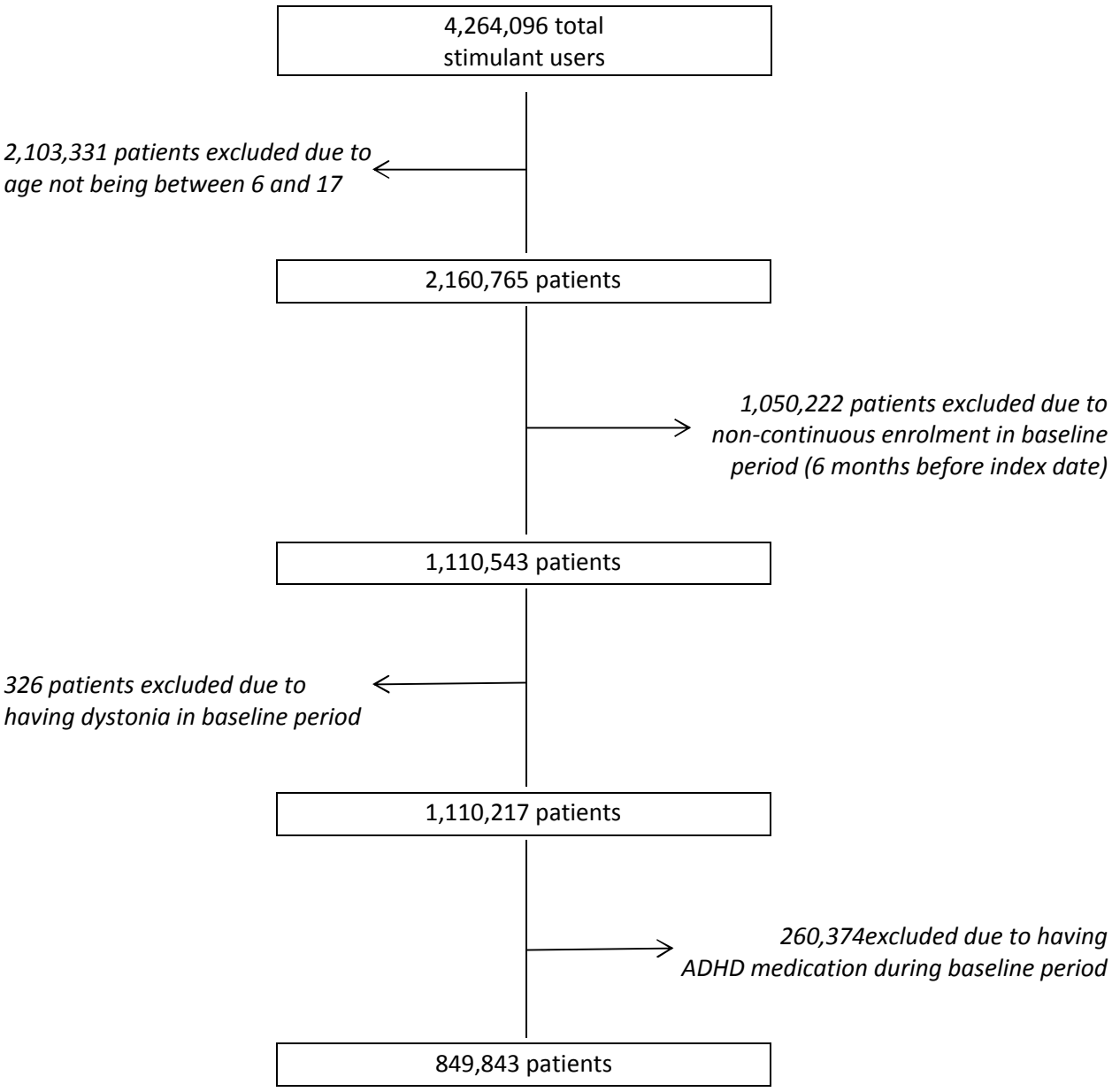
Figure 10.1. Selection of atomoxetine-treated patients eligible for inclusion.

10.1.2. Patient Count for Stimulant-Treated Patient Population

Figure 10.2 presents a flow diagram of the stimulant-treated patients screened for inclusion, the number of patients excluded for each exclusion criteria, and the total number of patients eligible for inclusion. Of the 4,264,096 stimulant users identified, patients were excluded via the following sequence of operations:

- 2,103,331 patients were excluded due to age not being between 6 and 17 years
- 1,050,222 patients were excluded due to non-continuous enrolment in baseline period (6 months before index date)
- 326 patients were excluded due to having dystonia in baseline period
- 260,374 patients were excluded due to having ADHD medication during baseline period

After application of the inclusion/exclusion criteria, 849,843 stimulant-treated patients were eligible for propensity score estimation. After propensity score matching, the number of stimulant-treated patients was 70,655, which represented 8.3% of the original, eligible stimulant population.



Abbreviations: ADHD = attention-deficit/hyperactivity disorder.

Figure 10.2. Selection of stimulant-treated patients eligible for inclusion.

10.2. Descriptive Data

10.2.1. Baseline Characteristics for Prematched and Propensity Score-Matched Patients

Baseline characteristics for the atomoxetine- and stimulant-treated patient cohorts (prematched and 1:1 propensity score-matched populations) are presented in Table 10.1. This table summarises patient characteristics such as demographics, diagnoses, concomitant medications, and healthcare utilisation.

Before propensity score matching, almost all included baseline characteristics were statistically different between the atomoxetine-treated and stimulant-treated cohorts (Table 10.1). The notable differences included a higher percentage of atomoxetine-treated patients being diagnosed with ADHD (49.8% vs. 43.4%), anxiety disorder (10.9% vs. 6.5%), and mood disorder (13.1% vs. 8.5%); and a higher percentage of atomoxetine-treated patients using concomitant medications with a risk of dystonia such as anticonvulsants (7.4% vs. 4.9%), antidepressants (13.0% vs. 7.8%), and antipsychotics (7.2% vs. 3.6%).

After propensity score matching, all baseline characteristics were well-balanced between the cohorts. As depicted in Figure 10.3, all of the standardised differences for the paired comparisons of baseline characteristics observed after propensity score matching approached the value "0", and none were above 0.10, indicating that the baseline characteristics of both the atomoxetine- and stimulant-treated cohorts were well-balanced in the propensity score-matched population. Therefore, propensity score matching successfully achieved balance between the cohorts for all baseline characteristics examined, and no additional variables were required for adjustment in the regression model.

After propensity score matching, the mean age of both the atomoxetine-treated and stimulant-treated cohorts was 11.6 years; additionally, gender (65.6% vs. 65.4% males), antidepressant use (13.0% vs. 12.5%), antipsychotic use (7.2% vs. 6.7%), and the median [range] number of psychotropic drugs used (1 [0-19] vs. 1 [0-15]) in the atomoxetine-treated and stimulant-treated cohorts were all consistent with one another.

Table 10.1. Baseline Characteristics Between Atomoxetine-Treated and Stimulant-Treated Groups for Before Propensity Match and Propensity Score-Matched Patients

			Before Matching (Original Cohort)						After Matching (Matched Cohort)					
Variable List			Atomoxetine		Stimulant				Atomoxetine		Stimulant			
Category	Variable	Type	N	Mean (SD) or %	N	Mean (SD) or %	p-value	Standard Difference	N	Mean (SD) or %	N	Mean (SD) or %	p-value	Standard Difference
Demographics	Age at Index	Mean (SD)	70,657	11.58 (3.38)	849,843	10.61 (3.48)	<0.0001	-0.283	70,655	11.58 (3.38)	70,655	11.64 (3.52)	0.0021	0.016
		Median [Range]	70,657	12.00 [6.00 - 17.00]	849,843	10.00 [6.00 - 17.00]			70,655	12.00 [6.00 - 17.00]	70,655	12.00 [6.00 - 17.00]		
	Gender	Female	24,309	34.4%	291,333	34.3%	0.5066	0.003	24,308	34.40%	24,473	34.6%	0.3559	-0.005
		Male	46,348	65.6%	558,510	65.7%	0.5066	-0.003	46,347	65.60%	46,182	65.4%	0.3559	0.005
	Region	Midwest	13,869	19.6%	133,912	15.8%	<0.0001	0.102	13,869	19.6%	13,982	19.8%	<.0001	-0.004
		Northeast	5,915	8.4%	68,465	8.1%	<0.0001	0.011	5,914	8.4%	6,201	8.8%	<.0001	-0.015
		South	21,194	30.0%	239,988	28.2%	<0.0001	0.039	21,193	30.0%	21,210	30.0%	<.0001	-0.001
		West	7,259	10.3%	70,378	8.3%	<0.0001	0.069	7,259	10.3%	7,535	10.7%	<.0001	-0.013
		Missing	21,501	30.4%	327,023	38.5%	<.0001	-0.17	21501	30.43%	20721	29.33%	<.0001	0.024
		Unknown	919	1.3%	10,077	1.2%	<.0001	0.01	919	1.30%	1006	1.42%	<.0001	-0.011
	Index Year	2006	6,176	8.7%	49,581	5.8%	<0.0001	0.112	6,175	8.7%	6,206	8.8%	0.05	-0.002
		2007	8,527	12.1%	65,307	7.7%	<0.0001	0.147	8,527	12.1%	8,475	12.0%	0.05	0.002
		2008	9,128	12.9%	80,378	9.5%	<0.0001	0.11	9,127	12.9%	9,219	13.1%	0.05	-0.004
		2009	9,746	13.8%	106,372	12.5%	<0.0001	0.038	9,746	13.8%	10,045	14.2%	0.05	-0.012
		2010	8,529	12.1%	108,833	12.8%	<0.0001	-0.022	8,529	12.1%	8,616	12.2%	0.05	-0.004
		2011	8,155	11.5%	114,965	13.5%	<0.0001	-0.06	8,155	11.5%	8,203	11.6%	0.05	-0.002
		2012	7,827	11.1%	117,830	13.9%	<0.0001	-0.084	7,827	11.1%	7,799	11.0%	0.05	0.001
		2013	6,078	8.6%	99,192	11.7%	<0.0001	-0.102	6,078	8.6%	5,898	8.4%	0.05	0.009
		2014	6,491	9.2%	107,385	12.6%	<0.0001	-0.111	6,491	9.2%	6,194	8.8%	0.05	0.015
Disorders[a]	ADHD	Yes	35,187	49.8%	368,962	43.4%	<0.0001	-0.128	35,186	49.8%	35,399	50.1%	0.2571	0.006
	Alcohol Dependence and	Yes	617	0.9%	2,390	0.3%	<0.0001	-0.078	616	0.9%	482	0.7%	<.0001	-0.022

