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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Integrated Postmarket Safety Review

Date:	June 15, 2020
Reviewers:	Ivone Kim, MD Division of Pharmacovigilance I Andrew D. Mosholder, MD, MPH Division of Epidemiology I
Team Leaders:	Carmen Cheng, PharmD Division of Pharmacovigilance I Kira Leishear White, PhD, MS Division of Epidemiology I
Division Directors:	Cindy Kortepeter, PharmD Division of Pharmacovigilance I CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Product Name:	ADHD Stimulants and Atomoxetine (See Appendix A)
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EXECUTIVE SUMMARY

This review provides the Office of Surveillance and Epidemiology's (OSE) evaluation of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for reports and epidemiological data of acute dystonia associated with products used to treat attention deficit hyperactivity disorder (ADHD), including stimulant medication and atomoxetine. This review follows the identification of two cases of acute dystonia with lisdexamfetamine use during a Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review.

FDA-approved treatments for ADHD include stimulant medications, comprised of amphetamine derivatives and methylphenidate products, and nonstimulant medication, comprised of the selective norepinephrine reuptake inhibitor atomoxetine. (b) (4)

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In this review, we identified 14 FAERS cases of acute dystonia associated with ADHD stimulants or atomoxetine. All 14 cases involved pediatric patients. Three cases described acute dystonia resulting from inappropriate ADHD medication dosage; two of these cases were a consequence of accidental ingestion and one case was the result of a medication error. Of note, the three cases of inappropriate ADHD medication dosage were the only cases in the series where causality was probable. Within the case series, there was inconsistency in the level of details about dystonic symptoms, medical history, clinical course, or concomitant drug use to allow for vigorous assessment of events. Therefore, we could not rule out other hyperkinetic movement disorders or other risk factors with certainty in all cases.

On balance, the epidemiologic literature does not provide much information on the occurrence of dystonia with ADHD stimulant medications or atomoxetine. One recently published observational, claims-based retrospective cohort study suggests that the incidence of dystonia is similar with pediatric use of atomoxetine or stimulants but did not determine an incidence in unexposed patients, so there could be a roughly equal risk for both treatments. Also, lack of information regarding the accuracy of the outcome definition in the claims-based study makes it difficult to interpret the incidence rates reported. A population-based study did not indicate that stimulant use was an important cause of dystonias in the population. A cross-sectional study found that the combination of stimulants plus an atypical antipsychotic was associated with more abnormal motor movements, but because of the limitations of the cross-sectional study design, those findings should be regarded as hypothesis-generating at best, and dystonia was not specifically analyzed.

We find insufficient evidence to support the postmarket safety signal of acute dystonia associated with ADHD stimulants or atomoxetine at this time. We identified a low number of cases in our FAERS case series. The totality of FAERS cases lacks the strength to support the association between acute dystonia and ADHD stimulants or atomoxetine. Information from the published epidemiologic literature on the risk of dystonia with ADHD drugs is limited, and by itself does not permit conclusions to be drawn.

1 INTRODUCTION

This review provides the Office of Surveillance and Epidemiology's (OSE) evaluation of the FDA Adverse Event Reporting System (FAERS) database and the medical literature for reports and epidemiological data of acute dystonia associated with products used to treat attention deficit hyperactivity disorder (ADHD), including stimulant medication and atomoxetine. This review follows the identification of two cases of acute dystonia with lisdexamfetamine use during a Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review.[1] Findings from this review will inform whether current labeling for ADHD stimulant medications and atomoxetine adequately reflects risk for acute dystonia.

1.1 BACKGROUND

Dystonia is a movement disorder featuring abnormal postures and repetitive movements caused by involuntary muscle contractions that can be intermittent or sustained. Dystonic movements may be characterized as patterned, twisting, or tremulous, and are distinguished by their consistent directionality; symptoms may be initiated or exacerbated by voluntary movement and may also be secondary to overflow muscle activation.[2,3] Classification of dystonia occurs across two dimensions: clinical characteristics and etiology. **Table 1** presents a brief schematic of dystonia classifications.

Table 1. Dystonia Classifications*

Clinical Characteristics	Age of onset	Infancy: birth to 2 years
		Childhood: 3-12 years
		Adolescence: 13-20 years
		Early adulthood: 21-40 years
		Late adulthood: >40 years
	Body distribution	Focal: affecting single body region
		Segmental: affecting two or more contiguous body regions
		Multifocal: affecting two noncontiguous or more noncontiguous or contiguous body regions
		Generalized: affecting the trunk and at least two other sites
		Hemidystonia: affecting more regions restricted to one side of the body
	Temporal pattern	Disease course: static vs. progressive
		Variability: Persistent, action-specific, diurnal, paroxysmal
	Associated features	Isolated or combined with another movement disorder
		Occurrence of other neurologic or systemic manifestations
Etiology	Nervous system pathology	Evidence of degeneration
		Evidence of structural (often static) lesions
		No evidence of degeneration or structural lesion
	Inherited or acquired	Inherited: autosomal dominant, autosomal recessive, X-linked recessive, mitochondrial
		Acquired: perinatal brain injury, infection, drug, toxic, vascular, neoplastic, brain injury, psychogenic
		Idiopathic: sporadic, familial

* Adapted from Albanese A et al[2]

Acute dystonia describes acquired dystonia.[3,4] Although the pathogenesis of acute dystonia remains unclear, dopaminergic-cholinergic imbalance in the basal ganglia is one proposed pharmacologic mechanism.[4,5] Treatment for acute dystonia includes antihistamines, anticholinergic agents, and benzodiazepines.[4,5]

1.2 REGULATORY HISTORY

This review focuses on FDA-approved ADHD stimulant medications and atomoxetine due to similarities in mechanism of action. Most ADHD stimulants and atomoxetine are approved for patients aged 6 years and older. Some ADHD stimulants have additional indications for the treatment of narcolepsy, binge eating disorder, or exogenous obesity. **Appendix A** lists all currently approved ADHD stimulants and atomoxetine products with their associated New Drug Application (NDA) numbers, Abbreviated New Drug Application (ANDA) numbers, FDA approval dates, approved indications, and approved ages for the ADHD indication.

