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Integrated Postmarket Safety Review

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Reviewers:	Mohamed A. Mohamoud PharmD, MPH, BCPS Dave Croteau MD, FRCPC Division of Pharmacovigilance I (DPV-I) Nilar Iorio, RPh Drug Utilization, Division of Epidemiology II (DEPI-II)
Team Leaders:	Carmen Cheng, PharmD DPV-I Corinne Woods, RPh, MPH DEPI-II
Division Directors:	Cindy Kortepeter, PharmD DPV-I Rajdeep Gill, PharmD Deputy Director for Drug Utilization (Acting) DEPI-II
Product Names:	ADHD Stimulants and Atomoxetine & Antipsychotics (see Appendices A and B)
Subject:	Drug-Drug Interaction: Acute Hyperkinetic Movement Disorder
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Applicants:	Multiple
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Special thanks to Dr. Ivone Kim for her high-level comments on this review

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EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) database and the medical literature for reports of acute hyperkinetic movement disorder associated with the combined use of Attention Deficit Hyperactivity Disorder (ADHD) stimulants (including methylphenidate products, amphetamine products, and atomoxetine) and antipsychotics [including first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA)]. For the purposes of this review, atomoxetine is included when referring to ADHD stimulants despite being a non-stimulant used to treat ADHD. In addition, this review includes U.S. drug utilization data describing concurrent use of ADHD stimulants (grouped into three distinct groups - namely methylphenidate products, amphetamine products, and atomoxetine) and antipsychotics (grouped into FGA and SGA), stratified by patient age, to provide context for the reported adverse events.

We identified 36 cases of acute hyperkinetic movement disorder associated with the concomitant use of ADHD stimulants and antipsychotics in FAERS and the medical literature. The majority of cases identified had features consistent with acute dystonic reactions (n=26) and a few cases had features of withdrawal emergent dyskinesias (n=7) or mixed movement disorders (n=3). From an ADHD stimulant perspective, most of the cases were reported with methylphenidate products (n=23), followed by amphetamine products (n=9), and atomoxetine (n=4). From an antipsychotic perspective, the cases identified were reported with SGAs (n=36) and no cases were reported with FGAs. Using our causality assessment criteria, we determined the drug-event causal association as probable in 11 cases and possible in 25 cases. It is notable that 33 reports were considered unassessable because of limited information, particularly on latency and exact DDI permutations, and therefore might represent potential additional cases. Based on outpatient dispensed prescriptions data analysis, the number of patients with concurrent ADHD stimulant and SGA or FGA prescriptions increased from 2015 to 2018. Lower rates of concurrency were observed between ADHD stimulant and FGA (~1%) compared to SGA (~10%).

Clinicians should be aware that the combination of ADHD stimulants and antipsychotics may increase the risk of acute hyperkinetic movement disorder, particularly acute dystonic reactions, in susceptible individuals; any permutation of addition, withdrawal, dose changes, or switch involving antipsychotics or ADHD stimulants in this setting has the potential of resulting in an acute hyperkinetic movement disorder. If the acute hyperkinetic movement disorder does not respond to anticholinergic therapy, reintroducing the patient's previous regimen may treat the adverse event as reported in our case series; this may be suggestive of a movement disorder akin to withdrawal emergent dyskinesia. To mitigate the risk of this complex dopaminergic pharmacodynamic DDI interaction between ADHD stimulants and SGAs, a slower taper or dose titration prior to the discontinuation or initiation of either agent or the initiation of a washout period when switching agents may be warranted. Counseling parents and caregivers about this risk is prudent because most of the cases occurred in children and adolescents.

Based on this review, OSE recommends the following:

- Update the Drug Interaction section for methylphenidate products, amphetamine products risperidone and aripiprazole with this pharmacodynamic drug interaction between ADHD stimulants and antipsychotics (i.e., risperidone and aripiprazole).
- No labeling changes are recommended for atomoxetine or the other antipsychotics

1 INTRODUCTION

This review evaluates the FDA Adverse Event Reporting System (FAERS) database and the literature for reports of acute hyperkinetic movement disorder associated with the combined use of Attention Deficit Hyperactivity Disorder (ADHD) stimulants (including methylphenidate products, amphetamine products, and atomoxetine) and antipsychotics [including first-generation antipsychotics (FGA) and second-generation antipsychotics (SGA)]. For the purposes of this review, atomoxetine is included when referring to ADHD stimulants despite being a non-stimulant used to treat ADHD.

During a Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review of all amphetamine products, including Adzenys ER (amphetamine extended-release) and Mydayis (mixed salts of a single-entity amphetamine product), the Division of Pharmacovigilance I (DPV-I) identified a literature case describing a potential drug-drug interaction (DDI) between dextroamphetamine-racemic and aripiprazole. The case described a 7-year-old boy with a history of ADHD who developed acute cervical dystonia after the withdrawal of dextroamphetamine-racemic while on aripiprazole.[1] The reintroduction of dextroamphetamine-racemic resulted in the resolution of the dystonic episode. Considering the biologic plausibility of this potential drug-drug interaction between ADHD stimulants and antipsychotics, given their effects on dopamine in the synaptic cleft, DPV-I initiated this review to determine if regulatory action is warranted.

In addition, this review includes U.S. drug utilization data describing concurrent use of ADHD stimulants (grouped into three distinct groups - namely methylphenidate products, amphetamine products, and atomoxetine) and antipsychotics (grouped into FGA and SGA), stratified by patient age, to provide context for the reported adverse events.

1.1 BACKGROUND

ADHD stimulants and antipsychotics are coadministered in conditions that are frequently reported as comorbid with ADHD namely bipolar, conduct, and Tourette's disorders.[2,3] Current guidelines and consensus statements recommend the combined use of ADHD stimulants and antipsychotics in the treatment of ADHD and comorbid disruptive behavioral disorders (DBD).[2,4] The combination of ADHD stimulants and antipsychotics is considered a third-line treatment reserved for patients with inadequate response to maximal doses of ADHD stimulants in combination with social behavioral therapy. This recommendation is primarily based on the efficacy of SGA as monotherapy in the treatment of aggression in children.[2,4]

ADHD stimulants are thought to work by increasing dopamine and norepinephrine at the synapse, while antipsychotics block the effect of dopamine at dopamine receptors.[5,6] Despite seemingly opposing mechanisms, the therapeutic benefit of combined ADHD stimulants and antipsychotics use has been rationalized by suggesting that they likely interact with different receptor subtypes (i.e., D1 vs. D2) and in different pathways of the brain (i.e., mesocortical vs. mesolimbic). However, a more complex dopamine transmission model may provide a better explanation.[7] During rest periods, neurons release dopamine into the synapse at a steady rate, maintaining dopamine at a certain tonic level. Stimuli that trigger neuron depolarization cause

larger amounts of dopamine to be released through phasic dopamine bursts. These bursts are thought to be the main activating force at postsynaptic receptors. By negative feedback mechanisms at presynaptic dopamine auto-receptors, a low tonic dopamine level during neuron rest periods leads to larger burst responses in response to neuron depolarization, and vice versa. Based on this complex dopamine transmission model, ADHD stimulants and antipsychotics would both result in increased tonic dopamine levels and decreased burst responses. Increased burst responses have been hypothesized to be one possible therapeutic mechanism in ADHD.[7] In fact, the main difference between the two classes may be that while ADHD stimulants cause postsynaptic dopamine receptor downregulation over time, antipsychotics cause upregulation. Interestingly, these opposite effects may cancel each other out if both medications are combined, decreasing risks of tolerance and adverse effects due to each drug class.[7] Therefore, any permutation of addition, withdrawal, dose change, or switch involving antipsychotics or ADHD stimulants has the potential of resulting in a relative hyperdopaminergic state leading to acute hyperkinetic movement disorders with the concurrent use of both medications.[7]

1.2 DRUG-INDUCED MOVEMENT DISORDERS

Drug-induced movement disorders (DIMDs) can be classified according to (1) their temporal profile (acute and occurring within hours to days after exposure; subacute and building up more slowly after days to weeks of exposure; and chronic following long-term therapy with the offending medication), (2) their phenomenology (e.g., dystonia, akathisia, parkinsonism, choreoathetosis), and (3) the pharmacological agent likely involved (e.g., FGA and SGA and other dopamine receptor blockers, antidepressants, anti-epileptics, and many others, including recreational drugs and toxic agents).[8] In general, DIMDs are treatable and tend to respond to discontinuation of the offending agent with the exception of tardive syndromes. Mechanisms underlying DIMDs involve blockade, facilitation or imbalance of dopamine, serotonin, noradrenaline and cholinergic neurotransmission in the basal ganglia. While DIMDs associated with antipsychotics are well characterized and may be either hyperkinetic (acute dystonic reactions, withdrawal emergent dyskinesia, akathisia, tardive dyskinesia) or hypokinetic (parkinsonism, neuroleptic malignant syndrome), DIMDs associated with ADHD stimulants are less well characterized but are typically hyperkinetic, tics being well recognized. Acute dystonic reactions, paroxysmal kinesigenic dystonia, chorea, and myoclonus have also been reported with ADHD stimulants.[9-11] Withdrawal emergent dyskinesias have not been reported with ADHD stimulants and are not labeled for SGAs but have the potential to occur with combined use of those products. Because acute dystonic reactions are observed with both antipsychotics and ADHD stimulants, it is the most likely DIMD to occur as a result of an ADHD stimulant and antipsychotic DDI, a combination of drugs often concurrently used in pediatric psychiatry.[2,4] Additionally, risk factors for acute dystonic reactions include younger age and male gender among others.[12,13] The pharmacological mechanism underlying acute dystonic reactions remains poorly understood but may entail a dopaminergic/cholinergic imbalance in the basal ganglia circuits or differential blockade of presynaptic and postsynaptic D2 receptors, which are short and long D2 isoforms respectively.[14,15]