			Before Matching (Original Cohort)						After Matching (Matched Cohort)					
Variable List			Atomoxetine		Stimulant				Atomoxetine		Stimulant			
	Abuse													
	Anxiety	Yes	7,678	10.9%	55,357	6.5%	<0.0001	-0.155	7,676	10.9%	7,462	10.6%	0.0657	-0.01
	Autistic	Yes	1,099	1.6%	9,246	1.1%	<0.0001	-0.041	1,099	1.6%	1,137	1.6%	0.4179	0.004
	Conduct	Yes	6,806	9.6%	82,170	9.7%	0.7531	0.001	6,805	9.6%	6,620	9.4%	0.0933	-0.009
	Congenital	Yes	735	1.0%	2,255	0.3%	<0.0001	-0.096	734	1.0%	578	0.8%	<.0001	-0.023
	Development Delays	Yes	1,914	2.7%	18,871	2.2%	<0.0001	-0.031	1,914	2.7%	1,958	2.8%	0.4734	0.004
	Infections	Yes	9,626	13.6%	128,722	15.2%	<0.0001	0.043	9,626	13.6%	9,486	13.4%	0.2762	-0.006
	Mood	Yes	9,256	13.1%	72,094	8.5%	<0.0001	-0.149	9,254	13.1%	8,983	12.7%	0.0315	-0.011
	Nervous System	Yes	8	0.0%	131	0.0%	0.3950	0.004	8	0.0%	5	0.0%	0.4054	-0.004
	Epilepsy and Seizure	Yes	878	1.2%	7,082	0.8%	<0.0001	-0.04	878	1.2%	860	1.2%	0.664	-0.002
	Substance Abuse	Yes	1,230	1.7%	5,162	0.6%	<0.0001	-0.105	1,229	1.7%	1,017	1.4%	<.0001	-0.024
	Tobacco Use	Yes	415	0.6%	2,135	0.3%	<0.0001	-0.052	415	0.6%	350	0.5%	0.0184	-0.013
	Tics and Tourette's	Yes	735	1.0%	2,255	0.3%	<0.0001	-0.096	734	1.0%	578	0.8%	<.0001	-0.023
	Trauma	Yes	357	0.5%	4,142	0.5%	0.5127	-0.003	357	0.5%	339	0.5%	0.494	-0.004
Continuous Counts	ADHD	Mean (SD)	70,657	0.55 (0.60)	849,843	0.47 (0.58)	<0.0001	-0.135	70,655	0.55 (0.60)	70,655	0.56 (0.60)	0.4845	0.004
		Median [Range]	70,657	0.00 [0.00 - 4.00]	849,843	0.00 [0.00 - 5.00]			70,655	0.00 [0.00 - 4.00]	70,655	1.00 [0.00 - 3.00]		
	Drug Class	Mean (SD)	70,657	0.84 (1.11)	849,843	0.71 (1.02)	<0.0001	-0.115	70,655	0.84 (1.11)	70,655	0.82 (1.12)	0.0088	-0.014
		Median [Range]	70,657	0.00 [0.00 - 9.00]	849,843	0.00 [0.00 - 13.00]			70,655	0.00 [0.00 - 9.00]	70,655	0.00 [0.00 - 11.00]		
	Psychiatric	Mean (SD)	70,657	1.02 (1.21)	849,843	0.80 (1.02)	<0.0001	-0.195	70,655	1.02 (1.21)	70,655	1.01 (1.18)	0.0536	-0.01
		Median [Range]	70,657	1.00 [0.00 - 19.00]	849,843	1.00 [0.00 - 17.00]			70,655	1.00 [0.00 - 19.00]	70,655	1.00 [0.00 - 15.00]		
	Total Costs	Mean (SD)	70,657	$2,155 ($7,636.70)	849,843	$1,548 ($8,382.03)	<0.0001	-0.076	70,655	$2,154 ($7,635.41)	70,655	$1,993 ($8,421.03)	0.0002	-0.02
		Median [Range]	70,657	$607.08 [$-14,675.46 - $590,848.26]	849,843	$467.32 [$-33,826.99 - $2,689,445.03]			70,655	$607.01 [$-14,675.46 - $590,848.26]	70,655	$571.53 [$-6,176.60 - $856,830.87]		

			Before Matching (Original Cohort)						After Matching (Matched Cohort)					
Variable List			Atomoxetine		Stimulant				Atomoxetine		Stimulant			
Drug Types[b]	Antibiotics	Yes	23,125	32.7%	271,023	31.9%	00.0017	-0.018	23,125	32.7%	23,194	32.8%	0.6958	0.002
	Anticonvulsants	Yes	5,196	7.4%	41,239	4.9%	<0.0001	-0.105	5,196	7.4%	5,007	7.1%	0.0521	-0.01
	Antidepressants	Yes	9,165	13.0%	66,406	7.8%	<0.0001	-0.17	9,163	13.0%	8,844	12.5%	0.0109	-0.014
	Antiemetics	Yes	1,030	1.5%	15,155	1.8%	<0.0001	0.026	1,030	1.5%	940	1.3%	0.0412	-0.011
	Antihistamines	Yes	6,346	9.0%	79,080	9.3%	0.0044	0.011	6,345	9.0%	6,188	8.8%	0.1418	-0.008
	Antipsychotics	Yes	5,087	7.2%	30,260	3.6%	<0.0001	-0.162	5,086	7.2%	4,708	6.7%	<.0001	-0.021
	Antivirals	Yes	1,375	2.0%	16,806	2.0%	0.5629	0.002	1,375	2.0%	1,400	2.0%	0.6317	0.003

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation.

[a] For list of ICD-9-CM diagnostic codes for prespecified comorbidities, see Annex 4 of the B4Z-MC-B031 Study Protocol (see Annex 2 of this document).

[b] For list of concomitant medications, see Annex 5 of the B4Z-MC-B031 Study Protocol (see Annex 2 of this document).

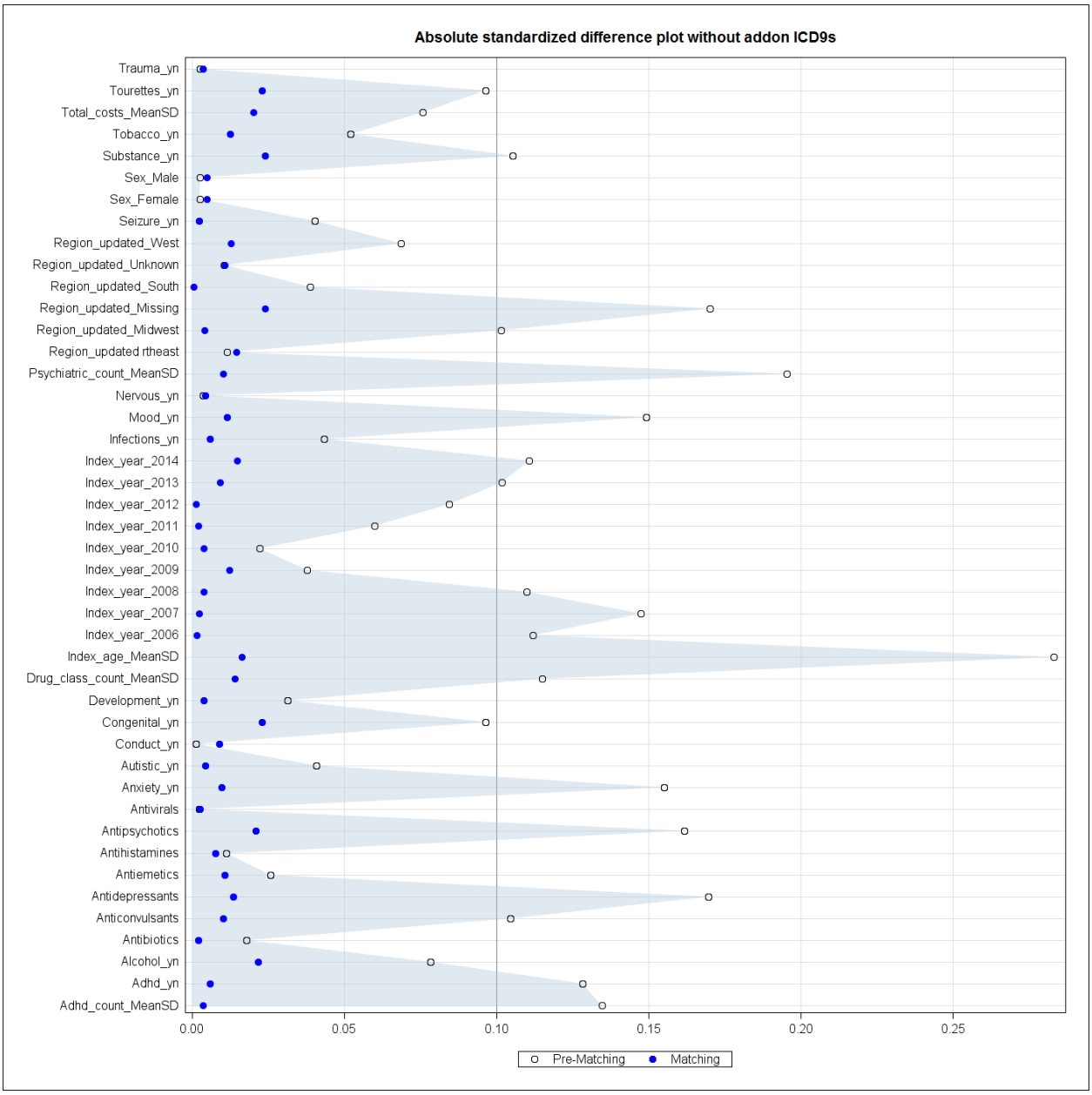


Figure 10.3. Balance of covariates before and after propensity score matching.

Figure 10.4 displays the distribution of propensity score by ADHD medication group. As expected, the atomoxetine users had a slightly higher distribution of propensity scores. However, the overlap between cohorts was strong, with all but 2 of the atomoxetine cohort being matched.

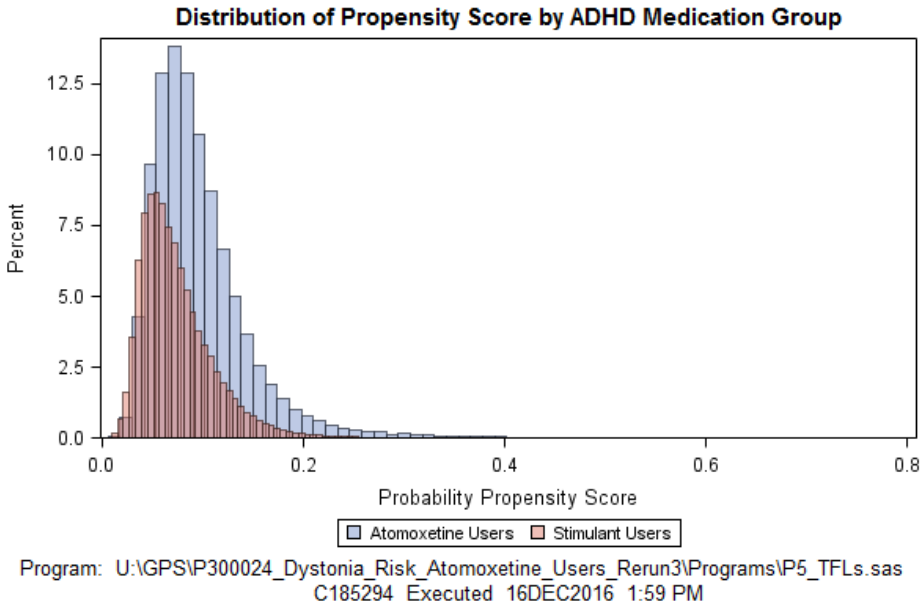


Figure 10.4. Distribution of propensity scores by ADHD medication group.

The distribution of the length of follow-up observed in the stimulant-treated cohort (top panel) and atomoxetine-treated cohort (bottom panel) is presented in Figure 10.5. There was slightly longer follow-up among the stimulant cohort, the mean [median] length of follow-up observed in the stimulant- and atomoxetine-treated cohorts were (0.51 [0.28] vs. 0.39 [0.22] years, respectively). This is evident in the total person-years of follow-up (Table 10.2), where the atomoxetine cohort had a total of 27,322 person-years of follow-up and the stimulant cohort had a total of 35,935 person-years.