OSE previously evaluated acute dystonia and ADHD medication in the context of drug interactions (DI).

- In May 2017, the Division of Pharmacovigilance (DPV) and the Division of Psychiatry[a] (DP) identified dystonia in the context of ADHD stimulant discontinuation and concomitant antipsychotic use as an adverse event of interest during routine surveillance of methylphenidate.[6]
- (b) (4)

1.3 RELEVANT PRODUCT LABELING

ADHD stimulants and atomoxetine are not labeled for acute dystonia. ADHD stimulants are labeled for other acute hyperkinetic movement disorders including dyskinesia, tremor, and tics and atomoxetine is labeled for tics in the ADVERSE REACTIONS sections of their product labelings. Relevant information from the ADVERSE REACTIONS section of the Mydayis and Concerta product labelings are copied below:

[a] The Division of Psychiatry was previously known as the Division of Psychiatric Products until the Office of New Drugs reorganization in April 2020.

- Section 6.2 ADVERSE REACTIONS section of the Mydayis (amphetamine) labeling[11]:
  Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, euphoria, dyskinesia, dysphoria, headache, tics, fatigue, aggression, anger, logorrhea, dermatillomania, and paresthesia (including formication).
- Section 6.6 ADVERSE REACTIONS section of the Concerta (methylphenidate) labeling[12]:
  Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs.

2 METHODS AND MATERIALS

2.1 FAERS CASE SELECTION CRITERIA

DPV evaluated all retrieved FAERS reports and identified cases for further analysis using the following inclusion and exclusion criteria. Cases were included if they met at least one of the inclusion criteria and cases were excluded if they met at least one of the exclusion criteria.

Inclusion Criteria

1. Case reports a diagnosis of acute dystonic reaction or acute dystonia by a physician
2. In absence of diagnosis by a physician, case describes signs or symptoms consistent with acute dystonic reaction or acute dystonia, i.e., oculogyric crisis, torticollis, opisthotonos, trismus, laryngospasm

Exclusion Criteria

1. Duplicate report
2. Case describes concomitant use of medications labeled for dystonia or extrapyramidal symptoms
3. Case describes non-specific movement abnormality, i.e., muscle twitching, musculoskeletal stiffness
4. Case describes patients with history of primary dystonia or family history of primary dystonia
5. Case describes acute dystonic symptoms occurring prior to exposure to ADHD stimulants or atomoxetine

2.2 CAUSALITY CRITERIA

DPV assessed cases of acute dystonia for a causal relationship with ADHD stimulants or atomoxetine using the World Health Organization - Uppsala Monitoring Center (WHO-UMC) classification system shown in **Table 2**.[13] We excluded cases from the case series if their causality assessment was deemed "unassessable" or "unlikely."

Table 2. Causality Classification and Criteria based on the WHO-UMC System

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs

Table 2. Causality Classification and Criteria based on the WHO-UMC System	
Causality Term	**Assessment Criteria**
	• Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely*	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Unassessable*	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
* Excluded from further analysis in the case series	

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 3**.

Table 3. FAERS Search Strategy*	
Date of search	December 7, 2019
Time period of search	All reports through December 6, 2019
Search type	FDA Business Intelligence System (FBIS) Quick Query
Product terms	Product active ingredient: • Amphetamine, amphetamine adipate, amphetamine adipate\dextroamphetamine, amphetamine aspartate, amphetamine aspartate monohydrate, amphetamine aspartate\amphetamine sulfate\dextroamphetamine saccharate\dextroamphetamine sulfate, amphetamine aspartate\dextroamphetamine saccharate, amphetamine hydrochloride, amphetamine phosphate, amphetamine sulfate, amphetamine sulfate\dextroamphetamine, amphetamine NOS, amphetamine\dextroamphetamine • Dextroamphetamine, dextroamphetamine hydrochloride, dextroamphetamine saccharate, dextroamphetamine sulfate • Lisdexamfetamine, lisdexamfetamine dimesylate • Methamphetamine, methamphetamine hydrochloride, methamphetamine saccharate • Methylphenidate, methylphenidate hydrochloride • Dexmethylphenidate, dexmethylphenidate hydrochloride • Atomoxetine, atomoxetine hydrochloride

Table 3. FAERS Search Strategy*	
MedDRA search terms (Version 22.0)	Standardised MedDRA Queries (SMQ): • *Dystonia (SMQ) Narrow search* Preferred Terms (PTs): • *Facial spasm, Laryngospasm, Muscle contractions involuntary, Oropharyngeal spasm, Posturing, Risus sardonicus, Tongue spasm, Uvular spasm*
* See **Appendix B** for a description of the FAERS database.	

2.4 LITERATURE SEARCH

2.4.1 DPV Literature Search

DPV searched the medical literature for additional case reports of dystonia with ADHD stimulants or atomoxetine. DPV utilized the literature strategy described in **Table 4**.