1.3 HISTORY OF NEWLY IDENTIFIED SAFETY SIGNAL (NISS)

(b) (4)

1.4 REGULATORY HISTORY

Appendix A presents all currently approved antipsychotics, their New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) numbers with FDA approval dates. Notably, five SGA agents currently have FDA approved indications in children and adolescents: risperidone, aripiprazole, olanzapine, paliperidone and quetiapine. **Appendix B** presents all currently approved ADHD stimulants, their NDA numbers with FDA approval dates. ADHD stimulants are FDA approved for the treatment of ADHD, narcolepsy, and exogenous obesity (a body mass index (BMI) at or above the 95th percentile for children of the same age and sex in pediatric patients. However, not all of the ADHD stimulants in this drug class are approved for each indication. Most ADHD stimulants are approved in patients 6 years of age and older. Notably, mixed salts of a single-entity amphetamine tablet (Adderall), amphetamine sulfate tablet (Evekeo), and dextroamphetamine sulfate tablet and solution are the three products approved for the treatment of ADHD in patients 3 years of age and older.

1.5 RELEVANT PRODUCT LABELING

The potential DDI between ADHD stimulants and antipsychotics is not currently labeled in the prescribing information of ADHD stimulants, FGAs, or SGAs.

Relevant product labeling for acute hyperkinetic movement disorders are presented below.

1.5.1 FGAs and SGAs

All FGAs and SGAs are labeled for dystonia. An example of the risperidone prescribing information is shown below.[3]

> **ADVERSE REACTIONS**
>
> *Dystonia*
>
> *Class Effect*: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups

All FGAs are additionally labeled for withdrawal emergent dyskinesia. SGAs are not labeled for withdrawal emergent dyskinesia. An example of the haloperidol prescribing information is shown below.[17]

> **WARNINGS & PRECAUTIONS**
>
> **Withdrawal Emergent Dyskinesia**
>
> Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from tardive dyskinesia (see WARNINGS, Tardive Dyskinesia) except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of HALDOL.

1.5.2 ADHD Stimulants

ADHD stimulants are labeled for dyskinesia, tremor, and tics. Atomoxetine is labeled for tics but not dyskinesia in the POSTMARKETING EXPERIENCE section. An example of the mixed salts of a single-entity amphetamine product prescribing information is shown below.[18]

> **ADVERSE REACTIONS**
>
> **Central Nervous System**
>
> Psychotic episodes at recommended doses, overstimulation, restlessness, irritability, euphoria, **dyskinesia,** dysphoria, depression, **tremor**, **tics**, aggression, anger, logorrhea, dermatillomania.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

Acute hyperkinetic movement disorder
Inclusion Criteria

Category 1: Reports with diagnosis of an acute* dystonic reaction/acute dystonia or acute* dyskinesia (e.g., chorea, choreoathetosis, ballism) by a healthcare professional were included in our case series.

Category 2: In the absence of a diagnosis by a healthcare professional, reports were included if they described acute* onset involuntary sustained muscle contractions or involuntary movements of the face, neck, trunk or extremities. Cases were also considered for inclusion if the patient was treated with benztropine, diphenhydramine or a benzodiazepine for the involuntary muscle contractions or involuntary movements

**Acute refers to the onset and progression of the symptoms or signs over a period of minutes to hours. It does NOT relate to the latency between antipsychotic/ADHD stimulant change and the hyperkinetic movement disorder onset which is addressed in causal association assessment.*

Exclusion Criteria
Reports were excluded for the following reasons:

- Patients with a family history of dystonia or diagnosis of primary dystonia
- Patients with late onset or hyperkinetic movement disorder consistent with tardive dyskinesia
- Non-specific movement abnormality (e.g., muscle twitching, muscle tightness, musculoskeletal stiffness, extrapyramidal disorder)
- Non-specific movement abnormality (e.g., muscle twitching, muscle tightness, musculoskeletal stiffness, extrapyramidal disorder)
- Other isolated hyperkinetic movement disorder (e.g., tics, akathisia, myoclonus)

Movement disorders were classified as acute dystonic reactions, withdrawal emergent dyskinesias, and mixed movement disorders/unclassifiable based on clinical features and response to anticholinergics.

2.2 DRUG-DRUG INTERACTION PERMUTATIONS

The potential DDI was classified using the permutations outlined in **Table 1**. This DDI is complex because the acute hyperkinetic movement disorders may potentially result from multiple permutations. The proposed mechanistic hypothesis entails a relative hyperdopaminergic state that can result from any of the permutations outlined in **Table 1**. Therefore, the antipsychotic and the ADHD stimulant can be the object drug (i.e., the drug that is affected by the precipitant drug) or the precipitant drug (i.e., the drug that causes the change to the object drug) and no such distinction was attempted beyond the classification presented in **Table 1**.

Table 1. DDI Permutations		
Antipsychotics		**ADHD Stimulants**
Scenario 1	Stable dose	Introduction or dose increment
Scenario 2	Stable dose	Withdrawal or dose reduction
Scenario 3	Introduction or dose increment	Stable dose
Scenario 4	Withdrawal or dose reduction	Stable dose
Scenario 5	Switched to*	Switched from*
Scenario 6	Switched from*	Switched to*
*Regardless whether there is an overlapping/concurrent administration, or titrations/taper of either drug ADHD=Attention Deficit Hyperactivity Disorder, DDI=drug-drug interaction		

2.3 CAUSALITY ASSESSMENT CRITERIA

We assessed all cases meeting the case definition for acute hyperkinetic movement disorder for a causal association with ADHD stimulant/antipsychotic DDI using elements from the Guidance for Industry: Good Pharmacovigilance Practice and Pharmacoepidemiologic Assessment.[19] We categorized the cases as probable, possible, unlikely, or unassessable based on the strength of the evidence for a causal association as described in **Table 2**. We excluded cases that we assessed as unlikely or unassessable from further analysis.

Table 2. Causal Association Categories and Assessment Criteria	
Category	**Assessment Criteria**
Probable	• Event with plausible temporal sequence to drug change (i.e., within 24 hours of drug changes outlined in **Table 1**) • Absence of factors with a potential contributory or confounding role; may have factors with an incidental role • Information regarding response to dechallenge, rechallenge, drug reintroduction, or repeat drug withdrawal is not required
Possible	• Event with reasonable yet less plausible temporal sequence to drug intake (i.e., 24 hours to one week after drug changes outlined in **Table 1**) • Presence of factors with a contributory role
Unlikely	• Event with improbable temporal sequence to drug intake • Presence of factors with a confounding role
Unassessable	• Causality cannot be assessed because information is insufficient or contradictory • More than one drug change performed shortly before the event (depending upon time on stable dose and latency of movement disorder), excluding drug class switches

We adapted the following definitions from Antoniri and colleagues[20] to assess causal association when other factors with a potential role were present:

- Incidental role of factors other than the suspect drug: having no or an insignificant effect on the adverse event reported and on the assessment of the causal role of the suspect drug
- Contributory role of factors other than the suspect drug: having some potential effect on the adverse event reported while allowing the assessment of the causal role of the suspect drug
- Confounding role of factors other than the suspect drug: having a potentially significant effect on the adverse event reported precluding the assessment of the causal role of the suspect drug

2.4 FAERS SEARCH STRATEGY

DPV-I 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	FBIS Drug Interactions Quick Query
Product terms	Includes reports listing either product groups as suspect only Group 1 Product List – MM Antipsychotics† Group 2 Product List – MM Stimulants†
MedDRA search terms (Version 22.0)	PTs: *Dyskinesia; Dystonia; Trismus; Choreoathetosis; Torticollis; Oculogyric crisis; Protrusion tongue; Oromandibular dystonia; Chorea; Opisthotonus; Grimacing; Spasmodic dysphonia; Buccoglossal syndrome; Pharyngeal dyskinesia; Athetosis; Dystonic tremor; Ballismus; Facial spasm; Laryngospasm; Muscle contractions involuntary; Oropharyngeal spasm; Posturing; Risus sardonicus; Tongue spasm; Uvular spasm*
Outcome	Serious‡

* See **Appendix C** for a description of the FAERS database.
† See **Appendix D** for a complete list of product terms used in the search.
‡ The following outcomes qualify as serious: death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events
FBIS: FAERS Business Intelligence System; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term

2.5 LITERATURE SEARCH

DPV-I searched the medical literature with the strategy described in **Table 4.**

Table 4. Literature Search Strategy	
Date of search	January 13, 2020
Database	PubMed (National Library of Medicine, Bethesda, MD), Embase (Reed Elsevier PLC, Amsterdam, Netherlands)

Table 4. Literature Search Strategy	
Search terms	**PubMed**: All antipsychotics OR ADHD stimulants AND "extrapyramidal[ti] OR "movement disorder" OR dyskinesia[ti] OR dyston* OR "oculogyric crisis" OR torticollis OR opisthotonos OR trismus OR laryngospasm OR interaction **Embase**: All antipsychotics OR ADHD stimulants AND ('movement disorder':ti OR extrapyramidal:ti OR dyskinesia:ti OR dystonia:ti OR dystonic:ti OR 'oculogyric crisis':ti OR torticollis:ti OR opisthotonos:ti OR trismus:ti OR laryngospasm:ti OR interaction:ti)
Years included in search	All years
Limits	English, Humans

2.6 DRUG UTILIZATION

2.6.1 Methods and Materials

Proprietary drug utilization databases available to the Agency were used to conduct these concurrency analyses. Detailed descriptions and limitations of the databases are included in **Appendix C**.