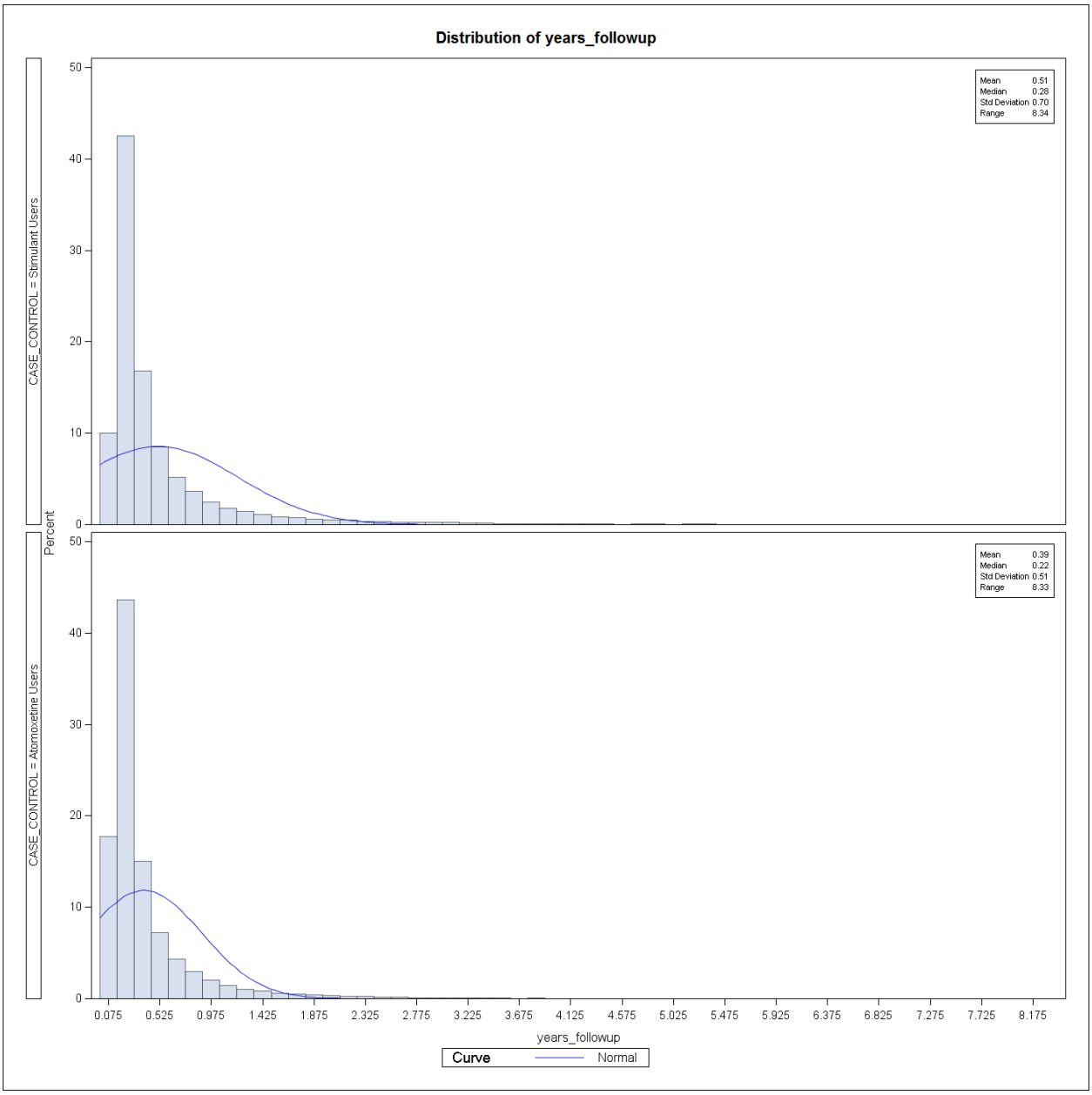


Figure 10.5. Distribution of the length of follow-up observed in each cohort.

10.3. Main Results

Table 10.2 presents incidence rates and HR of dystonia across propensity score-matched cohorts. The crude incidence rate of dystonia for the atomoxetine-treated cohort was 54.9per 100,000 person-years (95% CI: 27.1 to 82.7) compared to a crude incidence rate of 77.9 per 100,000 person-years (95% CI: 49.1 to 106.8) for the stimulant-treated cohort. After review and confirmation of the proportional hazard assumptions (data on file), and adjusting for sex, age, and index year, the adjusted HR for dystonia with atomoxetine use relative to stimulant use was found to be 0.68 (95% CI: 0.36 to 1.28; p=0.23).

Table 10.2. Incidence and Hazard Ratio of Dystonia Across Propensity Score-Matched Cohorts

				Crude Incidence Rates per 100,000 person-years		Hazard Ratio[a]		
Population	Number of Subjects	Number of # Dystonia Events[b]	Person-years	IR	95% CI	Adjusted HR	95% CI	p value
Atomoxetine initiator	70,655	15	27,322	54.9	[27.1, 82.7]	0.68	[0.36, 1.28]	0.23
Stimulant initiator	70,655	28	35,935	77.9	[49.1, 106.8]		1.0 (Reference)	---

Abbreviations: CI = confidence interval; HR = hazard ratio; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; IR = incidence rate; y/n = yes/no.

[a] Model covariates include atomoxetine (y/n), sex, age, and index year.

[b] # Dystonia events was defined by the following ICD-9-CM codes: 333.7, 333.72, 333.79, 333.81, 333.83, 333.84, and 333.89.

10.4. Clinical Summary of Dystonia Cases in Atomoxetine Cohort

The frequency of dystonia codes in the atomoxetine users (N=15) are displayed in Table 10.3. The percentage of patients with acute dystonia coded as due to drugs (ICD-9-CM 333.72) was 60%.

Table 10.3. Frequency of Dystonia Codes in Atomoxetine Users (N=15)

ICD-9-CM Code Description	N	(%)
Acute dystonia due to drugs (333.72)	9	60%
Other acquired torsion dystonia (idiopathic, non-familial dystonia) (333.79)	1	6.7%
Blepharospasm (333.81)	4	26.7%
Spasmodic torticollis (333.83)	1	6.7%
Other fragments of torsion dystonia (333.89)	0	0%

Abbreviations: ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification.

Table 10.4 presents a clinical summary of atomoxetine dose at time of dystonia and time to onset information for dystonia cases occurring within the atomoxetine users (N=15). The median dose

of atomoxetine at the time dystonia occurred in this cohort was 40 mg. The median time to onset of dystonia from atomoxetine initiation was just over three months (94.0 days). Of note, the earliest case of dystonia from time of atomoxetine initiation was 2 days. This patient also initiated lamotrigine (25mg) on the same day as the atomoxetine initiation; dystonia is a known side effect of lamotrigine treatment. Of the 15 cases, 6 had registered an increase in their atomoxetine dose during their follow-up time. However, none of those cases had the dystonia event occur within 14 days of a dose increase.

Table 10.4. Summary of Dystonia Cases Occurring within Selected Atomoxetine Users (N=15)

Variables	Sample Size	Mean	Median	Min	Max	SD	N (%)
Atomoxetine dose (mg) at time of dystonia	15	36.3	40.0	18	80	16.7	
Time (days) between atomoxetine initiation and dystonia	15	171.4	94.0	2	1083	268.2	
Did dystonia occur within 14 days of dose change? (yes)	6*	-	-	-	-	-	0 (0.0)
Time (days) between atomoxetine dose change and dystonia	6*	127.2	58.5	20	482	177.0	

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.

* The sample size represents the number of patients, out of the 15 total cases in the atomoxetine cohort, which had a change of their atomoxetine dose during the follow-up period.

10.5. Sensitivity Analysis

Table 10.5 presents incidence rates and HR of dystonia among atomoxetine users compared propensity score-matched cohorts excluding patients taking select medications with a known risk of dystonia (alprazolam, amitriptyline, amoxapine, benzquinamide, bupropion, buspirone, carbamazepine, cetirizine, chlorpromazine, citalopram, clomipramine, clozapine, desipramine, desloratadine, doxepin, droperidol, fluoxetine, haloperidol, imipramine, levodopa, loratadine, loxapine, mesoridazine, metoclopramide, molindone, nortriptyline, olanzapine, paroxetine, perphenazine, phenytoin, pimozide, prochlorperazine, promethazine, protriptyline, quetiapine, risperidone, thiethylperazine, thioridazine, thiothixene, trazodone, trifluoperazine, and ziprasidone). After excluding patients taking at least one of these medications in either the baseline or follow-up periods, the crude incidence rate of dystonia for the atomoxetine-treated cohort was 31.7 per 100,000 person-years (95% CI: 6.3to 57.0) compared to a crude incidence rate of 52.2 per 100,000 person-years (95% CI: 23.8 to 80.5) for the stimulant-treated cohort.

After review and consideration of the proportional hazard assumptions with model covariates including atomoxetine (y/n), sex, age, and index year, the adjusted HR was found to be 0.60 (95% CI: 0.23 to 1.59; p=0.31).

As mentioned in Section 9.8.2 (and in the Protocol), there was a second optional sensitivity analysis to assess sensitivity of results to the choice of comparator. However, this was only to be conducted if the primary analysis identified a significantly elevated risk of dystonia with atomoxetine use compared to stimulants. Consistent with the pre-specified analysis plan, this was not conducted because the primary analysis did not demonstrate a statistically significant increased risk of dystonia with atomoxetine use compared to stimulant use (Table 10.2).

Table 10.5. Incidence and Hazard Ratio of Dystonia Across Propensity Score-Matched Cohorts Excluding Patients Taking Medication with Known Risk of Dystonia

				Crude Incidence Rates per 100,000 person-years		Hazard Ratio[b]		
Population	Number of Subjects	Number of Dystonia# Events[a,c]	Person-years	IR	95% CI	Adjusted HR	95% CI	p value
Atomoxetine initiator	52,842	6	18,943	31.7	[6.3, 57.0]	0.60	[0.23, 1.59]	0.31
Stimulant initiator	53,243	13	24,926	52.2	[23.8, 80.5]		1.0 (Reference)	---

Abbreviations: CI = confidence interval; HR = hazard ratio; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; IR = incidence rate; y/n = yes/no.

[a] Excluded dystonia medications included alprazolam, amitriptyline, amoxapine, benzquinamide, bupropion, buspirone, carbamazepine, cetirizine, chlorpromazine, citalopram, clomipramine, clozapine, desipramine, desloratadine, doxepin, droperidol, fluoxetine, haloperidol, imipramine, levodopa, loratadine, loxapine, mesoridazine, metoclopramide, molindone, nortriptyline, olanzapine, paroxetine, perphenazine, phenytoin, pimozide, prochlorperazine, promethazine, protriptyline, quetiapine, risperidone, thiethylperazine, thioridazine, thiothixene, trazodone, trifluoperazine, and ziprasidone.

[b] Model covariates include atomoxetine (y/n), sex, age, and index year.

[c] Dystonia was defined by the following ICD-9-CM codes: 333.7, 333.72, 333.79, 333.81, 333.83, 333.84, and 333.89.

10.6. Adverse Events/Adverse Reactions

Not applicable.

11. Discussion

11.1. Key Results

11.1.1. Incidence and Hazard Ratio of Dystonia Across Propensity-Matched Cohorts

The crude incidence rate of dystonia for the atomoxetine-treated cohort was 54.9 per 100,000 person-years (95% CI: 27.1 to 82.7) compared to a crude incidence rate of 77.9 per 100,000 person-years (95% CI: 49.1 to 106.8) for the stimulant-treated cohort. After review and consideration of the proportional hazard assumptions with model covariates including atomoxetine (y/n), sex, age, and index year, there was no statistically significant increased risk of dystonia in the atomoxetine cohort, compared to the propensity score-matched stimulant cohort (adjusted HR=0.68; 95% CI: 0.36 to 1.28; p=0.23).

11.1.2. Clinical Summary of Dystonia within the Atomoxetine Cohort

Of the dystonia cases identified in the atomoxetine cohort (n=15), the earliest case of dystonia from time of atomoxetine initiation was 2 days (median time to onset=94 days) and no dystonia cases were within 14 days of a dose increase. The patient with dystonia occurring 2 days after atomoxetine initiation also initiated lamotrigine (25mg) on the same day; dystonia is a known side effect of lamotrigine treatment. Not considering the patient with time to onset of 2 days, the next earliest time to onset of dystonia from atomoxetine initiation was 18 days. This is inconsistent with the expected profile for drug-induced dystonia, where 90% of cases present within 5 days (Ayd 2000). Therefore, while 60% (n=9) of dystonia cases in the atomoxetine cohort were coded as due to drugs (ICD-9-CM 333.72), the time to onset data is not supportive that atomoxetine was the drug responsible. Furthermore, a review of medications and diagnoses recorded during the baseline and follow-up time for the 15 cases demonstrated that all 15 of the patients were either: 1) taking another medication known to cause extrapyramidal symptoms (EPS) and dystonias (e.g., an antipsychotic), 2) taking a medication for which the indication is a risk factor EPS or dystonia (e.g., antibiotics), or 3) had a time-to-onset for dystonia from atomoxetine initiation beyond what is expected for an acute, drug-induced dystonia (e.g., >14 days).

11.1.3. Sensitivity Analysis

After excluding patients taking medications with a known risk of dystonia, the crude incidence rate of dystonia for the atomoxetine-treated cohort was 31.7 per 100,000 person-years (95% CI: 6.3 to 57.0) compared to a crude incidence rate of 52.2 per 100,000 person-years (95% CI: 23.8 to 80.5) for the stimulant-treated cohort. The incidence rate decreased in both cohorts after excluding patients taking medications with a known risk of dystonia, compared to the incidence rates in the primary analysis. However, the conclusion of no statistically significant increased risk of dystonia in patients treated with atomoxetine compared to patients treated with stimulants remained the same (adjusted HR=0.60; 95% CI: 0.2 to 1.6; p=0.31).