Table 4. Literature Search Strategy		
Date of search	March 6, 2020	
Database	Embase	PubMed
Search terms	'extrapyramidal symptom'/exp AND ('methamphetamine'/exp OR 'amphetamine'/exp OR 'atomoxetine'/exp)	((((((atomoxetine) OR (dexmethylphenidate)) OR (methylphenidate)) OR (methamphetamine)) OR (lisdexamfetamine)) OR (dextroamphetamine)) OR (amphetamine)) AND ((dystonia) OR (dystonic))
Years included	All years	
Limits	English, humans, case report	

2.4.2 Division of Epidemiology (DEPI) Literature Search

A targeted search for epidemiologic studies relevant to the occurrence of dystonia with medications for ADHD was conducted. On February 12, 2020, PubMed was searched for the terms atomoxetine+dystonia, methylphenidate+dystonia, amphetamine+dystonia, lisdexamfetamine+dystonia, and stimulants+dystonia. The titles and abstracts yielded by this search were screened for articles presenting analytic data regarding dystonia with ADHD drug products. Case reports, nonclinical studies, review articles, articles not in English and articles that were otherwise irrelevant were excluded.

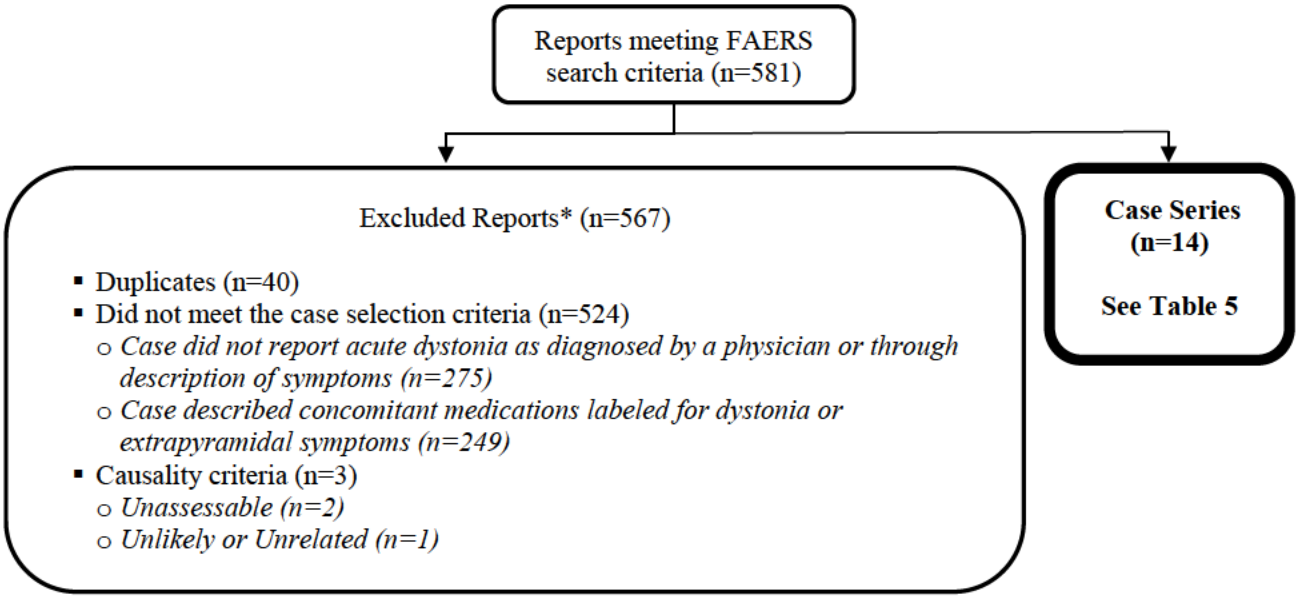
3 RESULTS

3.1 FAERS RESULTS

3.1.1 FAERS Case Selection

DPV retrieved 581 reports from the FAERS search delineated in **Table 3**. After accounting for duplicate reports and applying the case selection criteria in Section 2.1, we included 14 cases in the case series of acute dystonia with ADHD stimulants or atomoxetine (see **Figure 1**).

Figure 1. FAERS Case Selection



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above.

3.1.2 Summary of FAERS Cases

Appendix C contains a line listing of the 14 cases in this case series. **Table 5** displays descriptive characteristics of cases included in the series, including specific amphetamine, methylphenidate, and atomoxetine products reported.

Table 5. Descriptive Characteristics of Acute Dystonia with ADHD Stimulant Medication or Atomoxetine in FAERS Received by FDA Through December 6, 2019 (N=14)

Selected Characteristics	Total (n=14)	Amphetamine Products* (n=4)	Methylphenidate Products (n=10)	Atomoxetine* (n=1)
Proprietary Name		Vyvanse 2 Adderall 1 Not specified 1	Concerta 3 Quillivant XR 3 Metadate CD 1 Not specified 3	Strattera 1
Age (years)				
<5	3	0	3	0
5-9	8	2	6	0
10-14	2	1	1	0
15-19	1	1*	0	1*
Sex				
Male	8	2	6	0
Female	6	2*	4	1*
Country				
USA	8	3*	5	1*
Foreign	6	1	5	0
Year Reported				
2003-2007	2	1*	1	1*

Table 5. Descriptive Characteristics of Acute Dystonia with ADHD Stimulant Medication or Atomoxetine in FAERS Received by FDA Through December 6, 2019 (N=14)

Selected Characteristics	Total (n=14)	Amphetamine Products* (n=4)	Methylphenidate Products (n=10)	Atomoxetine* (n=1)
2008-2012	4	1	3	0
2013-2018	8	2	6	0
Prescribed Indication				
ADHD	10	4*	6	1*
ADD	2	0	2	0
Hyperactivity	1	0	1	0
Not prescribed	1	0	1	0
Dechallenge				
Positive	4	0	4	0
Not reported	10	4*	6	1*
Causality				
Possible	11	3	8	0
Probable	3	1*	2	1*
Serious outcome†				
(Total)	(13)	(4*)	(9)	(1*)
Other serious	10	3	7	0
Hospitalization	4	2*	2	1*
Required intervention	2	1*	1	1*

* A case reported a 15-year-old female with co-ingestion of Strattera and Adderall XR. The case is reflected in counts for amphetamine and atomoxetine columns.