2.6.2 Molecules Included

Table 5. Molecules Included in Drug Utilization Analyses

ADHD Stimulants*

- Amphetamine products
  - Single-entity amphetamine
  - Mixed salts of single-entity amphetamine
  - Dextroamphetamine/Amphetamine
  - Dextroamphetamine
  - Lisdexamfetamine
  - Methamphetamine
- Methylphenidate products
  - Methylphenidate
  - Dexmethylphenidate
- Selective norepinephrine reuptake inhibitor†
  - Atomoxetine

SGAs*	FGAs*
▪ Aripiprazole ▪ Asenapine ▪ Brexiprazole ▪ Cariprazine ▪ Clozapine ▪ Iloperidone ▪ Lurasidone ▪ Olanzapine ▪ Paliperidone ▪ Pimavanserin ▪ Quetiapine ▪ Risperidone ▪ Ziprasidone	▪ Chlorpromazine ▪ Fluphenazine ▪ Haloperidol ▪ Loxapine ▪ Molindone ▪ Perphenazine ▪ Prochlorperazine ▪ Pimozide ▪ Thiothixene ▪ Thioridazine ▪ Trifluoperazine

*Only oral and transdermal formulations of ADHD stimulant products and oral formulations of antipsychotic products were included. Combination products were NOT included.
†For the purposes of this analysis, atomoxetine was included in the "ADHD stimulants" category, despite its pharmacologic action as a selective norepinephrine reuptake inhibitor and not a stimulant.
ADHD=Attention Deficit Hyperactivity Disorder, FGA=first-generation antipsychotic, SGA=second-generation antipsychotic

2.6.3 Data Sources Used and Methodology

The IQVIA National Sales Perspectives™ (NSP) database was used to estimate manufacturer sales to various U.S. channels of distribution (retail, non-retail, and mail-order/specialty pharmacy settings) for ADHD stimulant and antipsychotic medications in 2018.

The Symphony Health Integrated Dataverse® (IDV) database was used to obtain the estimated number of patients with U.S. outpatient retail prescription claims for ADHD stimulants and antipsychotics, alone or concurrently, stratified by patient age (0-5, 6-11, 12-17, 18-64, 65 years and older), from 2015 through 2018, annually. Claims with any payment method were included: commercial health care insurance, Medicare, Medicaid, and out-of-pocket payment ("cash" payment).

Patient selection was based on the presence of a prescription claim using the national drug codes (NDCs) for ADHD stimulant and antipsychotic products. Episodes of therapy were determined using claims' days' supplies as submitted by the dispensing pharmacies. In general, pharmacies calculate days' supply by dividing the total number of tablets or capsules dispensed by the number of tablets or capsules prescribed per day. We defined continuous therapy by stringing claims together with a grace period of 50% the number of days' supply in the previous claim to allow for minor delays in prescription refilling. For example, if the total days' supply for a prescription claim was 30 days, a grace period of 50% of 30 days would allow for a subsequent claim within 15 days from the end of the previous claim to establish a patient's continuing therapy.

An episode of concurrency was identified when an episode in the base group, stimulants, overlapped with an episode in the concurrent group, antipsychotics. Patients who had an episode with overlapping day's supply of at least 1 day from both the base group and the concurrent group during a calendar year were identified as having concurrency for that year. Our analysis did not distinguish between patients having one versus multiple concurrent episodes during a calendar year and did not capture the indication of use for these instances of concurrency.

3 RESULTS

3.1 FAERS AND LITERATURE CASE SELECTION

The FAERS and literature search retrieved 270 reports. After accounting for duplicate reports and applying the case definition in Section 2.1 and causal assessment in section 2.3, 36 cases were included in the case series of acute hyperkinetic movements disorder reported with the concomitant use of ADHD stimulant and antipsychotic (see **Figure 1**).

Figure 1. FAERS and Literature Case Selection

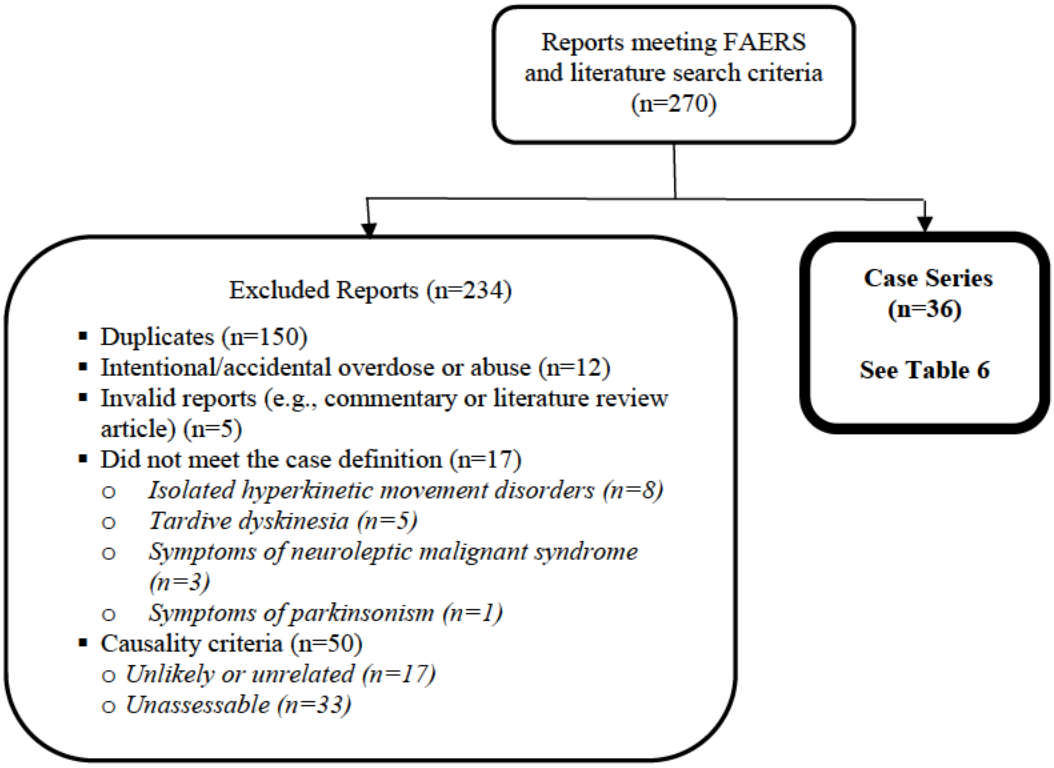


Table 6 summarizes the 36 cases of acute hyperkinetic movement disorder reported with a potential DDI between ADHD stimulants and antipsychotics. See **Appendix E** for the FAERS line listing of cases included in our case series. See **Appendix F** for the clinical details of each individual case listed in the FAERS line listing.

Table 6. Descriptive Characteristics of Cases Reporting a DDI Between ADHD Stimulants and Antipsychotics in FAERS and the Medical Literature Received by FDA Through December 6, 2019 or Published by January 13, 2020 (n=36)

Selected Characteristics	Methylphenidate products (n=23)	Amphetamine products (n=9)	Atomoxetine (n=4)
Age (years)			
0-5	2	-	-
6-12	19	7	1
13-17	2	-	3
18-65	-	2	-
Sex			
Male	21	7	3
Female	2	2	1
Country of reporter			
USA	15	5	2
Foreign	8	4	2
Time-to-onset			

Table 6. Descriptive Characteristics of Cases Reporting a DDI Between ADHD Stimulants and Antipsychotics in FAERS and the Medical Literature Received by FDA Through December 6, 2019 or Published by January 13, 2020 (n=36)			
Selected Characteristics	**Methylphenidate products (n=23)**	**Amphetamine products (n=9)**	**Atomoxetine (n=4)**
Within 24 hours of drug change	12	6	1
More than 24 hours to 7 days of drug change	11	3	3
Hyperkinetic movement disorder			
Acute dystonic reaction features	15	7	4
Withdrawal emergent dyskinesia features	6	1	-
Mixed movement disorder features/unclassifiable	2	1	-
Year received/published			
2001-2005	5	1	2
2006-2010	11	4	-
2011-2015	3	1	-
2016-2020	4	3	2
Antipsychotic product	Risperidone (15) Aripiprazole (6) Olanzapine (1) Paliperidone (1)	Risperidone (4) Aripiprazole (3) Quetiapine (1) Ziprasidone (1)	Aripiprazole (2) Risperidone (1) Olanzapine (1)
Antipsychotic total daily dose (range), mg	(n=21) Risperidone (0.5-4.5) Aripiprazole (2-30) Olanzapine (7.5) Paliperidone (3)	(n=8) Risperidone (0.25-4) Aripiprazole (2-5) Ziprasidone (40)	(n=2) Aripiprazole (5)
DDI permutation*	Scenario 1 (3) Scenario 2 (7) Scenario 3 (7) Scenario 4 (2) Scenario 5 (2) Scenario 6 (2)	Scenario 1 (1) Scenario 2 (3) Scenario 3 (2) Scenario 5 (2) Scenario 6 (1)	Scenario 1 (2) Scenario 5 (2)
Treatment of adverse event†			
Treatment with anticholinergic/benzodiazepine	11	2	3