11.2. Limitations

While MarketScan claims data are valuable for the efficient and effective examination of disease outcome and treatment patterns, claims data are collected for the purpose of payment and not research. Therefore, there are limitations associated with the use of claims data. These include:

- The presence of a claim for a filled prescription does not specify that the medication was consumed or that it was taken as prescribed.
- Only prescribed medicines are recorded in the database. No information about over-the-counter drug (e.g., aspirin) use is available.
- Lack of clinical details makes it hard to verify the validity of diagnosis codes and to refine statistical analyses. Data on important confounding variables (smoking, alcohol use, body weight, and height) are not available in the claims database.
- Diagnoses, medical procedures, and medicine dispensing will not be captured if no corresponding billing codes were generated. Likewise, the use of the ICD-9-CM codes, current procedural terminology codes, or national drug codes is subject to the incompleteness or inaccuracies of the coding in the database.
- The positive predictive value of dystonia from ICD-9-CM codes, and within the MarketScan population is not known.
- MarketScan claims are based on a large convenience sample. The data come mostly from large employers; medium and small firms are not represented. Because the sample is not random, it may contain biases or fail to generalise well to other populations.
- There is always the possibility of residual confounding, although the application of propensity score matching aims to minimise any confounding factors between the cohorts.

11.3. Interpretation

Very little is known about the relationship, if any, between atomoxetine and dystonia, an event known to be triggered by other drugs commonly used within an ADHD population such as antidepressants and antipsychotics. One manuscript was published in 2015 which identified 31 ICSRs of dystonia from the WHO Global ICSR Database, VigiBase, in association with atomoxetine treatment for children and adolescents up to 17 years of age through 01 September 2014 (Boyd 2015). These were identified based on disproportionality analysis. The possible mechanism for this signal was hypothesised by Boyd (2015) to be through inhibition of dopamine uptake. Dopamine receptor blockade is considered the most accepted mechanism for antipsychotic drug-induced dystonia. Atomoxetine is only a weak inhibitor of dopamine uptake. Results from the currently described large, retrospective cohort study conducted by Lilly, which adjusted for numerous demographics, comorbid diagnoses, and concomitant medication use, and included data through 31 December 2014, did not identify a significantly elevated risk of dystonia among atomoxetine users, compared to stimulant users.

Given the known risk of dystonia from other medications commonly used within the ADHD population, such as antipsychotics and antidepressants, balancing the use of these medications between the atomoxetine and stimulant cohorts was important. The primary analysis was able to

achieve this balance in concomitant medication use between atomoxetine and stimulant cohorts through propensity score matching. To further assess whether there was residual confounding by medication use, the sensitivity analysis was conducted to remove individuals who used a medication with known risk of dystonia. This approach was more strict for controlling for confounding by concomitant medication use compared to the propensity score matching approach of the primary analysis, but also resulted in a sacrifice to sample size and study power. Results from the sensitivity analysis were not different from the primary analysis, and also did not show a significantly increased risk of dystonia with atomoxetine use.

Comparing atomoxetine users to a cohort actively treated for the same indication (stimulant users) is a best practice within epidemiological studies and optimal for controlling for possible confounding by indication (Setoguchi and Gerhard 2013). However, the observed effect size for atomoxetine is then directly dependent on understanding the relationship, if any, between stimulants and dystonia. Similar to atomoxetine, there have been no epidemiological studies investigating stimulants and dystonia. However, there have been case reports of methylphenidate being used to treat facial dystonia (Eftekhari et al. 2015) and reports of a possible drug-drug interaction where dystonia occurs upon discontinuation of methylphenidate when patients were concurrently on an atypical antipsychotic medication (Benjamin and Salek 2005; Keshen and Carandang 2007; McLaren et al. 2010; Guler et al. 2015). If stimulants in some way treat or suppress dystonia, comparing atomoxetine to stimulants may have resulted in an upwardly biased estimate of effect. This was the rationale behind pre-specifying in the protocol an optional sensitivity analysis to the comparator group (See Section 8.7.6 of the B4Z-MC-B031 Study Protocol [in Annex 2 of this document]). In this optional sensitivity analysis, the incidence and risk of dystonia among atomoxetine users was to be compared to a cohort of untreated ADHD patients. Because dystonia risk in the primary analysis was not statistically significantly elevated in atomoxetine patients compared to stimulant users, this sensitivity analysis was not conducted.

The profile of antipsychotic-induced dystonia is well-understood, the reactions are common in young males and typically develop within a few days (approximately 7 days) of starting, or raising the dose of, an antipsychotic medication, or after reducing the dose of a medication used to treat extrapyramidal symptoms (APA 2013). To understand whether the cases of dystonia that occurred while on atomoxetine (n=15) fit a similar picture, the time between atomoxetine initiation, dose increase (when applicable), and the occurrence of dystonia was evaluated. The earliest case of dystonia from time of atomoxetine initiation was 2 days (median time to onset=94 days). However this patient also initiated lamotrigine (25mg) on the same day atomoxetine was initiated. Dystonia is a known side effect of lamotrigine treatment. Not considering the patient with time to onset of 2 days, the next earliest time to onset of dystonia from atomoxetine initiation was 18 days. No cases of dystonia occurred within 14 days of a dose increase. Therefore, the time to onset information among the atomoxetine cases of dystonia was not consistent with the expected clinical presentation of acute, drug-induced dystonia.

In summary, despite the identification of a “possible signal” between atomoxetine and dystonia by the WHO (Boyd 2015), there are no data from this retrospective cohort study of over 70,000

paediatric or adolescent users of atomoxetine to support a relationship. Neither the primary, nor the sensitivity analysis to more strictly adjust for potential confounding by concomitant medication use, support a statistically significant increased risk of dystonia with atomoxetine use, compared to a stimulant treated cohort propensity score matched for numerous baseline characteristics.

11.4. Generalisability

The Truven Health Analytics MarketScan database is one of the largest networks of employee-ensured claims databases that represent the generally insured patient population. This study used commercial claims, Medicaid, and Medicare data sources from Truven, and is generalisable to an insured population in the US. Baseline characteristics in our study cohort are consistent with that expected of a paediatric and adolescent ADHD population. Furthermore, 13% of the matched cohort were using an antidepressant during baseline. This is consistent with a study conducted between 2002 and 2008 that estimated among 3- to 18-year-old patients prescribed ADHD medication, 14.8% were concomitantly using an antidepressant (Barner et al. 2011). These baseline characteristics support generalisability of the study population and results toward a broader ADHD treated population.

12. Other Information

Not applicable.

13. Conclusion

Results of this cohort study did not show a statistically significant increased incidence and risk of dystonia with atomoxetine compared to stimulant use, among a cohort of paediatric and adolescent patients initiating treatment and naïve to ADHD medications in the previous 6 months. Furthermore, there was no clinically significant evidence to support an association based on the time to onset from atomoxetine initiation or dose increase. This study does not suggest dystonia is a potential risk of atomoxetine use, and, therefore, does not impact the benefit-risk balance of atomoxetine.

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. B4Z-MC-B031 Study Protocol

PASS Information

Title	The Risk of Dystonia among Children and Adolescents Treated with Atomoxetine within the Truven MarketScan Database: B4Z-MC-B031
Version identifier	Version 1.0
Date of last version	
EU PAS Register No:	ENCEPP/SDPP/11221
Active substance	N06BA09 atomoxetine hydrochloride
Medicinal product(s):	Strattera (atomoxetine)
Product reference:	UK/H/0686/002-009
Procedure number:	N/A
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	The primary objective of this study is to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6-17 years of age relative to a propensity score matched cohort of stimulant treated patients, using a cohort study design.
Country(-ies) of study	United States
Author	Kristin Joy Meyers, MPH PhD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 Telephone: +1 317 452 5421

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Company
MAH contact person	Stephen Motsko Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Motsko_stephen_paul@lilly.com +1 317 433 2931

1. Table of contents

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2. List of abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
CPRD	Clinical Practice Research Datalink
CRF	case report form
ERB	ethical review board
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
SAE	serious adverse event
SAR	serious adverse reaction

3. Responsible parties

Not applicable.

4. Abstract

Title: The Risk of Dystonia among Children and Adolescents Treated with Atomoxetine within the Truven MarketScan Database.
PI: Kristin Meyers, PhD MPH
Version Number: 1.0 Date:

Rationale and Background: Dystonia is a known adverse reaction with many medications including antipsychotics, antidepressants, and other psychotropics. However, little is known about whether atomoxetine carries a risk of dystonia. One publication reviewing individual case reports from the VigiBase database suggests a possible signal between dystonia and atomoxetine use (Boyd 2015). However, there are no published case reports or epidemiological studies on atomoxetine and dystonia. Nor are there any publications regarding dystonia among those with attention-deficit/hyperactivity disorder (ADHD). Lilly is conducting the currently proposed observational study to fill the gap in knowledge regarding the incidence of dystonia among children and adolescents treated with atomoxetine.

Research question and objectives: The primary objective of this study is to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6-17 years of age relative to a propensity score matched cohort of stimulant treated patients. This objective will be attained by estimating the hazard ratio (HR) from Cox proportional hazards regression.

Study design: Retrospective cohort study

Population: The source population will consist of children and adolescents (6-17 years of age) with at least 6 months (180 days) of continuous enrolment within the health plan prior to index date. From the source population, two cohorts will be generated: 1) an atomoxetine-treated cohort and 2) a comparator cohort of children and adolescents initiating a stimulant medication. No previous ADHD medication in the 6 month baseline period prior to first study prescription will be allowed. The propensity for atomoxetine initiation will be estimated and used to match atomoxetine initiators to stimulant initiators.

Variables: The endpoint of interest is incident dystonia (ICD-9 codes 333.7, 333.72, 333.79, 333.81, 333.83, 333.84, and 333.89). The primary exposure of interest is atomoxetine.

Data sources: The present study uses the United States (US) based commercial electronic claims database Truven Health Analytics MarketScan®. Prescription and diagnostic data are available in MarketScan from the period of 01 January 2006 through 31 December 2014.

Study size: Between 01 January 2006 and 31 December 2014, there were 369 690 unique users of atomoxetine identified in MarketScan; 280 985 of which did not use any other ADHD medications in the 6 months prior to first atomoxetine prescription (index date). Assuming we are able to find a 1:1 match for 60% of the atomoxetine cohort, there will be 168 591 patients in each cohort.

Data analysis: The atomoxetine initiators will be 1:1 propensity score matched to stimulant initiators. The incidence rate of dystonia will be estimated for each cohort and the HR will be estimated using Cox proportional hazard regression. A two-sided 95% confidence interval will

be computed for the HR and a p-value less than 0.05 will be considered as evidence for rejecting the null hypothesis of no difference in dystonia incidence.

Milestones: Planned milestones depend on protocol approval date. Currently aim for start of data collection 11 January 2016, end data collection 15 April 2016, and final study report by 30 June 2016.

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data collection	11 January 2016
End of data collection	15 April 2016
Registration in the EU PAS register	1 November 2015
Final report of study results	30 June 2016

7. Rationale and background

7.1. Background for Conducting a Retrospective Database Study

Dystonia is a known adverse reaction with many medications including antipsychotics, antidepressants, and other psychotropics. However, little is known about atomoxetine and dystonia.

The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring (also called Uppsala Monitoring Centre [UMC]) published a possible signal between atomoxetine and dystonia in children and adolescents in August 2015 (Boyd 2015). This signal was based on disproportionality analyses through data mining and review of individual case safety reports in VigiBase, a method described in Caster et al. 2014. Outside of this report from WHO, there are no published case reports or epidemiological studies on atomoxetine and dystonia. Nor are there any publications regarding dystonia among children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Information on patients with dystonia in the ADHD population is limited primarily to case reports of dystonia after drug administration, rather than from observational studies (Chong et al. 1999; Senecky et al. 2002; Benjamin and Salek 2005; Keshen and Carandang 2007; McLaren et al. 2010; Yilmaz et al. 2012).

Lilly is conducting the currently proposed observational study to evaluate whether there is an increased risk of dystonia among children and adolescents treated with atomoxetine, compared to a propensity score matched cohort of patients treated with a stimulant.