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome.

Abbreviations: ADHD=attention deficit hyperactivity disorder, ADD=attention deficit disorder

One of the 14 cases described ingestion of nonprescribed ADHD stimulant medication. Of the 13 cases describing exposure to prescribed ADHD medication, 2 cases reported prescribed and ingested dose that was higher than the FDA-recommended starting dose. Two of the 14 cases described accidental exposure to ADHD medications and 1 of 14 cases described a medication error resulting in ingestion of greater than prescribed dose. Of note, we did not identify cases describing drug abuse, misuse, or diversion.

Table 6 below displays characteristics of acute dystonic events for cases included in the case series, including clinical characteristics, diagnostic evaluation, and therapeutic interventions reported.

Table 6. Clinical Presentation, Concomitant Medication, Evaluation, and Management in Cases of Acute Dystonia and ADHD Stimulant Medication or Atomoxetine Received by FDA Through December 6, 2019

(N=14)

Selected Characteristics	Total (n=14)	Amphetamine Products* (n=4)	Methylphenidate Products (n=10)	Atomoxetine* (n=1)
Dystonic symptom region‡	8	3*	5	1*
Oromandibular	3	0	3	0
Cervical	4	2*	2	1*
Facial	3	1*	2	1*
Upper extremity	2	0	2	0
Dystonia NOS	1	1	0	0
Trunk	1	0	1	0
Oculogyric crisis	1	1*	0	1*
Lower extremity	1	1	0	0
Dysphonia				
Symptom distribution				
Focal	5	2	3	0
Segmental	3	0	3	0
Multifocal	4	2*	2	1*
Unspecified	2	0	2	0
Additional symptoms‡				
(Total)	(11)	(3)	(8)	(0)
Other neurologic	8	2	6	0
Psychiatric	4	1	3	0
Gastrointestinal	2	0	2	0
Pressured speech	1	0	1	0
Concomitant medication				
Yes	6	4*	2	1*
No	1	0	1	0
Not reported	7	0	7	0
Diagnostic evaluation‡				
(Total)	(4)	(2*)	(2)	(1*)
Laboratory	3	1*	2	1*
EEG	1	1*	0	1*
Cardiac evaluation	2	1	1	0
Brain imaging	1	0	1	0
Reported therapeutic intervention‡				
(Total)	(11)	(3)	(7)	(1)
Antihistamine	6	2*	4	1*
Benzodiazepine	3	1*	2	1*
Anticholinergic	2	0	2	0
Anticonvulsant	1	1*	0	1*
Steroids	1	0	1	0
Intravenous fluids	1	0	1	0

* A case reported a 15-year-old female with co-ingestion of Strattera and Adderall XR. The case is reflected in counts for amphetamine and atomoxetine columns.

‡ A case may report more than one dystonic symptom, other symptom, therapeutic intervention, or diagnostic evaluation.

Abbreviations: NOS=not otherwise specified, EEG=electroencephalogram

3.1.3 Representative FAERS Cases

We summarize representative cases reported with an ADHD amphetamine, methylphenidate, or atomoxetine product below.

FAERS Case #6606840, U.S.A., Expedited Report, 2008:
The case regards a 7-year-old male who began treatment with Vyvanse (lisdexamfetamine) 30mg per day for the treatment of ADHD. Concomitant medications included cetirizine for treatment of seasonal allergies and fluticasone propionate/salmeterol xinafoate for treatment of asthma. Sometime after his first dose of lisdexamfetamine, the child developed stiffness to bilateral arms, "mouth drawn to the side," back arching, dysphonia, and tics described as "hand clapping" and "licking lips." He also developed dizziness, agitation, and abnormal breathing. He presented to an emergency department (ED) where he received unspecified treatments prior to discharge home. All adverse events resolved and lisdexamfetamine was discontinued.

DPV Reviewer Comment: The patient developed reported symptoms despite taking the recommended starting dose of lisdexamfetamine. Of note, fluticasone propionate/salmeterol xinafoate is labeled for agitation, dysphonia, and muscle cramps and spasms in the ADVERSE REACTIONS section of the product labeling.[14,15] The narrative lacks information to rule out fluticasone propionate/salmeterol xinafoate contribution, therefore causality with lisdexamfetamine is possible.

FAERS Case #10283665, U.S.A., Direct Report, 2014:
The case regards a 4-year-old male who was prescribed Quillivant XR (methylphenidate) 25mg/5ml, 1ml (5mg) every morning for the treatment of ADHD. For his first dose, his mother administered 5ml (25mg). Approximately 5 hours later, the child developed "random arm movements, strange movements of mouth and tongue." The family contacted the primary care office who recommended diphenhydramine dosing and close observation after consultation with Poison Control. The child was evaluated in a primary care clinic 8 hours after ingestion. Physical exam was notable for diaphoresis, involuntary movements, and pressured and nonsensical speech. The treating physician consulted a toxicologist who recommended admission for observation of dystonic reaction. The child was admitted to the pediatric intensive care unit (PICU). Symptoms resolved about 5 hours after PICU admission and the child was discharged home.