Table 6. Descriptive Characteristics of Cases Reporting a DDI Between ADHD Stimulants and Antipsychotics in FAERS and the Medical Literature Received by FDA Through December 6, 2019 or Published by January 13, 2020 (n=36)			
Selected Characteristics	**Methylphenidate products (n=23)**	**Amphetamine products (n=9)**	**Atomoxetine (n=4)**
ADHD stimulant and/or antipsychotic withdrawal or dose reduction	12	4	1
ADHD stimulant and/or antipsychotic introduction or dose increment	5	3	-
Not reported	2	2	1
Relevant concomitant medications[†]	(n=12) Clonidine (5) Valproic acid (3) Carbamazepine (1) Oxcarbazepine (1) Clobazam (1) Guanfacine (1) Sertraline (1) Fluvoxamine (1) Lithium (1)	(n=2) Clonidine (1) Valproic acid (1) Sertraline (1)	(n=2) Valproic acid (1) Citalopram (1)
Causality Assessment			
Probable	8	2	1
Possible	15	7	3
Serious outcome[†,‡]			
Hospitalization	11	3	4
Disability	1	-	-
Other serious	12	7	1

[*]Refer to **Table 1** for the DDI permutation scenarios
[†]More than one treatment of adverse event, concomitant medication, or serious outcome may have been reported per case
[‡]For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.
DDI= drug-drug interaction

3.2 REPRESENTATIVE CASES

Below is a summary of representative cases describing the potential DDI between ADHD stimulants and antipsychotics. We selected these three cases to highlight the different ADHD stimulants involved and the two SGAs most frequently reported in association with this DDI.

3.2.1 Methylphenidate and Aripiprazole DDI

FAERS #7269879, Version 1,US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2010-DE-00374GD, 2010, USA, Expedited
A physician reported an 11-year-old child developed an acute dystonic reaction 33 hours after the discontinuation of osmotic-release oral system (OROS) methylphenidate while concomitantly on aripiprazole. The patient's past medical history was significant for ADHD and bipolar affective disorder. He was admitted to a child psychiatry inpatient unit because of increased emotional lability with physically aggressive behavior toward others and self-injurious behavior. Upon admission, the patient was taking aripiprazole 15 mg twice daily, OROS methylphenidate 108 mg daily for 4 years, lithium carbonate 600 mg every morning and 300 mg every night, and "nightly" clonidine at 0.2 mg twice daily. The patient had been treated with aripiprazole for 2 years and OROS methylphenidate for 4 years; neither medication had been increased in the previous 6 months. In attempt to simplify his medication regimen OROS methylphenidate was discontinued and the patient developed spasmodic muscular contraction of his jaw and difficulty opening his mouth. The patient was treated with intramuscular diphenhydramine 50 mg and within 30 minutes the patient had complete resolution of the dystonia. The patient disclosed that this adverse event occurred occasionally whenever he forgot to take his OROS methylphenidate.

Reviewer comments: This case describes the development of an oromandibular acute dystonic reaction in a child shortly after the discontinuation of OROS methylphenidate while on a stable dose of aripiprazole with no medication changes in the last 6 months (scenario 2). The causal association was assessed as probable due to the close temporal association, the absence of factors with a potential contributory or confounding role, and the adverse event occurring previously when the patient missed an OROS methylphenidate dose.

3.2.2 Dextroamphetamine and Risperidone DDI

FAERS #6588851, Version 1, B0510370A, 2008, Canada, Expedited
A physician reported an 18-year-old Caucasian male developed torticollis 1 day after the abrupt discontinuation of dextroamphetamine 10 mg while on risperidone 4 mg. The patients' past medical history was significant for ADHD and borderline intellectual functioning. His medications included dextroamphetamine 10 mg once daily. He had been taking dextroamphetamine for several years when he experienced deterioration of his level of functioning, social withdrawal, and episodes of unprovoked violent behavior. After an episode of unprovoked violent behavior his mother brought him to the emergency room, and he was admitted to the psychiatry unit. He did not use illicit substances or alcohol. He was diagnosed with psychosis with a suspected diagnosis of prodromal schizophrenia. He was initiated on risperidone 2 mg, which was titrated to 4 mg over 6 days. Two days later, his dextroamphetamine was abruptly discontinued. The next day, he developed torticollis which was relieved by 2 mg of intramuscular benztropine. He was then placed on 1 mg of oral benztropine twice daily, which was weaned over 10 days. After the discontinuation of benztropine he did not have a recurrence of dystonia. The dose of risperidone remained at 4 mg daily and his affect improved.

Reviewer comments: This case describes the development of a cervical acute dystonic reaction in an 18-year-old male shortly after the discontinuation of dextroamphetamine 10 mg while on a stable dose of risperidone for two days (scenario 2). The causal association was assessed as probable due to the close temporal association, and the absence of factors with a contributory or confounding role.

3.2.3 Atomoxetine and Aripiprazole DDI

FAERS #12395574, Version 1, TR-ELI_LILLY_AND_COMPANY-TR201605006892, 2016, Turkey, Expedited

A physician reported a 13-year old female developed difficulty swallowing and contraction around her mouth hours after she was switched from atomoxetine 80 mg to aripiprazole 5 mg. Her past medical history was significant for ADHD and a mild intellectual disability. The patient had no significant personal or family history of head trauma, acute/chronic diseases, or susceptibility to intoxication. She was prescribed atomoxetine to treat her ADHD symptoms. She was seen in the clinic with complaints of increased sexual desire, excessive talking, and poor sleep patterns. Due to the hypomanic symptoms atomoxetine was switched to aripiprazole 5 mg. Sixteen hours after the discontinuation of atomoxetine and five hours after the first dose of aripiprazole, she was referred to the emergency room due to difficulty swallowing and contraction around her mouth. Her neurological exam revealed facial asymmetry and reduced speech intelligibility. Routine laboratory assessment and cranial tomography were normal. She was diagnosed with aripiprazole induced acute dystonic reaction, and she was administered intramuscular biperiden 5 mg for treatment. The patient's symptoms resolved within minutes of treatment, and she was discharged with a prescription for oral biperiden (4 mg daily). During a follow-up visit 3 days after discharge, her physical and neurological exams were normal. The patient began risperidone treatment without recurrence of the acute dystonic reaction.

Reviewer comments: This case describes the development of an oropharyngeal acute dystonic reaction in 13-year-old female shortly after the discontinuation of atomoxetine 80 mg and the initiation of aripiprazole 5 mg (scenario 5). The causal association was assessed as probable due to the close temporal association, and the absence of factors with a contributory or confounding role. Atomoxetine is a selective inhibitor of the noradrenaline transporter and weak inhibitor of the dopamine transporter. Aripiprazole 5 mg has a low risk for developing acute dystonic reactions due to its partial agonist activity. The combination of abrupt cessation of atomoxetine and the immediate initiation of aripiprazole in this milieu is likely a causal factor in this adverse event.

3.3 DRUG UTILIZATION

3.3.1 Settings of Care – Manufacturer Sales Data

In 2018, the estimates of manufacturer sales of ADHD stimulants indicated that approximately 92% of manufacturer sales were distributed to the outpatient retail pharmacy setting, 6% to the non-retail pharmacy setting (including hospitals, clinics, long-term care, home health, and others), and 2% to the mail-order/specialty pharmacy setting. In 2018, approximately 71% of

oral antipsychotics total sales were distributed to the outpatient retail pharmacy, 25% to non-retail settings, and 4% to mail-order/specialty pharmacies.[a] We focused our analysis on the outpatient retail pharmacy setting. Data from non-retail setting were not included in this review.

3.3.2 Patient Data

Tables A and **B** in **Appendix G** display the estimated number of patients with a U.S. outpatient retail pharmacy prescription for an ADHD stimulant or an antipsychotic from 2015 through 2018, annually. The number of patients with ADHD stimulant prescriptions increased by approximately 10% (approximately 9.9 million to 10.9 million from 2015 to 2018). The number of patients with SGA or FGA prescriptions during the study period increased by approximately 34% (approximately 7.1 million to 9.6 million) and 18% (approximately 2.0 million to 2.4 million), respectively.