Feasibility for conducting this observational study was considered in both a US-based electronic claims database (Truven Health Analytics MarketScan®) as well as the United Kingdom based Clinical Practice Research Datalink (CPRD) (Annex 7). MarketScan is larger with nearly 370 000 atomoxetine exposed children and adolescents. Whereas fewer than 3 000 children and adolescents of the same age were identified as exposed to atomoxetine within CPRD. Therefore, in the interest of sample size, this study will use the Truven MarketScan® data.

7.2. Atomoxetine and ADHD

Attention-deficit/hyperactivity disorder is a common neurodevelopment disorder of childhood, which often persists into adulthood. Attention-deficit/hyperactivity disorder is characterised by developmentally inappropriate levels of inattention, hyperactivity, or a combination of these, which impair functioning in multiple settings. The prevalence of ADHD ranges between 2 to 18% in community samples (Rowland et al. 2002). The prevalence of ADHD was approximately 11% among children aged 4-17 years in 2011, a 42% increase in prevalence from 2003 (Visser et al. 2014). In addition to increased prevalence of diagnoses, the prevalence of medication for ADHD treatment has increased as well, with more than two thirds of those with current ADHD taking medication in 2011 (Visser et al. 2014).

Medications to treat ADHD are classified as either stimulants or non-stimulants. Stimulant medication options include methylphenidate (e.g., Ritalin®), amphetamine (e.g., Adderall®), dextroamphetamine (e.g., Dexedrine®), and dexmethylphenidate (e.g., Focalin®).

Atomoxetine (Strattera®) was the first non-stimulant option when it was approved in the US in 2002. Atomoxetine is a selective inhibitor of the presynaptic norepinephreine transporter and has a minimal effect on other noradrenergic receptors, other neurotransmitter receptors, or transporters. Atomoxetine is indicated for the treatment of ADHD in children 6 years of age and older, adolescents and adults. Eight years later, two other non-stimulant monotherapies, both alpha-2-adrenergic agonists, were approved by the Food and Drug Administration for ADHD: guanfacine (Intuniv®) and clonidine (Catapres®). The European Medicines Agency also approved Intuniv in 2015.

Based on a retrospective claims-based analysis between 2003-2007 (prior to the approval of guanfacine and clonidine), it was estimated that 16.7-19.7% of medically treated patients with ADHD aged 6-17 years were prescribed atomoxetine as an index medication, whereas 42.6-51.2% were prescribed methylphenidate and 32.2-37.7% amphetamine (Christensen et al. 2010). Since the approval of other non-stimulant medications, the percent of index medications being atomoxetine has decreased. Issues of persistence, adherence, drug switching and drug holidays are common among the ADHD treated population. Barner et al. estimated the mean persistence (days of continuous therapy without a 30-day gap) for atomoxetine users aged 3-18 years of age was 153 days (Barner et al. 2011).

7.3. Dystonia

7.3.1. Definitions

Dystonia denotes abnormal movements that are slow or so sustained that they may appear as abnormal postures. Dystonia may involve a single body part such as in torticollis, may involve adjacent body parts, or may be more generalised. The movements are generally absent during sleep and are exacerbated by emotional stress or voluntary activity (CIOIMS 1999). Drug-induced dystonia is often early onset (within one week of commencement of treatment) but can be late onset (after several weeks, months, or years of treatment) (CIOMS 1999).

7.3.2. Risk Factors

Risk factors for dystonia are classified as either medication or non-medication related. Many classes of medications are associated with extrapyramidal symptoms which includes dystonia events. The most common drug class associated with dystonia is antipsychotics, such as pimozide, thiothizene, mesoridazine, thioridazine, molindone, perphenazine, loxapine, risperidone, olanzapine, haloperidol, trifluoperazine, chlorpromazine, clozapine, quetiapine, and ziprasidone. The reactions to antipsychotics are common in young males and typically develop within a few days (approximately 7 days) of starting, or raising the dose of, an antipsychotic medication, or after reducing the dose of a medication used to treat extrapyramidal symptoms (APA DSM-5, 2013).

Other classes (individual medications) associated with extrapyramidal symptoms (involving dystonia) include: antiparkinson drugs (levodopa), antihistamines (promethazine, cetirizine, loratadine, desloratadine), anticonvulsants (phenytoin, carbamazepine), antiemetics (metoclopramide, benzquinamide, thiethylperazine, prochlorperazine, droperidol), antidepressants (amitriptyline, doxepin, amoxapine, nortriptyline, fluoxetine, clomipramine, trazodone, protriptyline, desipramine, imipramine, paroxetine, citalopram), and other psychotropic medications (bupropion, buspirone, alprazolam) (Gill et al. 1997; Aronson 2006).

Non-medication related factors which are associated with increased risk of dystonic symptoms include temporal lobe seizures, viral infections, bacterial infections, trauma, space-occupying lesions in the peripheral nervous system, lesions in the central nervous system, and endocrinopathies (hypoparathyroidism) (APA DSM-5, 2013).

7.3.3. Epidemiology of Dystonia

Epidemiological data on dystonia is difficult to establish (Steeves et al. 2012). Methodologies across studies vary for case definition, ascertainment, as well as the broad range of causes and ages affected. A meta-analysis of studies conducted within largely adult populations estimated a prevalence of primary dystonia of 16.43 per 100,000 (95% CI 12.09-22.32) (Steeves et al. 2012). Focusing on results for those <29 years of age, the prevalence of various types of dystonia ranged from 0-7.6 per 100,000 (Steeves et al. 2012). No publications were identified estimating the incidence of dystonia in children and adolescents.

8. Research question and objectives

The primary objective of this study is to evaluate the incidence and risk of dystonia among atomoxetine treated patients between 6-17 years of age relative to a propensity score matched cohort of stimulant treated patients.

8.1. Study design

The proposed study is a retrospective cohort study using secondary data from the Truven Health Analytics MarketScan® database.

To address the primary objective, two cohorts will be generated:

1) **Atomoxetine treated cohort**: 6-17-year-old patients initiating atomoxetine use. The new-user design is a reasonable strategy to reduce bias when healthcare databases are used (Johnson et al. 2013).
2) **Stimulant treated cohort**: 6-17-year-old patients initiating a stimulant medication.

The null hypothesis is that there is no increased risk of dystonia among paediatric and adolescent users of atomoxetine, relative a propensity score matched population of stimulant users. This null hypothesis will be formally tested using Cox proportional hazards regression.

Children are increasingly being treated simultaneously with ADHD and psychotropic medications (Safer et al. 2003). A study conducted between 2002 and 2008 estimated that, of 3-18-year-old patients prescribed ADHD medication, 14.8% were concomitantly using an antidepressant and 12.3% an antipsychotic (Barner et al. 2011). Many psychotropic medications carry a known risk for dystonia (as described in Section 7.3.2). Therefore, it is important to ensure a similar distribution of common comorbities and concomitant medication use between the atomoxetine and comparator cohort. Selecting a comparator which is using a medication to treat the same indication as atomoxetine will reduce bias due to these confounding factors. Furthermore, propensity score matching will be used to achieve balance of numerous characteristics across groups, including demographics, medical diagnoses, concomitant medications, and healthcare utilisation.

Sensitivity analysis (See Section 8.7.6) will be conducted to assess whether after propensity score matching, there is residual confounding by concomitant medication use. Also, if the primary analysis demonstrates a significantly elevated risk, a second sensitivity analysis will be done comparing dystonia risk in the atomoxetine cohort relative to an untreated ADHD cohort. This would rule out possible bias in the primary analysis due to the choice of comparator drug.

8.2. Setting

8.2.1. Study Population

The source population will consist of children and adolescents (6-17 years of age) with at least 6 months (180 days) of continuous enrolment in the health plan prior to index date. For the purpose of this study, continuous enrolment will be defined as no enrolment gap greater than 31

consecutive days during the baseline period. This ensures at least 6 months of data proceeding cohort entry to characterise baseline variables for study subjects. Two cohorts will be created from this source population (described below) for primary analysis. Baseline patient characteristics will be compared across the exposed cohort of interest and comparator cohort prior to, and after, propensity score matching. The detailed list of variables to be compared is listed in Annex 3.

Inclusion criteria:

- 6-17 years of age
- Continuous enrolment in the health plan for a minimum of 6 months prior to index date. Continuous enrolment will be defined as no enrolment gap exceeding 31 consecutive days at any given time in the course of the study.
- Treatment with either atomoxetine or stimulant (for primary analysis)
- Untreated ADHD (for sensitivity analysis, see Section 8.7.6)

Exclusion criteria:

- Diagnosis of dystonia (as defined in Table 1) during the baseline period prior to index.

8.2.2. Atomoxetine-treated cohort

All patients with at least one prescription of atomoxetine will be identified. The date of the first atomoxetine prescription serves as the index date, and the 6 months prior will provide baseline data (Figure 1). No use of other ADHD medications is allowed during the 6 month baseline period. A diagnosis of ADHD is not required.

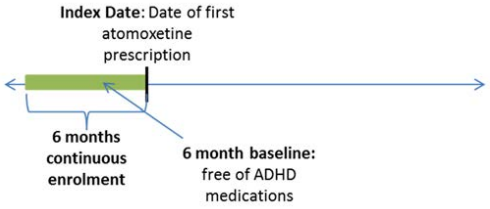

Figure 1. **Depiction of atomoxetine cohort identification: including baseline period and index date.**

8.2.3. Stimulant treated comparator cohort

A comparator cohort of children and adolescents receiving a stimulant medication (medications as listed in Table 2) will also be identified from the source population. Stimulants include amphetamines (N06BA01, N06BA02, N06BA03, N06BA12) or methylphenidates (N06BA04, N06BA11). The date of first stimulant prescription serves as the index date, and the 6 months immediately prior to the index date will provide baseline data. From this pool of stimulant initiators, the comparator cohort will be generated by propensity score matching to the

atomoxetine users. The propensity score will be based on variables specified *a priori* as predictors of atomoxetine use and/or dystonia. To better capture unknown, measured confounders, and increase comparability between the atomoxetine and stimulant cohorts, comorbid conditions present in at least 100 atomoxetine users which demonstrate different distributions across the atomoxetine and stimulant cohorts will be additionally considered for inclusion in the propensity score (described in Section 8.7.2). The propensity score matching process will result in a cohort of individuals who were not using stimulants, but had a similar distribution in the propensity to be prescribed atomoxetine.

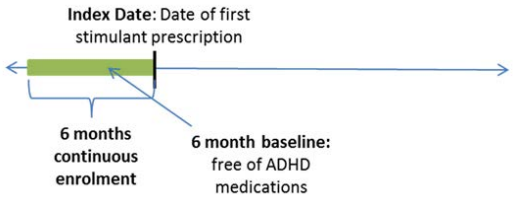

Figure 2. **Depiction of stimulant cohort identification: including baseline period and index date.**

8.2.4. Study period

Medication and outcome data is available from Truven beginning 01 January 2006 through 31 December 2014. Given the 6 month baseline period, this study will include atomoxetine prescriptions which were initiated on or after 01 July 2006. The index date for each cohort was described above. Follow-up time will be defined using an as-treated design. Exposed individuals will only contribute person time during an active study prescription.

After index, patients are followed until the first of the following censoring events:

- The end of the prescription period, defined as last days supply plus 30 day grace period, (for exposed cohort only)
- First event of dystonia (as defined by ICD-9-CM codes listed in Table 1)
- Switch to other ADHD drug (atomoxetine user switching to stimulant or alpha-2-adrenergic agonist, stimulant user switching to atomoxetine or alpha-2-adrenergic agonist; see Table 2)
- Gap in health plan enrollment greater than 31 days
- End of study period, 31 December 2014

8.3. Variables

The **primary endpoint** is incident dystonia, as defined by the ICD-9-CM codes in Table 1. Codes specific to dyskinesia or genetic/familial forms of dystonia were excluded. The primary analysis will consider diagnosis for any of the outlined dystonia codes. Only the first event of

dystonia occurring after the initiation of the drug, and within the follow-up period will be counted.