DPV Reviewer Comment: The medication dosing error resulted in a Quillivant XR dose 4 times higher than prescribed. Of note, Quillivant XR is approved for patients aged 6 years and older[16] and use in this patient is considered off-label. The strength of the causal relationship between the adverse events and Quillivant XR lies in the tight temporal association in the absence of concomitant drug exposures or comorbidities to provide a plausible explanation for events; causality with Quillivant XR is probable.

FAERS Case #4047780, U.S.A., Direct Report, 2003:
The case describes a 15-year-old, 57.6 kg female who developed a dystonic reaction after accidental ingestion of Strattera (atomoxetine). The patient ingested atomoxetine 160mg after mistaking atomoxetine for headache medication. She had a history of ADHD for which she took

Adderall XR 20mg daily; she received the atomoxetine prescription but had not initiated therapy. Approximately 12 hours after ingestion, she developed hallucinations, jerking of extremities, and dystonic twitching of her face. She presented to an ED where she received diphenhydramine and lorazepam and was discharged home. At 36 hours post-ingestion, she developed mild myoclonic and dystonic movements of the extremities and intermittent diplopia. She had no seizure-like activity, change in mental status, or fever. She presented to an ED again and received diphenhydramine. At 48 hours post-ingestion, she had hallucinations and dystonic movements of her extremities. She was admitted to the hospital where she received diphenhydramine, valproic acid, and lorazepam. Diagnostic evaluation including an EEG, liver function tests, and renal tests were normal. All symptoms resolved and the patient was discharged home. Atomoxetine was discontinued.

DPV Reviewer Comment: The ingested dose of atomoxetine is over five times the recommended dose for this patient's weight.[17] The case does not report dosing of Adderall XR relative to atomoxetine exposure and does not report whether the patient continued Adderall XR therapy during the symptomatic period. However, the temporal association of the accidental and excessive dosage of atomoxetine suggests a probable causal association.

3.2 LITERATURE SEARCH RESULTS

3.2.1 DPV Literature Search Results

DPV performed a literature search for additional case reports of acute dystonia with ADHD stimulant medication or atomoxetine using the strategy delineated in **Table 4**. After applying the case selection criteria in Section 2.1, we identified no additional cases for inclusion in the case series.

3.2.2 DEPI Literature Search Results

The PubMed search for atomoxetine+dystonia yielded 3 publications, one of which was the study by Meyers et al.[18] first identified by DPV. The remaining articles did not meet inclusion criteria, being a case report[b] and a review article.

The PubMed search for methylphenidate+dystonia yielded 33 publications. A paper by Nutt et al.[19] provided descriptive epidemiology of dystonia and was the only publication that will be reviewed herein. Of the 32 excluded articles, 2 described nonclinical data, 13 were case reports,[b] 2 were not in English, 1 was a review article, and 14 were otherwise not relevant.

The PubMed search for amphetamine+dystonia yielded 62 publications, one of which was the aforementioned Meyers article. Of the 61 excluded articles, 23 described nonclinical data, 11 were case reports,[b] 2 were not in English, 5 were review articles, and 20 were otherwise not relevant.

The PubMed search for lisdexamfetamine+dystonia did not yield any publications.

[b] Case reports excluded in the DEPI literature search were captured in the DPV FAERS and literature search.

Finally, the PubMed search for stimulants+dystonia yielded 137 articles, including the aforementioned articles by Meyers et al.[18] and Nutt et al.[13] One other relevant article by Sharp and Perdue[20] described a cross-sectional study evaluating abnormal movements among children using stimulants, atypical antipsychotics, or both; this study will be reviewed herein. Of the remaining articles, 58 described nonclinical data, 21 were case reports,[b] 10 were not in English, 7 were review articles, and 38 were otherwise not relevant.

The three relevant articles identified from the PubMed search will be reviewed below.

1. Meyers et al.

- *Author, publication year and affiliation/funding*

All authors were employees of Eli Lilly and Company, based in the United States and Italy. The article was published in 2018.

- *Objective*

The objective of this study was to assess the risk of dystonia with atomoxetine and with stimulants, in children and adolescents.

- *Design*

This was a retrospective observational cohort study.

- *Methods*

The data source was the Truven Health Analytics MarketScan database, an employer-sponsored health insurance claims database. The study time period was from January 2006 to December 2014. Subjects were users of either atomoxetine or stimulants (methylphenidate and amphetamines) aged 6-17 years and had no prescriptions for additional ADHD treatments (study drugs, alpha-2 agonists or modafinil) during a six-month baseline period. Their first prescription for atomoxetine or a stimulant defined their index date. Subjects with dystonia during the baseline period (six months prior to index date) or enrollment discontinuities greater than 31 days were excluded. Follow-up began at the index date and continued until the subject had a dystonia diagnosis, the prescription ended (plus a 30-day extension), the subject switched treatment groups, or the subject had a lapse in enrollment exceeding 31 days. The outcome of dystonia was defined by the following International Classification of Diseases (ICD9) diagnoses: "acquired torsion dystonia (333.7), acute dystonia due to drugs (333.72), other acquired dystonia including idiopathic, non-familial dystonia (333.79), blepharospasm (333.81), spasmodic torticollis (333.83), organic writer's cramp (hand dystonia, 333.84) and other fragments of torsion dystonia (333.89)." Potential confounding was addressed by use of propensity score matching (1:1), with covariates reflecting demographic characteristics, psychiatric diagnoses, diagnoses of tics or Tourette's syndrome, medication use, and metrics of health care utilization. The risk of the outcome was evaluated with a Cox proportional hazards model that had terms for treatment, gender, age, and calendar year.

