

PASS Information

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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 dexamethylphenidate (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. 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, 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 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 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 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 preceding 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.

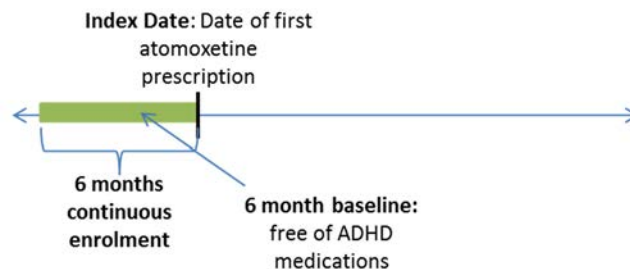


Figure 1. Depiction of atomoxetine cohort identification: including baseline period and index date.

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.

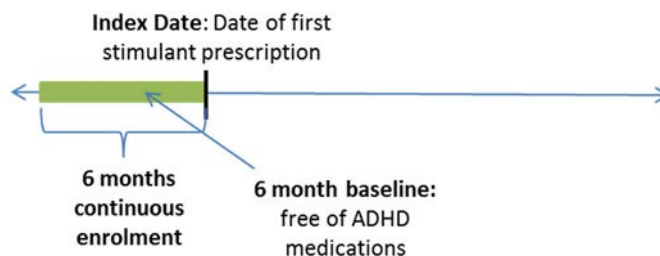


Figure 2. Depiction of stimulant cohort identification: including baseline period and index date.

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 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, 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, $\alpha=0.05$) 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:

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

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

12. References

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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 concomitant 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	Variable 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: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - 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 Comorbidities

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 unspecified 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
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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 opioid 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 intracranial 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 of ribs, six ribs
807.x7	Fracture of ribs, seven ribs
807.x8	Fracture of 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	
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349.89	Other specified disorders of nervous system
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Infections	
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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	Poliomielitis and other non-arthropod borne viral diseases of central nervous system
050-059	Viral diseases accompanied by exanthem
060-066	Arthropod-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 venereal 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

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 Occurring 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 January 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) occurring at any time after atomoxetine initiation 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 queried 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