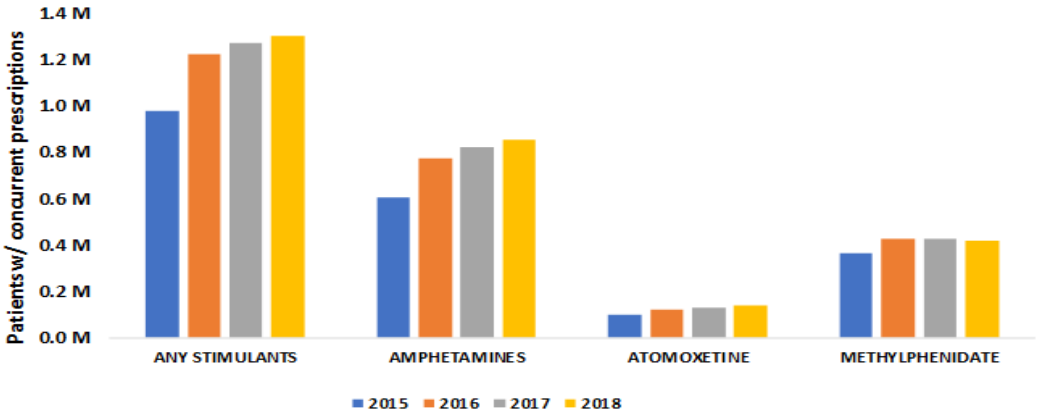
3.3.3 Concurrency Analysis: ADHD Stimulants with SGAs

Table A in **Appendix G** displays the estimated number of patients with concurrent prescription claims for stimulants with *SGAs* from U.S. retail pharmacies, 2015 through 2018, annually. During the study period, the number of patients with concurrent ADHD stimulant and *SGA* prescriptions increased by approximately 33% from around 1.0 million in 2015 to 1.3 million in 2018. In 2018, out of 10.9 million patients with ADHD stimulant prescriptions, approximately 12% had at least one concurrent *SGA* prescription, an increase from 10% in 2015. In 2018, out of 9.6 million patients with *SGA* claims, 14% had at least one concurrent ADHD stimulant prescription, a similar rate to 2015.

Among the 1.3 million patients with concurrent ADHD stimulant and *SGA* prescriptions in 2018, patients with amphetamine products accounted for the majority (~65%), followed by methylphenidate products (~32%), and atomoxetine (~11%). These proportions remained relatively constant from 2015 to 2018 (see **Figure 2** below).

[a] IQVIA, National Sales Perspectives™, Jan 2015-Dec 2018. Extracted December 2019. File: NSP_Stimulants_Antipsychotics_2018_redefinedGroup xlsx

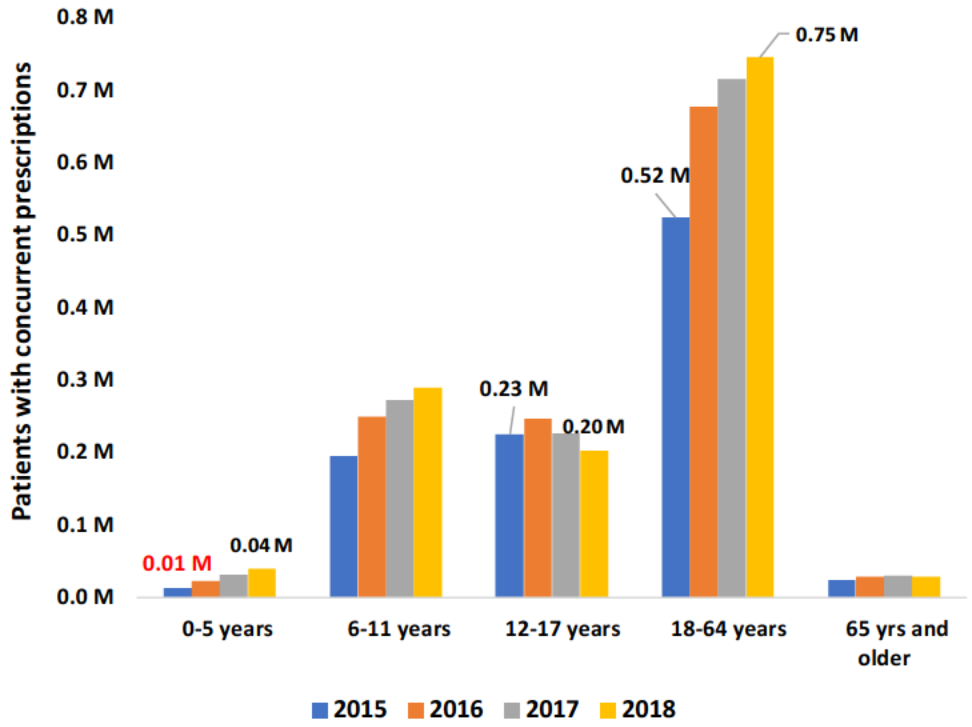
Figure 2. Estimated number of patients with concurrent prescriptions for ADHD stimulants and *SGAs*, stratified by drug group, from U.S. outpatient retail pharmacies, 2015-2018



Source: Symphony Health IDV® (Integrated Dataverse). Years 2015-2018. Data extracted Dec 2019.
ADHD=Attention Deficit Hyperactivity Disorder, SGA=second-generation antipsychotic

Findings also indicate that among pediatric patients aged 0-5 years, the number of patients with concurrent ADHD stimulants and *SGA* prescriptions increased approximately 3-fold, from 13,000 to 39,000, during this review period. In general, the number of patients with concurrent ADHD stimulants and *SGA* prescriptions has increased in all age groups throughout the study period, except in patients aged 12 to 17 years (data shown in **Figure 3** below).

Figure 3. Estimated number of patients with concurrent prescriptions for ADHD stimulants and *SGAs*, stratified by patient age, from U.S. outpatient retail pharmacies, 2015-2018



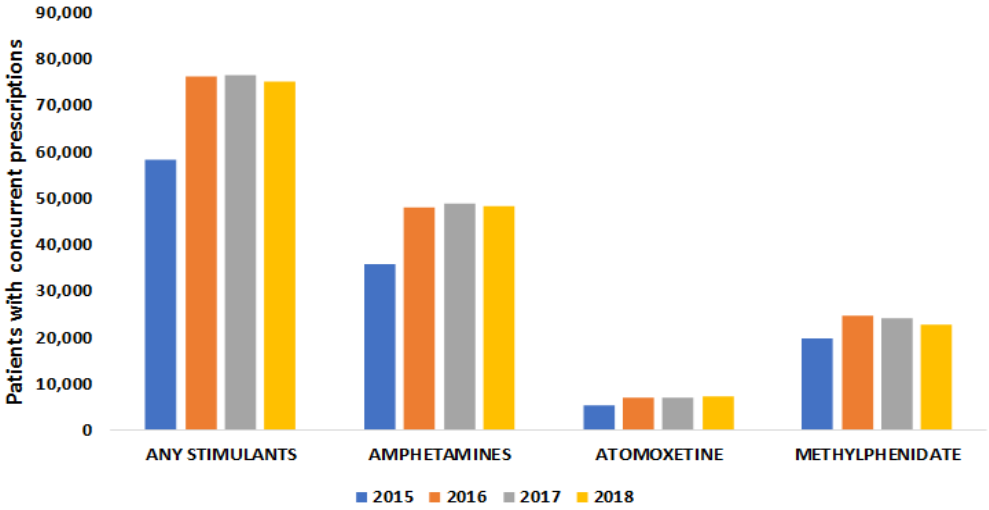
Source: Symphony Health IDV® (Integrated Dataverse). Years 2015-2018. Data extracted Dec 2019
ADHD=Attention Deficit Hyperactivity Disorder, SGA=second-generation antipsychotic

3.3.4 Concurrency Analysis: ADHD Stimulants with FGAs

Table B in **Appendix G** displays the nationally estimated number of patients with concurrent prescriptions for ADHD stimulants and *FGAs* from 2015 through 2018, annually. During the study period, the number of patients with concurrent ADHD stimulant and *FGA* prescriptions increased by approximately 29% from approximately 58,000 in 2015 to 75,000 in 2018. In 2018, out of 10 million patients with an ADHD stimulant claim, approximately 75,000 (~1%) had at least one concurrent *FGA* claim. This was relatively unchanged from 2015. In 2018, an estimated 2.3 million patients had *FGA* claims, of which 3% had at least one concurrent ADHD stimulant claim, a similar rate to 2015.

Among patients with ADHD stimulant prescriptions in 2018, concurrent use of amphetamine products and *FGAs* accounted for the majority (~60%), followed by methylphenidate products (~30%), and atomoxetine (~10%). These proportions remained relatively constant during the time examined (see **Figure 4** below).