- *Results*

A total of 70,657 atomoxetine users and 849,843 stimulant users were eligible for the study; after propensity score matching there were 70,655 subjects in each treatment group, and all

covariates had standardized mean differences below 0.1. Sixty-five percent of the matched subjects were male and the mean age of the matched subjects was 11.6 years. Roughly 50% of matched subjects in both groups had a diagnosis of ADHD; the most common medications in the baseline period were antibiotics and antidepressants.

In the matched cohort, fifteen atomoxetine-treated subjects and 28 stimulant-treated subjects experienced dystonia during follow-up. The incidence of dystonia among atomoxetine-treated subjects was 55 (95% CI 27-83) per 100,000 person-years, and the incidence among stimulant-treated subjects was 78 (95% CI 49-107) per 100,000 person-years. The hazard ratio (HR) for dystonia, atomoxetine:stimulants, was 0.68 (95% CI: 0.36-1.28). In a sensitivity analysis that excluded patients on concomitant drugs thought to be associated with dystonia, the HR was 0.60 (95% CI: 0.23-1.59).

Please note that FDA had access to Lilly's internal documents regarding this study (i.e., protocol and study report). The published description of the study is consistent with Lilly's internal documents.

- *Strengths and limitations*

Strengths of this study include its use of a national database to provide a large sample (important in view of the rarity of the outcome) and use of propensity score matching to balance baseline characteristics between treatment groups. However, the study has important limitations. First, no information was available on the accuracy of the outcome definition (i.e., no information on sensitivity or positive predictive value of the selected ICD9 codes). The validity of an outcome of dystonia in claims data has not been evaluated by the Sentinel initiative.[21] A systematic review of the validity of claims data for neurological conditions found no studies addressing the validity of dystonia diagnoses,[22] so there appears to be little information about the validity of dystonia ICD codes.) The assessment of the risk of dystonia with atomoxetine was made only in relation to the risk with stimulants, so this study cannot exclude the possibility that both types of treatment increase dystonia. The outcome data were sparse and so the statistical precision of the HR (0.68; 95% CI 0.36-1.28) was somewhat limited, though quantitatively, with the upper bound of the confidence interval being 1.28, an increased risk of around 30% was excluded at the 95% confidence level.

- *Conclusions*

This study found no difference in the risk of dystonia among pediatric patients treated with atomoxetine versus stimulants.

DEPI Reviewer Comment: In view of the above-mentioned limitations, the inferential value of this result is limited, perhaps the most that could be said is that it is inconsistent with a very large difference in risk between the two treatments.

2. Sharp and Perdue

- *Author, publication year and affiliation/funding*

The authors were staff at the Carilion Clinic in Roanoke, Virginia. The article was published in 2007.

- *Objectives: primary & secondary*

The objective of this study was to assess abnormal movements among children treated with psychostimulants, atypical antipsychotics, both in combination, or neither.

- *Design*

This was a cross-sectional study of patients in treatment at the authors' clinic.

- *Methods:*

One of the authors administered a structured brief motor exam to randomly selected patients of their clinic, aged 5-14 years, who were being treated with either a stimulant, an atypical antipsychotic, or neither. Subjects had no history of movement disorders prior to beginning treatment at the clinic. The exam had 10 items and the range of possible scores was 0-30.

- *Results:*

Of the 24 children assessed, 5 were treated with a stimulant, 11 were treated with both a stimulant and an atypical antipsychotic, 5 were treated with an atypical antipsychotic, and 3 were treated with neither a stimulant nor an atypical antipsychotic. All had received their medication for at least a month. The mean movement abnormality rating score for those on both types of drugs was 6.1, the mean score with stimulants alone was 1, the mean score with atypical antipsychotics alone was 2, and children treated with neither scored 0. **Table 7** presents these results.

Table 7. Abnormal motor scores by treatment, Sharp et al.

Treatment	N	Mean Motor Exam Score
Stimulant	5	1
Atypical antipsychotic	5	2
Stimulant+atypical antipsychotic	11	6.1
Neither	3	0

- *Strengths and limitations*

Strengths of the study include random selection of subjects and systematic scoring of abnormal movements by a pediatrician. Limitations include possible lack of blinding to treatment by the rater, the small sample size, and the cross-sectional design which by studying only prevalent users could have missed cases of abnormal movements leading to early discontinuation of treatment.

- *Conclusions*

The authors concluded that their results suggest an interaction between stimulants and atypical antipsychotics resulting in a higher prevalence of abnormal movements in children receiving combined therapy.

DEPI Reviewer Comment: The authors' interpretation is reasonable. In view of the study limitations noted above, these results are probably best viewed as hypothesis-generating. Unfortunately, there do not appear to have been any larger or more systematically conducted studies of this association.

3. Nutt et al.

- *Author, publication year and affiliation/funding*

The authors were affiliated with the Mayo Clinic and Oregon Health Sciences University. Funding was from the Dystonia Foundation and the National Institutes of Health. The year of publication was 1988.

- *Objectives: primary & secondary*

The objective was to examine the epidemiology of dystonia (focal or generalized).

- *Design*

This was a descriptive, retrospective cohort study conducted by chart review.

- *Methods*

The data were obtained from the Mayo Clinic and the Rochester Epidemiology Project. The authors reviewed all charts with potential cases of dystonia (focal or generalized) in the Mayo Clinic system for the years 1950-1982. Diagnoses were arrived at by consensus, and classified as possible, probable, or definite, and charts were examined for the presence of hypothesized risk factors. Cases of tardive dyskinesia were excluded, as were cases of dystonia that had been present for less than 6 months. Incidence and prevalence in the community were calculated, though the article did not describe the methodology for these.