Table 1. ICD-9-CM Codes Used to Define Dystonia in Present Study

ICD-9-CM Code	Code Description
333.7	Acquired torsion dystonia
333.72	Acute dystonia due to drugs
333.79	Other acquired torsion dystonia (idiopathic, non-familial dystonia)
333.81	Blepharospasm
333.83	Spasmodic torticollis
333.84	Organic writers cramp (hand dystonia)
333.89	Other fragments of torsion dystonia

The **primary exposure of interest** is atomoxetine (N06BA09). Dose information for atomoxetine will also be queried. Attention-deficit/hyperactivity disorder medications are outlined in Table 2. Use of the other medication will not be allowed in the 6 month baseline period prior to index date. Modafinil is not currently approved in the US for the treatment of ADHD, but is sometimes used off-label for this indication.

Table 2. ATC Codes for ADHD Medications

ATC Code	Name	Drug Class
N06BA09	atomoxetine	Norepinephrine reuptake inhibitor
N06BA01	amphetamine (includes mixed salt amphetamine)	Stimulant
N06BA02	dexamphetamine	Stimulant
N06BA03	dextromethamphetamine	Stimulant
N06BA04	methylphenidate	Stimulant
N06BA11	dexmethylphenidate	Stimulant
N06BA12	lisdexamfetamine	Stimulant
N06BA07	modafinil	Stimulant
C02AC01	clonidine	Alpha-2-adrenergic agonist
C02AC02	guanfacine	Alpha-2-adrenergic agonist

Baseline characteristics to be assessed are outlined below in Annex 3 and include demographics, measures of resource utilisation, comorbidities, and concomitant medication use. Of particular interest for inclusion are baseline characteristics which are also risk factors for dystonia (Section 7.3.2), including: use of drugs with known adverse reaction of dystonia (antipsychotics, antihistamines, anticonvulsants, antiemetics, antidepressants, psychotropics), seizure disorders, infections, trauma, and disorders of the nervous system.

8.4. Data sources

The present study uses the US-based electronic claim database Truven Health Analytics MarketScan®. MarketScan contains individual level de-identified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs. Since their creation in the early 1990s, the MarketScan database has grown into one of the largest collections of de-identified patient-level data ain the nation. This database reflects real world treatment patterns and costs by tracking millions of patients as they travel through the healthcare system offering detailed information about numerous aspects of care. Data from individual patients are integrated from all providers of care, maintaining all healthcare utilisation and cost record connections at the patient level. Used primarily for research, this database is fully Health Insurance Portability and Accountability Act (HIPAA) compliant. Research using MarketScan data has been widely published in peer-reviewed journals. In the most recent full data year, MarketScan claims databases contain data on 50 million lives. Its sample size is large enough to allow creation of nationally representative data sample of American with employer provided health insurance or Medicaid.

As with any data source, there are limitations to using MarketScan. Some limitations results from data structure, others are due to the sample population. Key common limitations include:

- Lack of clinical details makes it hard to verify the validity of diagnosis codes and to refine statistical analyses. Data on important confounding variables (smoking, alcohol use, body weight, and height) are not available in the claims database.
- Diagnoses, medical procedures, and medicine dispensing will not be captured if no corresponding billing codes were generated. Likewise, the use of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, current procedural terminology codes, or national drug codes is subject to the incompleteness or inaccuracies of the coding in the database;
- MarketScan claims are based on a large convenience sample. The data come mostly from large employers; medium and small firms are not represented. Because the sample is not random, it may contain biases or fail to generalise well to other populations.
- Only prescribed medicines are recorded in the database. No information about over-the counter drug (e.g., aspirin) use is available.

8.5. Study size

A feasibility assessment within MarketScan was conducted to determine the anticipated sample size (see Annex 7 for details).

Between 01 January 2006 and 31 December 2014, there were 369 690 unique users of atomoxetine identified in MarketScan, 280 985 of which did not use any other ADHD medications in the 6 months prior to first atomoxetine prescription (index date). Assuming we are able to find a 1:1 match for 60% of the atomoxetine cohort, there will be 168 591 patients in each the atomoxetine cohort and comparator cohort. The expected background incidence rate of dystonia is not known because no epidemiological studies of dystonia incidence among children and adolescents were identified. Power was estimated using the software nQuery + nTerim 3.0 (http://www.statsols.com/products/nquery-advisor-nterim/) for a log-rank test of survival in two

groups for fixed time, constant HR. Power was estimated for 3 different baseline incidence rates (ranging from 5 to 15 per 100 000).

The power to detect an HR ranging from 1.5-3 under the three baseline dystonia rates are depicted in Table 3.

Table 3. Power to Detect Various HR Under Three Scenarios for Incidence Rate of Dystonia in Reference Group

HR	5 per 100 000	10 per 100 000	15 per 100 000
3	82%	98%	99%
2.5	64%	90%	98%
2.0	38%	65%	82%
1.5	14%	25%	35%
Assumptions: two-sided, alpha=0.05, 168 591 patients in each group followed for average of 1 year.			

8.6. Data management

Data management and statistical analysis will be done using SAS® Proprietary Software version 9.2. Datasets and analytic programs will be kept on a secure server and archived per Lilly record retention procedures.

8.7. Data analysis

The primary analysis will be a comparison of the risk of dystonia in patients initiating atomoxetine relative to a propensity score matched cohort of individuals initiating a stimulant. This comparison will be carried out using Cox proportional hazards regression. Overview of the analysis strategy, followed by details of the propensity score development and matching, as well as the implementation of regression models are described below.

8.7.1. Analysis overview

- Estimate the propensity for atomoxetine initiation for each patient in the atomoxetine cohort and the stimulant comparator cohort
- Use Greedy 1:1 matching algorithm to form propensity score matched samples
- Assess balance between cohorts across all baseline covariates using standardised differences
- Revise and finalise propensity score, as needed
- Estimate the HR (with 95% confidence interval) of dystonia associated with atomoxetine using a Cox proportional hazards regression model.
- Perform sensitivity analyses
- Assess generalisability by summarising population characteristics and outcomes for patients included and excluded by matching process

8.7.2. Propensity score estimation

As the cohorts were not formed by randomization, but were observed based on usual care, comparisons between cohorts may be confounded by selection bias. To adjust for measured confounders, comparisons between cohorts will be performed using propensity score matching. The aim of propensity score matching is to create groups where treatment is unrelated to any baseline characteristics, similar to the balance achieved through randomisation in clinical trials (Rosenbaum and Rubin 1983).

The propensity score for each patient in the atomoxetine and stimulant cohorts will be defined by the probability of being in the atomoxetine treated cohort. The propensity score will be estimated using logistic regression, with treatment status as the dependent (i.e., outcome) variable. Independent (i.e., predictor) variables for the propensity score model include those listed in Annex 3, drawn from the 6-month baseline period. These measures were selected based on literature and expert opinion as potentially moderately related to both treatment status and dystonia, or strongly related to either.

To consider potential confounders not specified *a priori*, we will tabulate the most frequently occurring diagnoses, procedures, or drugs dispensed in the baseline period among the two cohorts. We will consider any characteristics that are present in at least 100 atomoxetine users. Any characteristics differing substantially between atomoxetine and stimulant cohort (based on univariate statistical significance, α=0.05) will be considered for inclusion in the propensity score model. While the potential exists for unmeasured confounders, risk factors for dystonia are largely medication related, and therefore captured in the MarketScan database. Furthermore, because atomoxetine only has one approved indication (ADHD), we are confident the diagnoses included in the propensity score (which include ADHD, as well as common comorbid psychiatric and development disorders) are appropriately representing possible confounders.

8.7.3. Propensity score matching

A greedy 1:1 matching algorithm (D'Agostino 1998) will be used to match each atomoxetine initiator with an appropriate untreated control patient. The algorithm will use ranked-based Mahalanobis distance with a caliper of 0.2 standard deviations of the logit of the propensity score (Austin 2010; Rosenbaum 2010).

8.7.4. Evaluation of quality of propensity score matching

The quality of the propensity score matching for achieving balance of baseline characteristics between groups will be assessed prior to initiating outcome analysis. Balance is assessed via two measures. The first is t-tests or chi-square tests (as appropriate) to assess differences between the cohorts across all measured baseline covariates before and after matching. Second, the standardised difference, defined as the difference in means between the 2 groups divided by a measure of the standard deviation of the variable, will be computed in the matched subsets. For continuous variables, the standardised difference is estimated by:

$$d = \frac{(\overline{X}_1 - \overline{X}_2)}{\sqrt{\frac{S_1^2 + S_2^2}{2}}}$$

Where $\overline{X}_1$ and $\overline{X}_2$ denote the sample mean of a baseline variable in each group, and S_1^2 and S_2^2denote the sample variances, respectively.

For binary categorical variables, the standardised difference is estimated by:

$$d = \frac{(\widehat{p_1} - \widehat{p_2})}{\sqrt{\frac{\widehat{p_1}(1-\widehat{p_1}) + \widehat{p_2}(1-\widehat{p_2})}{2}}}$$

Where $\widehat{p_1}$ and $\widehat{p_2}$ denote the proportion of a binary baseline variable in the treatment and control group, respectively.

The standardised difference provides a metric for assessing variables with larger residual imbalance after propensity score matching. As a rule of thumb, standardised differences greater than 0.10 indicated imbalance and will require further adjustment in outcome models (Austin and Mamdani 2006). Baseline characteristics of the matched cohorts will be presented, in table and graphical form, both pre and post matching.

The above balance diagnostics may identify imbalances that result in the need for a revision to the propensity score model, the need for specific sensitivity analyses, or other changes to the analysis plan. To improve balance the following methods may be utilised: using a smaller caliper for matching, trimming non-overlapping regions, requiring exact fits on specific variables, adding to or reducing the propensity model. Once again, the propensity score model and any adjustments to the analysis plan will be finalised prior to initiating any analysis of the outcome measures.

The 1:1 matching was selected to optimize control of selection bias, though it can result in a larger subset of patients excluded from the primary analysis. Baseline characteristics and outcomes of patients excluded from the analysis will be summarised relative to the set of patients included in the analysis. This will allow for more appropriate interpretation regarding the generalisability of results. See Annex 6 for table shell which outlines how the differences between the cohorts will be presented, pre-match, after-match, and those who do not find a match and are therefore excluded.

8.7.5. Outcomes analysis

The primary comparison of dystonia incidence between patients treated with atomoxetine and patients treated with a stimulant will be assessed by a propensity score matching analysis and Cox proportional hazard regression. Only patients matched on propensity score are included in the analysis. The index date for follow-up is date of first study prescription (see Sections 8.2.2 and 8.2.3). The end of follow-up is the end of the at-risk period (as defined in Section 8.2.4) or last date of enrollment, whichever comes first. Variables in the regression model will include treatment (atomoxetine or stimulant), gender, age at index, index date, and any propensity score variable which did not reach balance between the two arms after matching.

The incidence rate of dystonia will be reported as the number of events per 100 000 person years for each cohort (example of results presentation in Table 4). The HR will be estimated comparing incidence in atomoxetine users compared to stimulant users. A two-sided 95% confidence interval will be computed for the HR and a p-value less than 0.05 will be considered as evidence for rejecting the null hypothesis of no difference in dystonia incidence. Diagnostics will be conducted to assess the proportionality assumption for the Cox regression. If required, a modification to the model to accommodate departures from proportionality will be executed (e.g., stratified partial likelihood estimation).

Table 4. Incidence and hazard ratio (HR) of dystonia across the propensity matched cohorts

	Number of Subjects	Number of Dystonia* Events	Crude Incidence Rate per 100,000 person-years (95% CI)	Adjusted HR (95% CI)
Atomoxetine Initiator				
Stimulant Initiator				1.0 (Reference)
*Dystonia as defined by ICD-9-CM codes: 333.7, 333.72, 333.79, 333.81, 333.83, 333.84, 333.89.				

8.7.6. Sensitivity analyses

Sensitivity analyses will be performed to assess the robustness of the pre-specified analyses to potential issues of confounding and bias.