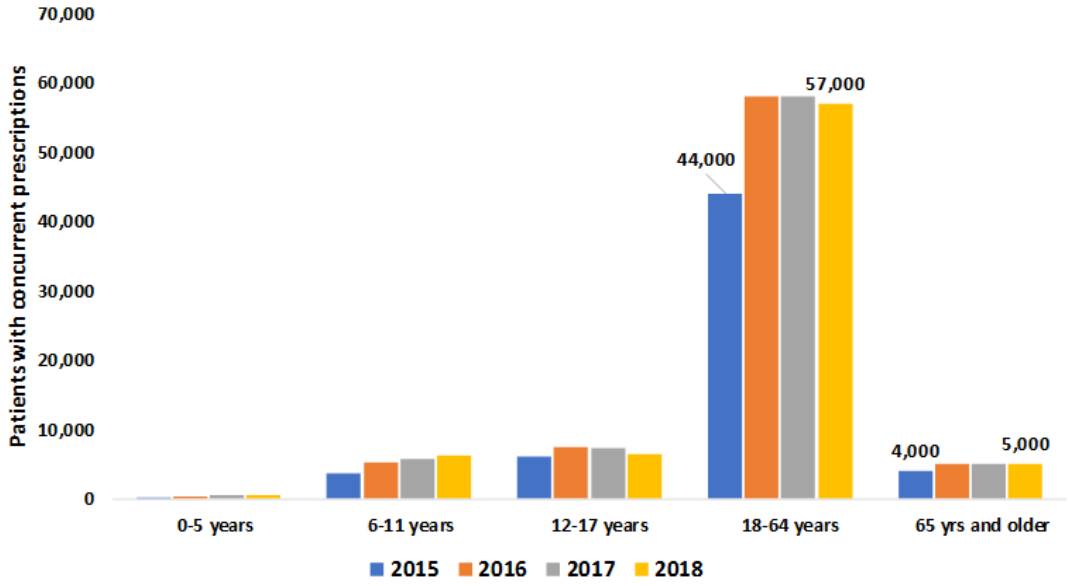
Figure 4. Estimated number of patients with concurrent prescriptions for ADHD stimulants and *FGAs*, stratified by drug group, from U.S. outpatient retail pharmacies, 2015-2018



Source: Symphony Health IDV® (Integrated Dataverse). Years 2015-2018. Data extracted Dec 2019
ADHD=Attention Deficit Hyperactivity Disorder, FGA=first-generation antipsychotic

In general, the number of patients receiving an ADHD stimulant and *FGA* together has slightly increased in all age groups throughout the study period (see **Figure 5** below).

Figure 5. Estimated number of patients with concurrent prescriptions for ADHD stimulants and *FGAs*, stratified by age, from U.S. outpatient retail pharmacies, 2015-2018



Source: Symphony Health IDV® (Integrated Dataverse). Years 2015-2018. Data extracted Dec 2019
ADHD=Attention Deficit Hyperactivity Disorder, FGA=first-generation antipsychotic

4 DISCUSSION

We identified 36 cases of acute hyperkinetic movement disorder associated with the concomitant use of ADHD stimulants and antipsychotics in FAERS and the medical literature. The majority of cases identified had features consistent with acute dystonic reactions (n=26) and a few cases had features of withdrawal emergent dyskinesias (n=7) or mixed movement disorders (n=3). From an ADHD stimulant perspective, most of the cases were reported with methylphenidate products (n=23), followed by amphetamine products (n=9), and atomoxetine (n=4). From an antipsychotic perspective, all 36 cases identified were reported with SGAs and no cases were reported with FGAs. The cases included in our case series were received from a variety of countries (U.S. cases n=22; foreign cases n=14) reducing the likelihood of selective reporting from a specific country. Using our causality assessment criteria, we determined the drug-event causal association as probable in 11 cases and possible in 25 cases. It is notable that 33 reports not included in our case series were considered unassessable because of limited information, particularly on latency and exact DDI permutations, and therefore those might represent potential additional cases.

In our case series, most of the cases were reported in males (n=31). This corresponds to the diagnosis of ADHD being three to four times more common in males than in females.[2] Additionally, most of the cases were reported in children and adolescents (n=34). Compared to adults, children and adolescents experience extrapyramidal symptoms more frequently, but acute dystonic reactions are still rare.[3,13] The combined use of ADHD stimulants and SGAs in children and adolescents has increased as diagnostic comorbidity has become better understood.[2] This may be associated with conditions frequently reported as comorbidities in pediatric patients with ADHD such as bipolar disorder, DBD, Tourette's disorder, and irritability associated with autistic disorder.[2] In our drug utilization analysis from 2015 to 2018, the number of patients with concurrent ADHD stimulant and SGA prescriptions increased slightly, whereas concurrency with FGA prescriptions remained low. This suggests that FGAs are used less frequently in this population and the use of FGAs has likely been substituted by SGAs in recent years.[21]

The dopaminergic pharmacodynamic DDIs between methylphenidate products and antipsychotics has multiple permutations. Among DDI cases reported with methylphenidate/amphetamine products, the most commonly reported permutation involved two different scenarios. The first scenario (Scenario 2 in Table 1) involves the discontinuation of the methylphenidate while concomitantly on SGA (n=7). In these cases, the close temporal relationship between the ADHD simulant discontinuation and the onset of the movement disorder with other variables remaining constant suggests that the ADHD stimulant discontinuation was the most likely cause of the acute hyperkinetic movement disorder. Methylphenidate exerts its activity through the inhibition of norepinephrine and dopamine reuptake into the presynaptic neuron thus enhancing the level of dopamine in the synaptic cleft. On the other hand, SGAs are selective monoaminergic antagonists with high affinity for D2 receptors. Therefore, we can hypothesize that once the methylphenidate is withdrawn a net decrease in the available tonic dopamine results in increased relative D2 blockade and lead to acute hyperkinetic movement disorders as it may be observed when antipsychotic monotherapy is initiated. Notably, in this DDI scenario no cases reported dose reduction of methylphenidate while concomitantly on SGA.

The second most common DDI scenario (Scenario 3 in **Table 1**) with methylphenidate products involves the introduction or dose increase of the antipsychotic while the patient is on a stable dose of ADHD stimulant (n=7). In this scenario the potential DDI mechanism causing acute hyperkinetic movement disorders may be the downregulation of D2 receptors by the chronic ADHD stimulant exposure as the primary driver in combination with an enhanced D2 blockage by the newly introduced or dose-increased antipsychotic. Although the introduction or dose increase of the antipsychotic alone could potentially be the reason for the adverse event in this DDI scenario (through a mechanism akin to the initiation of antipsychotic monotherapy), the antipsychotic doses reported in these cases were generally low. In clinical trials, there were similar rates of extrapyramidal adverse events with such low antipsychotic doses compared to placebo.[22] Therefore, the movement disorder occurring with this scenario is likely the result of a DDI.

Notably, we identified multiple other potential permutations of the DDI between methylphenidate/amphetamine products and SGAs that were less frequently reported but also resulted in acute hyperkinetic movement disorders. One such DDI scenario involves the introduction of methylphenidate while on a stable dose of antipsychotic (Scenario 1 in **Table 1**). Most of these DDI cases described features consistent with an acute dystonic reaction suggesting that this is the most likely DIMD to occur as result of this DDI permutation. Movement disorders with features similar to withdrawal emergent dyskinesias could be explained by the sole discontinuation or dose reduction of the SGA in cases with DDI permutation Scenarios 4 and 6 (**Table 1**). The occurrence of withdrawal emergent dyskinesias being limited to FGAs (based on labeling) supports a DDI between SGAs and ADHD stimulants.

The dopaminergic pharmacodynamic DDIs between amphetamine products (n=9) and antipsychotics were less commonly reported compared to methylphenidate products (n=24), despite the drug utilization analysis showing that the amphetamine products were most frequently prescribed (compared to methylphenidate products and atomoxetine) among patients with concurrent antipsychotic prescriptions. Our drug utilization analysis also showed that the number of patients with concurrent prescriptions for ADHD stimulants and SGAs increased 3-fold (from 13,000 to 39,000) in pediatric patients younger than 5 years of age during the study period. The increase in concurrent use for these products could possibly have been impacted by the 2011 American Academy of Pediatrics Clinical Practice Guideline changes, including expanding the diagnosis and treatment of ADHD in preschool children age 4 years and older.[23] Notably, there are three amphetamine products approved for the treatment of ADHD in patients 3 years of age and older.

The dopaminergic pharmacodynamic DDIs between amphetamine products and antipsychotics also had multiple permutations. The mechanisms supporting the causal relationship of this DDI are likely similar to methylphenidate products. However, unlike methylphenidate products amphetamines products are substrate type releasers and can increase dopamine by inhibition of dopamine transporter and the inhibition of vesicular monoamine transporter 2 (VMAT-2) releasing dopamine from vesicular storage.[24] Additionally, amphetamines may also reduce the binding of antipsychotics to D2 receptors within the striatum as evidenced by their ability to reduce the binding of other D2 antagonists.[25] Theoretically, amphetamine may competitively

inhibit SGA leading to increased antipsychotic binding once the stimulant is withdrawn or dose reduced precipitating acute hyperkinetic movement disorders.

The dopaminergic pharmacodynamic DDIs between atomoxetine (n=4) and antipsychotics were less frequently reported compared to methylphenidate products (n=24) and amphetamine products (n=9). Atomoxetine is a selective inhibitor of the norepinephrine transporter and a weak inhibitor of the dopamine transporter. However, studies found that atomoxetine can increase dopamine concentrations in the brain through the weak inhibition of dopamine transporter and can cause the downregulation of D2 receptors in a dose dependent manner.[26,27] Therefore, the abrupt cessation of atomoxetine and immediate initiation of antipsychotics (Scenario 5 in **Table 1**) may also result in acute hyperkinetic movement disorders.