- *Results*

A total of 34 cases of dystonia were identified (31 focal and 3 generalized), yielding an incidence of 24 per million per year for focal dystonia and 2 per million per year for generalized dystonia. The prevalence of focal dystonia was estimated at 295 per million, and the prevalence of generalized dystonia was estimated at 34 per million. Most cases had an age at onset of adulthood. With respect to drug exposures, one patient with spasmodic dysphonia had used methylphenidate.

- *Strengths and limitations*

Strengths of the study include the fact that it was population-based in the Rochester, Minnesota community and included expert adjudication of cases. However, all diagnoses were adjudicated retrospectively without clinical examination. The requirement that the dystonia be of at least six month's duration may have eliminated some cases related to drug exposure.

- *Conclusions*

The incidence of focal plus generalized dystonia in this study was approximately 26 per million per year. Exposure to stimulants did not appear to be a significant risk factor among these cases (i.e., 1 out of 34).

DEPI Reviewer Comment: The observed incidence in this study (26 per million per year) was lower than the incidences reported from the MarketScan study by Meyers et al. (i.e., 55 and 78 per 100,000 person-years for atomoxetine and stimulants, respectively). However, the Mayo Clinic study adjudicated the diagnoses and did not consider diagnoses present less than 6

months. That, plus the fact that the Mayo Clinic study analyzed a smaller number of specific diagnoses over a broader age range, may account for the discrepancy. In addition, the positive predictive value of the claims-based outcome definition used in the MarketScan study is unknown, so some false positive diagnoses may have been included in that analysis.

4 DISCUSSION

This review evaluated adverse event reports and the medical literature for evidence of acute dystonia associated with exposure to ADHD stimulants or atomoxetine. Dystonia is an unlabeled adverse event for ADHD stimulants and atomoxetine. Previous OSE evaluations and the majority of published case reports evaluate dystonia with ADHD stimulants and atomoxetine in the context of drug interaction with antipsychotic medications. However, there are published reports of potential dystonia signals with methylphenidate and atomoxetine based on data from the World Health Organization (WHO) VigiBase[c] database.[23,24]

We identified 14 FAERS cases of acute dystonia associated with ADHD stimulants or atomoxetine. All 14 cases involved pediatric patients. This may reflect differential rates of ADHD recognition and therefore treatment in children versus adults.[25,26] Three cases described acute dystonia resulting from inappropriate ADHD medication dosage; two of these cases were a consequence of accidental ingestion and one case was the result of a medication error. Of note, the three cases of inappropriate ADHD medication dosage were the only cases in the series where causality was probable. Of the 14 cases in the series, 6 reported concomitant medication use. Of the six cases, four described concomitant medication labeled for muscle rigidity and spasticity in setting of drug withdrawal, muscle cramps and spasms, dyskinesia, or tardive dyskinesia. Two of the six cases specified concomitant medications were initiated at least 1 month prior to ADHD medication and the remaining four cases did not specify temporality of concomitant drug initiation to the reported adverse event. Within the case series, there was inconsistency in the level of details about dystonic symptoms, medical history, and clinical course to allow for vigorous assessment of events. Therefore, we could not rule out other hyperkinetic movement disorders or other risk factors with certainty in all cases.

On balance, the epidemiologic literature does not provide much information on the occurrence of dystonia with ADHD stimulant medications or atomoxetine. One recently published claims-based, observational retrospective cohort study suggests that the incidence of dystonia is similar with pediatric use of atomoxetine or stimulants, but did not determine an incidence in unexposed patients, so there could be a roughly equal risk for both treatments. Also, lack of information regarding the accuracy of the outcome definition in the claims-based study makes it difficult to interpret the incidence rates reported. A population-based study did not indicate that stimulant use was an important cause of dystonias in the population, and a cross-sectional study found that the combination of stimulants plus an atypical antipsychotic was associated with more abnormal motor movements but did not specifically study dystonias. However, because of the cross-sectional design of this study, those findings should be regarded as hypothesis-generating at best.

[c] VigiBase is the WHO global database of individual case safety reports.

5 CONCLUSION

We find insufficient evidence to support the postmarket safety signal of acute dystonia associated with ADHD stimulants or atomoxetine at this time. We identified a low number of cases in our FAERS case series. The totality of FAERS cases does not have the strength to support the association between acute dystonia and ADHD stimulants or atomoxetine. Information from the published epidemiologic literature on the risk of dystonia with ADHD drugs is limited, and by itself does not permit conclusions to be drawn.

6 RECOMMENDATIONS

OSE recommends continued pharmacovigilance of ADHD stimulant medications and atomoxetine. Based on this review, OSE does not have any labeling recommendations at this time.