- **Assess sensitivity to confounding by concomitant medication use**: The primary analysis will balance concomitant medication use between atomoxetine and stimulant cohorts through the propensity score process. However, because psychotropic medications are increasingly prescribed to an ADHD population (Safer et al. 2003), and have known risks for dystonia, it is important to assess for residual confounding by medication use. Therefore, we will subset the primary analysis to only those with no use of any medications, at any time (baseline or follow-up), with known risk of dystonia (medications as listed in Section 7.3.2). This approach is the most strict for controlling for confounding by concomitant medication use, but will also result in a sacrifice to sample size and study power.
- **Assess sensitivity to comparator group**: Only if a significantly elevated risk of dystonia with atomoxetine use relative to stimulants is identified will we conduct this sensitivity analysis to the choice of comparator. Using a treated comparator with the same indication (as done for the primary analysis proposed here) is a best practice to control for confounding by indication (and factors related to indication) in pharmacoepidemiology (Setoguchi and Gerhard 2013). However, the observed effect size for atomoxetine is then directly dependent on understanding the association, if any, between stimulants and dystonia. There have been case reports of methylphenidate being used to *treat* facial dystonia (Eftekhari K et al. 2015) and reports of a possible drug-drug

interaction where dystonia occurs upon discontinuation of methylphenidate when concurrently on an atypical antipsychotic medication (Benjamin and Salek 2005; Keshen and Carandang 2007; McLaren et al. 2010; Guler et al. 2015). On the contrary, there is one case report of an adolescent who experienced a focal dystonia after methylphenidate initiation (Tekin et al. 2015). The relationship, if any, between stimulants and dystonia is not well understood. However, if stimulants in some way treat or supress dystonia, comparing atomoxetine to stimulants may result in an upwardly biased estimate of effect for atomoxetine.

- To conduct this analysis, the atomoxetine cohort from the primary analysis will be compared to an untreated ADHD population. For the untreated patients (who have (ICD-9-CM codes 314.0-9), the index date is derived from the distribution of the number of days from the initial ADHD diagnosis to initial atomoxetine prescription among the treated patients. The index date is selected at random and assigned to the nonusers according to the distribution of time between diagnosis and prescription derived from the treated cohort. Therefore, the overall distribution of the index date of the non-users matches that of the users' time for the first atomoxetine prescription. Non-users who had ADHD before the assigned index date will be excluded from the analysis. This approach for matching index date between atomoxetine users and non-users at cohort entry based on the prescription time distribution in users has been reported as a way to control for time-related bias (Zhou et al. 2005).
- Untreated patients will be followed until first of following: dystonia, initiation of an ADHD medication, gap in enrolment of greater than 30 days, end of study period. The propensity score will be re-created using the same methodology and variables as considered for primary analysis.

8.7.7. Additional descriptive analyses

To further assist in understanding and interpreting the primary analysis, cases of dystonia occurring while on atomoxetine will be summarised for the following: dose of atomoxetine at time of dystonia, time since initiation of atomoxetine, time since increasing dose of atomoxetine, and tabulation of timing and type of any newly initiated medications with known risk of dystonia during follow-up time (see Table 2 in Annex 6 for mock table).

8.8. Quality control

The study will use an existing database, which has been used primarily for research, fully HIPAA compliant. The study programmes for data management or statistical analyses will be validated by individual(s) outside the study team to ensure data integrity and accuracy. All study programmes, log files, and output files will be stored on the secure sever, and archiving any statistical programming performed to generate the results.

8.9. Limitations of the research methods

Claims databases, such as the Truven MarketScan, are valuable for efficient and effective examination of health care outcomes, treatment patterns, and health care resource utilisation. However, they do come with limitations. Claims data are collected for the purpose of payment, not research. Limitations associated with this include that the presence of a claim for a filled prescription does not indicate that the medication was taken as prescribed. Second, medications filled over-the-counter or obtained outside of a pharmacy setting, which may potentially confound the primary analysis, will not be observed in claims data. Third, the presence of a diagnosis on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Furthermore, absence of a diagnosis code does not guarantee absence of the condition. The positive predictive value of dystonia using ICD-9 codes in administrative claims databases is unknown. Finally, certain information is not readily available in claims data that could have an effect on study outcomes, such as certain clinical and disease-specific parameters.

8.10. Other aspects

None.

9. Protection of human subjects

All information about this observational study and individual medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. This study will be conducted in accordance with applicable laws and regulations of the US, where the study is being conducted, as appropriate.

10. Management and reporting of adverse events/adverse reactions

During the course of retrospective observational research, information pertaining to adverse reactions will not be discovered as the study does not involve identifiable patient data associated with a Lilly drug. The data in this study are only being analysed in aggregate, study data sets do not include safety measures, and there will be no medical chart review or review of free text data fields.

11. Plans for disseminating and communicating study results

This study will be registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). A final study report will be generated and available for dissemination to regulatory bodies upon request.

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Annex 1. List of Standalone Documents

Annex No.	Date	Title
1	08 October 2015	List of standalone documents
2	08 October 2015	ENCePP Checklist
3	08 October 2015	List of variables to consider for propensity score
4	08 October 2015	ICD-9 Diagnostic codes for prespecified comorbidities
5	08 October 2015	List of concominant medications
6	08 October 2015	Mock results tables
7	08 October 2015	Additional information

Annex 2. ENCePP Checklist for Study Protocols

Not applicable.

Annex 3. List of Variables to Consider for Propensity Score

ICD-9 codes and medication lists relevant for each variable (where appropriate) in Annex 4.

Variable Name	Varible Type
Demographic	
Index date	
Age (at index date)	Continuous (6-17)
Sex	Dichtomous (M/F)
Geographic region	Categorical
Diagnoses	
ADHD	Dichtomous (Yes/No)
Number of ADHD diagnoses	Continuous (0-)
Mood disorder (includes bipolar and depression)	Dichtomous (Yes/No)
Anxiety	Dichtomous (Yes/No)
Conduct disorder, including oppositional defiant disorder	Dichtomous (Yes/No)
Autistic disorder	Dichtomous (Yes/No)
Number of comorbid psychiatric conditions (count of # of above listed codes)	Continuous (0-)
Seizure disorder	Dichtomous (Yes/No)
Tics or Tourette's disorder	Dichtomous (Yes/No)
Congenital disorder	Dichtomous (Yes/No)
Developmental delays and retardation	Dichtomous (Yes/No)
Substance abuse	Dichtomous (Yes/No)
Alcohol abuse or dependence	Dichtomous (Yes/No)
Tobacco use disorder	Dichtomous (Yes/No)

Trauma	Dichtomous (Yes/No)
Central nervous system disorder	Dichtomous (Yes/No)
Infections	Dichtomous (Yes/No)
Medications	
Antidepressants	Dichtomous (Yes/No)
Antipsychotic	Dichtomous (Yes/No)
Anticonvulsant and anxiolytic	Dichtomous (Yes/No)
Antihistamines	Dichtomous (Yes/No)
Antiemetics	Dichtomous (Yes/No)
Antibiotics	Dichtomous (Yes/No)
Antiviral	Dichtomous (Yes/No)
Number of prescription drug classes used	Continuous (0-)
Healthcare Utilisation	
Visits to: - Critical care services - Non-primary care specialists - Primary care - Emergency departments	Each visit type a separate, countinous (count for # of visits) variable
Number of laboratory tests	Continuous (0-)
Number of diagnostic procedures	Continuous (0-)
Health care costs: - Total costs - Total patient cost - Total professional cost - Total facility cost - Emergency room cost - Pharmaceutical cost	Each cost type a separate, countinous variable

Annex 4. ICD-9-CM Diagnostic Codes for Prespecified Comorbities

Attention-deficit/hyperactivity disorder (ADHD)		
314.0x	**Attention deficit disorder of childhood**	
	314.00	Without mention of hyperactivity
	314.01	With hyperactivity
314.1	**Hyperkinesis with developmental delay**	
314.2	**Hyperkinetic conduct disorder**	
314.8	**Other specified manifestations of hyperkinetic syndrome**	
314.9	**Unspecified hyperkinetic syndrome**	

Mood disorders		
296.0x	**Bipolar I disorder, single manic episode**	
	296.0	unspecified degree
	296.01	mild degree
	296.02	moderate degree
	296.03	severe degree without psychotic behavior
	296.04	severe degree specified as with psychotic behavior
	296.05	in partial or unspecified remission
	296.06	in full remission
296.1x	**Manic disorder, recurrent episode**	
	296.1	unspecified degree
	296.11	mild degree
	296.12	moderate degree
	296.13	severe degree without psychotic behavior
	296.14	severe degree specified as with psychotic behavior
	296.15	in partial or unspecified remission
	296.16	in full remission
296.2x	**Major depressive affective disorder single episode**	
	296.2	unspecified degree
	296.21	mild degree
	296.22	moderate degree
	296.23	severe degree without psychotic behavior
	296.24	severe degree specified as with psychotic behavior
	296.25	in partial or unspecified remission
	296.26	in full remission
296.3x	**Major depressive disorder recurrent episode**	
	296.3	unspecified degree

	296.31	mild degree
	296.32	moderate degree
	296.33	severe degree without psychotic behavior
	296.34	severe degree specified as with psychotic behavior
	296.35	in partial or unspecified remission
	296.36	in full remission
296.4x	**Bipolar I disorder, most recent episode manic**	
	296.4	unspecified degree
	296.41	mild degree
	296.42	moderate degree
	296.43	severe degree without psychotic behavior
	296.44	severe degree specified as with psychotic behavior
	296.45	in partial or unspecified remission
	296.46	in full remission
296.5x	**Bipolar I disorder, most recent episode depressed**	
	296.5	unspecified degree
	296.51	mild degree
	296.52	moderate degree
	296.53	severe degree without psychotic behavior
	296.54	severe degree specified as with psychotic behavior
	296.55	in partial or unspecified remission
	296.56	in full remission
296.6x	**Bipolar I disorder, most recent episode mixed**	
	296.6	unspecified degree
	296.61	mild degree
	296.62	moderate degree
	296.63	severe degree without psychotic behavior
	296.64	severe degree specified as with psychotic behavior
	296.65	in partial or unspecified remission
	296.66	in full remission
296.7	**Bipolar I disorder, most recent episode unspecified**	
296.8x	**Other and unspecified bipolar disorders**	
	296.8	Bipolar disorder, unspecified
	296.81	Atypical manic disorder
	296.82	Atypical depressive disorder
	296.89	Other bipolar disorders
296.9x	**Other unspecificed episode mood disorder**	
	296.9	Unspecified episodic mood disorder
	296.99	Other specified episodic mood disorder
300.1	**Dissociative, conversion and factitious disorders**	
309.1	**Prolonged depressive reaction**	

311	**Depressive disorder no elsewhere classified**

Anxiety disorders		
300.0x	**Anxiety states**	
	300.0	Anxiety state, unspecified
	300.01	Panic disorder without agoraphobia
	300.02	Generalized anxiety disorder
	300.09	Other anxiety states
300.2x	**Phobic disorders**	
	300.2	Phobia, unspecified
	300.21	Agoraphobia with panic disorder
	300.22	Agoraphobia without mention of panic attacks
	300.23	Social phobia
	300.29	Other isolated or specific phobias
300.3	**Obsessive compulsive disorders**	
300.5	**Neurasthenia**	
300.6	**Depersonalization disorder**	
300.7	**Hypochondriasis**	
300.8	**Somatoform disorders**	
300.9	**Unspecified nonpsychotic mental disorder**	
308	**Predominant disturbance of emotions**	
308.1	**Predominant disturbance of consciousness**	
308.2	**Predominant psychomotor disturbance**	
308.3	**Other acute reactions to stress**	
308.4	**Mixed disorders as reaction to stress**	
308.9	**Unspecific acute reaction to stress**	
313.0	**Overanxious disorder specific to childhood and adolescence**	

Conduct disorders		
312.0x	**Undersocialized conduct disorder aggressive type**	
	312.00	unspecified degree
	312.01	mild degree
	312.02	moderate degree
	312.03	severe degree
312.1x	**Undersocialized conduct disorder unaggressive type**	
	312.1	unspecified degree
	312.11	mild degree
	312.12	moderate degree
	312.13	severe degree
312.2x	**Socialized conduct disorder**	
	312.2	unspecified degree

	312.21	mild degree
	312.22	moderate degree
	312.23	severe degree
312.3x	**Disorders of impulse control no elsewhere classified**	
	312.3	Impulse control disorder, unspecified
	312.31	Pathological gambling
	312.32	Kleptomania
	312.33	Pyromania
	312.34	Intermittent explosive disorder
	312.35	Isolated explosive disorder
	312.39	Other disorders impulse control
312.4	**Mixed disturbance of conduct and emotions**	
312.8x	**Other specified disturbances of conduct not elsewhere classified**	
	312.81	Conduct disorder, childhood onset type
	312.82	Conduct disorder, adolescent onset type
	312.89	Other conduct disorder
312.9	**Unspecified disturbance of conduct**	
313.81	**Oppositional defiant disorder**	