In our case series, the most commonly reported antipsychotics were risperidone (n=21) and aripiprazole (n=10). This may be because risperidone and aripiprazole have been studied as adjunctive treatments for DBDs.[28] Risperidone binds more tightly to the D2 receptor than dopamine compared to other SGAs. Therefore, risperidone dissociation from the D2 receptors is slower than other SGAs, resembling FGAs.[29] On the other hand, aripiprazole is a partial dopamine agonist with high affinity for D2 receptors. Its unique mechanism is thought to limit the risk of extrapyramidal adverse events.[30] However, in the scenario of abrupt changes in dopamine level aripiprazole can act as a dopamine antagonist causing acute hyperkinetic movement disorders to emerge. Accordingly, dopaminergic tone in the surrounding milieu is very important when determining the pharmacological profile of aripiprazole.[30] Differential effect on pre- and post-synaptic dopamine receptors may also be a determining factor. The cases identified with other SGAs suggest that this DDI interaction is not unique to risperidone and aripiprazole and may occur with other SGAs. Additionally, several cases included in our case series reported clonidine (n=6) and valproic acid (n=5) as concomitant medications. However, their contributing role in causing acute hyperkinetic movement disorders, if any, remains unclear.[31,32]

Combination therapy with ADHD stimulants and antipsychotics is common. Despite the efficacy of antipsychotics for DBD and stimulants for ADHD the evidence for combined use is currently limited.[33] Some studies have shown that combined use of ADHD stimulants and antipsychotics are not associated with higher rates of adverse events.[33] The small sample sizes in these studies may be inadequate to rule out rare adverse events.[33] Clinicians should be aware that the combination of ADHD stimulants and antipsychotics may increase the risk of acute hyperkinetic movement disorder, particularly acute dystonic reactions, in susceptible individuals. Therefore, any permutation of addition, withdrawal, dose changes, or switch involving antipsychotics and ADHD stimulants has the potential of resulting in an acute hyperkinetic movement disorder. If the acute hyperkinetic movement disorder does not respond to anticholinergic therapy, reintroducing the patient's previous regimen may treat the adverse event as reported in our case series; this may be suggestive of a movement disorder akin to antipsychotic withdrawal emergent dyskinesia. To mitigate the risk of this complex dopaminergic pharmacodynamic DDI interaction between ADHD stimulants and SGAs a slower taper or dose titration prior to the discontinuation or initiation of either agent or the initiation of a washout period when switching agents may be warranted. Counseling parents and caregivers about this risk is prudent because most of the cases occurred in children and adolescents.

It should also be noted that some assumptions were made when examining concurrency using prescription data only, such as: (1) the patient takes each dispensed prescription as indicated, (2) the days' supply for a prescription accurately reflects how the patient ultimately will take the prescription, and (3) at least one day's overlap of stimulant and antipsychotics prescriptions may indicate possible concurrent therapy.

We focused our concurrency analyses on utilization data generated from outpatient retail pharmacy prescription claims. Therefore, these estimates may not apply to other settings of care in which these products are used, such as mail-order, specialty pharmacies, and non-retail settings (e.g., administration of antipsychotic drugs under medical supervision in the emergency room and psychiatric units, etc.). Moreover, these are national estimates, but no statistical tests were performed. Prescription data rely on data sources from dispensing pharmacies and some age misclassification may have occurred.

5 CONCLUSION

OSE concludes that there is evidence to support a DDI between methylphenidate/amphetamine products and risperidone/aripiprazole resulting in acute hyperkinetic movement disorders, particularly acute dystonic reactions. However, because of atomoxetine's distinct mechanism of action and the limited number of reported cases with atomoxetine and other antipsychotics there is insufficient evidence to update these labels at this time.

6 RECOMMENDATIONS

Based on this review, OSE recommends the following:

- Update the DRUG INTERACTION section for methylphenidate products, amphetamine products risperidone and aripiprazole with this pharmacodynamic drug interaction between ADHD stimulants and the aforementioned antipsychotics (i.e., risperidone and aripiprazole). See below suggested language.

  > Because a predominant action of methylphenidate/amphetamine is to increase extracellular dopamine levels, methylphenidate/amphetamine products may be associated with pharmacodynamic interactions when coadministered with certain antipsychotics (i.e., risperidone or aripiprazole). Hyperkinetic movement disorders, including acute dystonic reactions and less frequently withdrawal emergent dyskinesias, could emerge in patients, especially children and adolescents, receiving both medications concurrently when 1) one is added onto the other, 2) one is withdrawn, or 3) the dose of one is adjusted, upward or downward. Switch from one to the other with or without overlap may also result in acute hyperkinetic movement disorders. Accordingly, if the acute hyperkinetic movement disorder does not respond to anticholinergic therapy, reintroducing the patient's previous regimen may treat the adverse event. To mitigate the risk of this

complex dopaminergic pharmacodynamic drug-drug interaction between ADHD stimulants and antipsychotics a slower taper or dose titration prior to the discontinuation or initiation of either agent or the initiation of a washout period when switching agents may be warranted

- No labeling changes are recommended for atomoxetine or other antipsychotics

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8 APPENDICES

8.1 APPENDIX A. CURRENTLY MARKETED ANTIPSYCHOTICS

Typical Antipsychotics*				
Generic Name	**Trade Name**	**Application Number(s) N=NDA; A=ANDA**	**Sponsor Name**	**FDA Approval Date / Date Range**
Chlorpromazine hydrochloride		A084112; A084114; A083329	West-Ward Pharmaceuticals International LTD; USL Pharma LLC	Approved prior to 1/1/1982
Fluphenazine decanoate		A071413	Fresenius Kabi USA LLC	7/14/1987
Fluphenazine hydrochloride		A040146; A074725; A089556; A089804	Pharmaceutical Associates Inc Fresenius Kabi USA LLC Mylan Pharmaceuticals Inc	8/12/1988 - 9/16/1996
Haloperidol	Haldol	A071208	Sandoz Inc	11/17/1986
Haloperidol decanoate		N018701	Janssen Pharmaceuticals Inc	1/14/1986
Haloperidol lactate		N015923; A071617	Janssen Pharmaceuticals Inc; Teva Pharmaceuticals USA	Approved prior to 1/1/1982 – 12/1/1988
Loxapine	Adasuve	N022549	Galen LTD	12/21/2012
Loxapine succinate		A072206	Watson Laboratories Inc	6/15/1988
Perphenazine		A089685	Sandoz Inc	12/8/1988
Pimozide	Orap	N017473	Teva Pharmaceuticals USA	8/27/1997
Prochlorperazine		A040058	G and W Laboratories Inc	11/24/1993
Prochlorperazine edisylate		A204147	Emcure Pharmaceuticals LTD	10/15/2013
Prochlorperazine maleate		A040101	Sandoz Inc	7/19/1996
Thioridazine hydrochloride		A088004	Mylan Pharmaceuticals Inc	3/15/1983
Thiothixene		A071093	Mylan Pharmaceuticals Inc	6/23/1987
Trifluoperazine hydrochloride		A040209	Mylan Pharmaceuticals Inc	7/7/1997
*Includes Reference Listed Drug or Reference Standard only				

Atypical Antipsychotics*				
Generic Name	**Trade Name**	**Application Number(s) N=NDA; A=ANDA**	**Sponsor Name**	**FDA Approval Date(s) / Date Range**
Aripiprazole	Abilify; Abilify; Maintena Abilify MyCite	N021436; A202102; A203906; N202971; N207202	Otsuka Pharmaceutical Co LTD; Alembic Pharmaceuticals LTD; Amneal Pharmaceuticals	11/15/2002- 11/13/2017
Aripiprazole lauroxil	Aristada; Aristada Initio Kit	N207533; N209830	Alkermes Inc	10/5/2015; 6/29/2018
Asenapine maleate	Saphris	N022117	Forest Laboratories LLC	3/12/2015

Atypical Antipsychotics*				
Generic Name	**Trade Name**	**Application Number(s) N=NDA; A=ANDA**	**Sponsor Name**	**FDA Approval Date(s) / Date Range**
Brexpiprazole	Rexulti	N205422	Otsuka Pharmaceutical Co LTD	7/10/2015
Cariprazine	Vraylar	N204370	Allergan Sales LLC	9/17/2015
Clozapine	Clozaril; FazaClo; Versacloz	N019758; N021590; N203479	Heritage Life Sciences Barbados Inc; Jazz Pharmaceuticals III International LTD; Tasman Pharma Inc	9/26/1989-2/6/2013
Iloperidone	Fanapt	N022192	Vanda Pharmaceuticals Inc	5/6/2009
Lurasidone	Latuda	N200603	Sunovion Pharmaceuticals Inc	12/7/2011
Olanzapine	Zyprexa; Zyprexa Zydis	N020592; N021253; N021086	Eli Lilly and Co	9/30/1996-3/29/2004
Olanzapine pamoate	Zyprexa Relprevv	N022173	Eli Lilly and Co	12/11/2009
Paliperidone	Invega	N021999	Janssen Pharmaceuticals Inc	8/26/2008
Paliperidone palmitate	Invega Sustenna; Invega Trinza	N022264; N207946	Janssen Pharmaceuticals Inc	7/31/2009; 5/18/2015
Pimavanserin tartrate	Nuplazid	N207318; N210793	Acadia Pharmaceuticals Inc	6/28/2018
Quetiapine fumarate	Seroquel; Seroquel XR	N020639; N022047	AstraZeneca Pharmaceuticals LP; AstraZeneca UK LTD	9/26/1997; 5/17/2007
Risperidone	Risperdal; Risperdal M-Tab; Risperdal Consta; Perseris Kit	N020272; N020588; N021444; N021346; N210655	Janssen Pharmaceuticals Inc; Indivior Inc	6/10/1996-7/27/2018
Ziprasidone hydrochloride	Geodon	N020825	Pfizer Inc	2/5/2001
Ziprasidone mesylate	Geodon	N020919	Pfizer Inc	6/21/2002
*Includes Reference Listed Drug or Reference Standard only				