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8 APPENDICES

8.1 APPENDIX A. MARKETED ADHD STIMULANT MEDICATIONS AND ATOMOXETINE

Drug Class	Generic Name	Proprietary Name	Application Number	Formulation	Initial Approval	Indication	ADHD Indicated Ages
Amphetamine Products	Amphetamine	Adzenys ER	NDA 204325	Extended release oral suspension	9/15/2017	ADHD	≥6 years
		Adzenys XR-ODT	NDA 204326	Extended release orally disintegrating tablet	1/27/2016	ADHD	≥6 years
		Dyanavel XR	NDA 208147	Extended release oral suspension	10/19/2015	ADHD	≥6 years
		Evekeo	ANDA 200166	Tablet	8/9/2012	Narcolepsy ADHD Exogenous Obesity	≥3 years
		Evekeo ODT	NDA 209905	Orally disintegrating tablet	1/30/2019	ADHD	6 years – 17years
	Mixed salts of a single-entity amphetamine product: dextroamphetamine saccharate/amphetamine aspartate monohydrate/dextroampheta-mine sulfate/amphetamine sulfate	Adderall	NDA 11522	Oral tablet	1/19/1960	ADHD Narcolepsy	≥3 years
		Adderall XR	NDA 21303	Capsule	10/11/2011	ADHD	≥6 years
	Mixed salts of a single-entity amphetamine product	Mydayis	NDA 022063	Extended release capsule	6/20/ 2017	ADHD	13 years – 17 years
	Dextroamphetamine	Dexedrine	NDA 17078	Sustained release capsule	8/2/1976	Narcolepsy ADHD	≥6 years
	Lisdexamfetamine	Vyvanse	NDA 21977	Capsule	2/23/2007	ADHD Severe Binge Eating Disorder (adults)	≥6 years
		Vyvanse	NDA 208510	Chewable tablet	1/28/2017	ADHD Moderate to Severe Binge Eating Disorder (adults)	≥6 years
	Methamphetamine	Desoxyn	NDA 005378	Oral tablet	12/13/1943	ADHD	≥6 years

Drug Class	Generic Name	Proprietary Name	Application Number	Formulation	Initial Approval	Indication	ADHD Indicated Ages
Methylphenidate Products	Dexmethylphenidate	Focalin	NDA 021278	Tablet	11/13/2001	ADHD	≥6 years
		Focalin XR	NDA 021802	Extended release capsule	5/26/2005	ADHD	≥6 years
	Methylphenidate	Adhansia XR	NDA 212038	Extended release capsule	2/27/2019	ADHD	≥6 years
		Aptensio XR	NDA 205831	Extended release capsule	4/17/2015	ADHD	≥6 years
		Concerta	NDA 021121	Extended release tablet	8/1/2000	ADHD	≥6 years
		Cotempla XR-ODT	NDA 205489	Extended release orally disintegrating tablet	6/19/2017	ADHD	6 years – 17 years
		Daytrana	NDA 21514	Transdermal system	4/6/2006	ADHD	6 years – 17 years
		Journay PM	NDA 209311	Extended release capsule	8/8/2018	ADHD	≥6 years
		Metadate CD	NDA 21259	Extended release capsule	4/3/2001	ADHD Narcolepsy	≥6 years
		Methylin	NDA 21419	Oral solution	12/19/2002	ADHD Narcolepsy	≥6 years
		Methylin	NDA 21475	Chewable tablet	4/15/2003	ADHD Narcolepsy	≥6 years
		Quillivant XR	NDA 202100	Extended release oral suspension	9/27/2012	ADHD	≥6 years
		Quillichew ER	NDA 207960	Extended release chewable tablet	12/4/2015	ADHD	≥6 years
		Ritalin	NDA 10187	Tablet	12/5/1955	ADHD Narcolepsy	≥6 years
		Ritalin LA	NDA 21284	Extended release	6/5/2002	ADHD	6 years – 12 years
		Ritalin SR	NDA 18029	Sustained release	3/30/1982	ADHD Narcolepsy	≥6 years
Selective Norepinephrine Reuptake Inhibitor	Atomoxetine	Strattera	NDA 21411	Capsule	11/26/2002	ADHD	≥6 years

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX C. FAERS LINE LISTING OF DYSTONIA AND ADHD STIMULANT MEDICATION OR ATOMOXETINE CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	7/26/2012	8683669	1	US-JNJFOC-20120709555	1.91667	Male	USA	OT
Duplicate of 1	9/5/2012	8683669	2	US-WATSON-2012-15254	1.91667	Male	USA	HO,OT
2	10/12/2016	12840017	3	US-PFIZER INC-2016473615	4	Male	USA	HO
3	7/2/2014	10283665	1		4	Male	USA	HO
4	4/30/2014	10143647	2	US-PFIZER INC-2014118042	5	Male	USA	
5	4/29/2015	11075906	1	IE-UCBSA-2015012861	6.001	Female	IRL	OT
6	4/11/2016	12252036	1	US-SHIRE-US201604255	6.20945	Female	USA	OT
7	7/17/2018	15154435	1	TR-NEOS THERAPEUTICS, LP-2018NEO00086	7	Female	TUR	OT
Duplicate of 7	7/9/2018	15121744	1	TR-BRECKENRIDGE PHARMACEUTICAL, INC.-2051581	7	Female	TUR	HO
Duplicate of 7	7/23/2018	15182704	1	TR-PURDUE PHARMA-CAN-2018-0008862	7	Female	TUR	OT
Duplicate of 7	12/3/2018	15680029	1	TR-SUN PHARMACEUTICAL INDUSTRIES LTD-2018R1-178713	7	Female	TUR	OT
8	3/25/2008	6606840	1	SPV1-2008-00545	7	Male	USA	OT
9	5/11/2012	8563547	1		7	Female	USA	RI,OT
10	9/24/2008	6769077	1	CA-JNJFOC-20080903262	8	Female	CAN	OT
11	6/23/2006	6071225	2	PL-JNJFOC-20060603543	9.57	Male	POL	OT
12	10/10/2016	12834299	1	GB-SHIRE-GB201613683	11	Male	GBR	HO,OT
13	11/3/2015	11695053	1	JP-JNJFOC-20151024560	13	Male	JPN	OT
14	12/19/2003	4047780	1		15	Female	USA	HO,RI
Duplicate of 14	1/30/2004	4086169	2	USA040156226	16	Female	USA	HO
Duplicate of 14	1/2/2004	4060630	3	USA031255042	15	Female	USA	HO

* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: HO=hospitalization, OT=other medically significant event, RI=required intervention

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