Autistic disorder		
299.0x	**Autistic disorder**	
	299.00	current or active state
	299.01	residual state

Epilepsy and seizure disorders		
345.0x	**Generalized nonconvulsive epilepsy**	
	345.00	without mention of intractable epilepsy
	345.01	with intractable epilepsy
345.1x	**Generalized convulsive epilepsy**	
	345.10	without mention of intractable epilepsy
	345.11	with intractable epilepsy
345.2	**Petit mal status**	
345.3	**Grand mal status**	
345.4x	**Localization-related (partial) epilepsy and epileptic syndromes with complex parital seizures**	
	345.40	without mention of intractable epilepsy
	345.41	with intractable epilepsy
345.5x	**Localization-related (partial) epilepsy and epileptic syndromes with simple parital seizures**	
	345.50	without mention of intractable epilepsy
	345.51	with intractable epilepsy
345.6x	**Infantile spasms**	

	345.60	without mention of intractable epilepsy
	345.61	with intractable epilepsy
345.7x	**Epilepsia partialis continua**	
	345.70	without mention of intractable epilepsy
	345.71	with intractable epilepsy
345.8x	**Other forms of epilepsy and recurrent seizures**	
	345.80	without mention of intractable epilepsy
	345.81	with intractable epilepsy
345.9	**Epilepsy unspecified**	
	345.90	without mention of intractable epilepsy
	345.91	with intractable epilepsy

Tics and Tourettes		
307.2	**Tics**	
	307.20	Tic disorder, unspecified
	307.21	Transient tic disorder
	307.22	Chronic motor or vocal tic disorder
	307.23	Tourette's disorder

Development delays		
315.0x	**Developmental reading disorder**	
	315.00	unspecified
	315.01	Alexia
	315.02	developmental dyslexia
	315.09	other specific developmental reading disorder
315.1	**Mathematics disorder**	
315.2	**Other specific developmental learning difficulties**	
315.3x	**Developmental speech or language disorder**	
	315.31	Expressive language disorder
	315.32	Mixed receptive-expressive language disorder
	315.34	Speech and language developmental delay due to hearing loss
	315.35	Childhood onset fluency disorder
	315.39	Other developmental speech or language disorder
315.4	**Developmental coordination disorder**	
315.5	**Mixed development disorder**	
315.8	**Other specified delays in development**	
315.9	**Unspecified delay in development**	

Substance abuse		
305.2x	**Nondependent cannabis abuse**	
	305.20	unspecified
	305.21	continuous

	305.22	episodic
	305.23	in remission
305.3x	**Nondependent hallucinogen abuse**	
	305.30	unspecified
	305.31	continuous
	305.32	episodic
	305.33	in remission
305.4x	**Nondependent desative, hypnotic or anxiolytic abuse**	
	305.40	unspecified
	305.41	continuous
	305.42	episodic
	305.43	in remission
305.5x	**Nondependent opiod abuse**	
	305.50	unspecified
	305.51	continuous
	305.52	episodic
	305.53	in remission
305.6x	**Nondependent cocaine abuse**	
	305.60	unspecified
	305.61	continuous
	305.62	episodic
	305.63	in remission
305.7x	**Nondependent amphetamine or related acting sympathomimetic abuse**	
	305.70	unspecified
	305.71	continuous
	305.72	episodic
	305.73	in remission
305.8x	**Nondependent antidepressant type abuse**	
	305.80	unspecified
	305.81	continuous
	305.82	episodic
	305.83	in remission
305.9x	**Nondependent other mixed or unspecified drug abuse**	
	305.90	unspecified
	305.91	continuous
	305.92	episodic
	305.93	in remission

Alcohol dependence and abuse		
303.9x	**Other and unspecified alcohol dependence**	
	303.90	unspecified

	303.91	continuous
	303.92	episodic
	303.93	in remission
305.0x	**Nondependent alcohol abuse**	
	303.00	unspecified
	303.01	continuous
	303.02	episodic
	303.03	in remission
291.x	Alcohol induced mental disorders	
V11.3	Alcoholism	

Tobacco use disorder	
305.1	**Tobacco use disorder**

Trauma	
800.x	Fracture of vault of skull
801.x	Fracture of base of skull
802.3x	Mandible, open
803.xx	Other and unqualified skull fractures
804.xx	Multiple fractures involving face and skull
851.xx	Cerebral laceration and contusion
852.xx	Subarachnoid, subdural and extradural hemorrhage, following injury
853.xx	Other and unspecified intracranical hemorrhage following injury
854.xx	Intracranial injury of other and unspecified nature
805.xx	Fracture of vertebral column
806.xx	Fracture of vertebral column with spinal cord injury
807.1x	Fracture of rib, open
807.3	Open fracture of sternum
807.4	Flail chest
807.6	Fracture of larynx and trachea, open
807.x6	Fracture or ribs, six ribs
807.x7	Fracture or ribs, seven ribs
807.x8	Fracture or ribs, eight or more ribs
808.1	Open fracture of acetabulum
808.3	Open fracture of pubis
808.43	Multiple closed pelvic fractures with disruption of pelvic circle
808.5	Open fracture of other specified part of pelvis
809.1	Fracture of bones of trunk, open
812.5x	Fracture of lower end of humerus, open
820.1x	Transcervical fracture, open

820.3x	Pertrochanteric fracture of femur, open
820.9	Fracture of unspecified part of neck of femur, open
823.3x	Fracture of shaft of tibia and fibula, open
827.1	Other, multiple, and ill-defined fractures of lower limb, open
860.1	Pneumothorax with open wound into thorax
860.3	Hemothorax with open wound into thorax
860.5	Pneumohemothorax with open wound into thorax
861.xx-869.x	Injury to internal organs
874.1x	Open wound, larynx and trachea, complicated
875.1	Open wound of chest wall, complicated
884.x	Multiple and unspecified wounds, upper limb
887.x	Traumatic amputation of arm and hand
894.x	Multiple and unspecified wounds, lower limb
896.x	Traumatic amputation of foot
897.x	Traumatic amputation of leg
901.xx	Injury to blood vessels of thorax
902.xx	Injury to blood vessels of abdomen and pelvis
903.xx	Injury to blood vessels of upper extremity
904.xx	Injury to blood vessels of lower extremity and unspecified sites
926.xx	Crushing injury of trunk
929.x	Crushing injury of multiple and unspecified sites
952.xx	Spinal cord injury without evidence of spinal bone injury
959.8	Injury, other specified sites, including multiple

Disorders of the nervous system	
349.89	Other specified disorders of nervous system

Infections	
001-009	Intestinal infectious diseases
010-018	Tuberculosis
020-027	Zoonotic bacterial diseases
030-041	Other bacterial diseases
042-042	Human immunodeficiency virus
045-049	Poliomuelitis and other non-arthropod borne viral diseases of central nervous system
050-059	Viral diseases accompanied by exanthem
060-066	Arhropod-borne viral diseases
070-079	Other diseases due to viruses and chlamydiae
080-088	Rickettsioses and other arthropod-borne diseases
090-099	Syphilis and other veneral diseases

100-118	Mycoses
120-129	Helminthiases
130-136	Other infectious and parasitic diseases
137-139	Late effects of infectious and parasitic diseases
320-322	Meningitis
323	Encephalitis
480-488	Pneumonia and influenza

Annex 5. List of Concomitant Medications

Medication class	THERCLS label	THERCLS value
Antihistamines	Antihistamines & Comb, NEC	1
Antibiotics	Antibiot, aminoglycosides	4
	Antibiot, antifungal	5
	Antibiot, cephalosporin and rel	6
	Antibiot, B-lactam antibiotics	7
	Antibiot, Chloramphenicol & Comb	8
	Antibiot, Erthromycin & Macrolide	9
	Antibiot, penicillins	10
	Antibiot, tetracyclines	11
	Antibiot, misc	12
	Antituberculosis agents, NEC	13
	Antiinfect, antibiotics, EENT	133
Antivirals	Antivirals, NEC	14
	Antiinfect, antivirals, EENT	134
Antiemetics	Antiemetics, NEC	160
Anticonvulsants and anxiolytics	Anticonvulsants, benzodiazepines	64
	Anticonv, hydantoin derivatives	65
	Anticonv, oxazolidinediones	66
	Anticonv, succinimides	67
	Anticonv, misc	68
	Anxiolytic/sedative/hypnotic NEC	75
	ASH, barbiturates	73
	ASH, benzodiazepines	74
Antidepressants	Psychother, antidepressants	69
Antipsychotics	Psychother, Tranq/antipsychotics	70

Annex 6. Mock Results Tables

Table 1. Comparison of baseline characteristics before and after matching, as well as for the unmatched individuals

	Before Propensity Score Match					After Propensity Score Match					Unmatched Subjects				
	Atomoxetine User		Non-medication user			Atomoxetine User		Non-medication user			Atomoxetine User		Non-medication user		
Characteristic	**N/Average**	**% / St. Dev**	**N**	**%**	**Standardized Difference**	**N**	**%**	**N**	**%**	**Standardized Difference**	**N**	**%**	**N**	**%**	**Standardized Difference**
Demographic															
Age at index (years)															
Male															
Geographic Region															
Northeast															
North Central															
South															
West															
Unknown															
Psychiatric Diganoses															
ADHD															
Number of ADHD diagnoses															
Mood disorder															
Conduct disorder															
Autistic disorder															
Number of psychitatric comborbidities															
Other relevant diagnoses															
Seizure															
Tics or Tourettes															
Congential disorder															
Developmental delays															
Substance abuse															
Alcohol abuse															
Tobacco use disorder															
Trauma															
Central nervous system disorder															
Infections															

Medication use																
Antidepressants																
Antipsychotic																
Anticonvulsant/Anxiolytic																
Antihistamines																
Antiemetics																
Antivirals																
Number of prescription drug classes used																
Healthcare Utilization																
# Primary care visits																
# Non-primary care visits																
# Critical care services																
# of emergency department visits																
# of laboratory tests																
# of diagnostic procedures																
Total health care costs																

Table 2. Summary of Dystonia Cases Occuring within Atomoxetine User cohort (N=)

	Average	Median	Min	Max	St. Deviation
Dose at time of dystonia					
Time since initiating atomox (days)					
Occur within 14 days of dose increase (yes/no)					
Time since dose increase (days)					
Occur within 14 days of other medication initiation					
Time since other medication initiation (days)					

Annex 7. Additional Information

Feasibility for conducting this observational study was considered in both a US-based electronic claims database (Truven Health Analytics MarketScan®) as well as the United Kingdom based Clinical Practice Research Datalink (CPRD).

In Truven, all users of atomoxetine with medications prescribed between 01 Janurary 2006 and 31 December 2014 were identified, and stratified by age (6-17 years and ≥18 years). Then the number of users with a first dystonia diagnosis (ICD-9-CM codes 333.7, 333.72, 333.79, 333.81, 333.83, 333.83, 333.84, 333.89) occuring at any time after atomoxetine intiation were counted. There were no limits placed on time since atomoxetine initiation. The same analysis was applied to CPRD, instead searching for dystonia coded by the following CPRD Read Codes: F137200, F136.00, F137.00, F13B.00, FyuB.00, F138.00, F137y00, F13A.00.

Truven was selected as the feasible dataset to use for this study given the larger sample size. To support the study design (which excludes atomoxetine initiators using another ADHD medication within 6 months of atomoxetine initiation), we further queired in Truven the number of atomoxetine users that had no use of methylphenidates, amphetamines, clonidine or guanfacine in the 6 months prior to the first atomoxetine prescription.

Results of the feasibility counts are provided below.

Counts for feasibility in Truven database

	6-17 years of age	**≥18 years of age**
Atomoxetine User	369 690	241,180
Atomoxetine user, naïve to other ADHD tx within 6 months of first atomoxetine prescription	280 985	
Atomoxetine + Incident Dystonia	850	768

Counts for feasibility in CPRD database

	6-17 years of age	**≥18 years of age**
Atomoxetine User	2 918	581
Atomoxetine + Incident Dystonia (any type)	1	0

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Approver: Kraig S Kinchen (AM\QD36701)
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