8.2 APPENDIX B. CURRENTLY MARKETED ADHD STIMULANTS

Drug class	Generic name	Brand name (Application No.)	Formulation	Initial approval date
Amphetamine Products	Amphetamine	Adzenys ER (NDA 204325)	Extended-release oral suspension	September 15, 2017
		Adzenys XR-ODT (NDA 204326)	Extended-release orally disintegrating tablet	January 27, 2016
		Dyanavel XR (NDA 208147)	Extended-release oral suspension	October 19, 2015
		Evekeo (ANDA 200166)	Tablet	August 9, 2012
		Evekeo ODT (NDA 209905)	Orally disintegrating tablet	January 30, 2019
	Mixed salts of a single-entity amphetamine product: Dextroamphetamine saccharate\Amphetamine aspartate monohydrate\Dextroamphetamine sulfate\Amphetamine sulfate	Adderall (NDA 11522)	Oral tablet	January 19, 1960
		Adderall XR (NDA 21303)	Capsule	October 11, 2001
	Mixed salts of a single-entity amphetamine product	Mydayis (NDA 022063)	Extended-release capsule	June 20, 2017
	Dextroamphetamine	Dexedrine (NDA 17078)	Sustained-release capsule	August 2, 1976
	Lisdexamfetamine	Vyvanse (NDA 21977)	Capsule	February 23, 2007
		Vyvanse (NDA 208510)	Chewable tablet	January 28, 2017
	Methamphetamine	Desoxyn (NDA 005378)	Oral tablet	December 31, 1943
Methylphenidate Products	Dexmethylphenidate	Focalin (NDA 021278)	Tablet	November 13, 2001
		Focalin XR (NDA 021802)	Extended-release capsule	May 26, 2005
	Methylphenidate	Adhansia XR (NDA 212038)	Extended-release capsule	February 27, 2019
		Aptensio XR (NDA 205831)	Extended-release capsule	April 17, 2015
		Concerta (NDA 021121)	Extended-release tablet	August 1, 2000
		Cotempla XR-ODT (NDA 205489)	Extended-release orally disintegrating tablet	June 19, 2017
		Daytrana (NDA 21514)	Transdermal system	April 6, 2006

Drug class	Generic name	Brand name (Application No.)	Formulation	Initial approval date
		Journay PM (NDA 209311)	Extended-release capsule	August 8, 2018
		Metadate CD (NDA 21259)	Extended-release capsule	April 3, 2001
		Methylin (NDA 21419)	Oral solution	December 19, 2002
		Methylin (NDA 21475)	Chewable tablet	April 15, 2003
		Quillivant XR (NDA 202100)	Extended-release oral suspension	September 27, 2012
		Quillichew ER (NDA 207960)	Extended-release chewable tablet	December 4, 2015
		Ritalin (NDA 10187)	Tablet	December 5, 1955
		Ritalin LA (NDA 21284)	Extended-release capsule	June 5, 2002
		Ritalin SR (NDA 18029)	Sustained-release tablet	March 30, 1982
Selective norepinephrine reuptake inhibitor	Atomoxetine	Strattera (NDA 21411)	Capsule	November 26, 2002

8.3 APPENDIX C. FDA ADVERSE EVENT REPORTING SYSTEM & DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

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.

IQVIA National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IDV (Integrated Dataverse)™ from Symphony Health

IDV (Integrated Dataverse) ™ from Symphony Health contains longitudinal patient data sources that capture adjudicated prescription, medical, and hospital claims across the United States for all payment types, including commercial plans, Medicare Part D, cash, assistance programs, and Medicaid. The IDV contains over 10 billion prescription claims linked to over 280 million unique prescription patients with an average of 5 years of prescription drug history. Claims from hospital and physician practices include over 190 million patients with CPT/HCPCS medical procedure history, as well as ICD-9/10 diagnosis history, of which nearly 180 million prescription drug patients are linked to a diagnosis. The overall sample represents over 65,000 pharmacies, 1,500 hospitals, 800 outpatient facilities, and 80,000 physician practices.

8.4 APPENDIX D. PRODUCT LISTS

Group 1 Product List - MM Antipsychotics (product active ingredient)

- Aripiprazole, aripiprazole cavoxil, aripiprazole lauroxil
- Asenapine, asenapine hemipamoate, asenapine maleate
- Brexiprazole
- Cariprazine, cariprazine hydrochloride
- Clozapine
- Iloperidone
- Lurasidone
- Olanzapine, olanzapine pamoate
- Paliperidone, paliperidone palmitate
- Pimavanserin, pimavanserin tartrate
- Quetiapine, quetiapine fumarate
- Risperidone
- Ziprasidone, ziprasidone hydrochloride, ziprasidone hydrochloride\ ziprasidone mesylate, ziprasidone mesylate, ziprasidone\ziprasidone hydrochloride
- Chlorpromazine, chlorpromazine hibenzate, chlorpromazine hydrochloride, chlorpromazine\chlorpromazine hydrochloride
- Fluphenazine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride
- Haloperidol, haloperidol decanoate, haloperidol lactate
- Loxapine, loxapine hydrochloride, loxapine succinate
- Molindone, molindone hydrochloride
- Perphenazine, perphenazine decanoate, perphenazine dimaleate
- Prochlorperazine, prochlorperazine dimethanesulfonate, prochlorperazine edisylate, prochlorperazine maleate
- Pimozide
- Thiothixene, thiothixene hydrochloride, thiothixene\thiothixene hydrochloride
- Thioridazine, thioridazine hydrochloride
- Trifluoperazine, trifluoperazine hydrochloride

Group 2 Product List – MM Stimulants (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

8.5 APPENDIX E. FAERS LINE LISTING OF DRUG-DRUG INTERACTION CASE SERIES (N=36)†

FAERS Case #	Version	Outcome*	Age (Years)	Sex	Country	Manufacturer Control #	Case Type
12578402	1	OT	7	Male	Germany	DE-AUROBINDO-AUR-APL-2016-09578	Expedited
15988137	1	HO	9	Male	USA	US-AUROBINDO-AUR-APL-2018-052378	Expedited
3931499	2	HO,OT	16	Female	USA	USA030331656	Non- Expedited
6180809	1	OT	6	Male	USA	SPVI-2006-01570	Expedited
11166157	1	HO	9	Male	Turkey	PHHY2015TR064897	Expedited
11393483	1	OT	9	Female	USA	US-TEVA-586012USA	Expedited
11393486	1	OT	7	Male	USA	US-TEVA-586011USA	Expedited
11882362	1	HO	6	Null	Turkey	TR-SUN PHARMACEUTICAL INDUSTRIES LTD-2015RR-108927	Expedited
12319295	2	OT	13	Male	USA	US-PFIZER INC-2016231224	Expedited
12395574	1	HO	13	Female	Turkey	TR-ELI_LILLY_AND_COMPANY-TR201605006892	Expedited
12395579	1	HO	17	Male	Turkey	TR-ELI LILLY AND COMPANY-TR201605006862	Expedited
12658918	1	OT	7	Male	U.K.	GB-SUN PHARMACEUTICAL INDUSTRIES LTD-2016R1-122119	Expedited
13383618	3	HO,OT	9	Male	USA	US-PFIZER INC-2017129063	Expedited
16377995	1	OT	8	Female	USA	US-ASTRAZENECA-2019SE79450	Expedited
5837897	1	HO	13	Male	USA	US-SOLVAY-00305002231	Expedited
5913995	2	HO	9	Male	USA	8012483	Expedited
5952421	1	OT	13	Male	USA	PHBS2005US18990	Expedited
14303348	1	OT	12	Male	USA	US-OTSUKA-17389024	Expedited
14541267	1	OT	10	Male	Netherlands	NL-OTSUKA-DJ20104204	Expedited
3820584	1	HO	12	Male	Austria	PHBS2002AU08184	Expedited
3906986	3	HO	10	Male	USA	NSADSS2003006196	Expedited
5820458	2	OT	5	Male	USA	US-JNJFOC-20050601892	Non- Expedited
5821770	1	HO	5	Male	USA	PHEH2000US03611	Non- Expedited
6073459	1	HO,OT	45	Male	USA	2004112113	Non- Expedited
6332221	1	OT	11	Female	USA	PHBS2007US09069	Expedited
6588851	1	HO	18	Male	Canada	B0510370A	Expedited
6748881	4	HO	8	Male	USA	PT-JNJFOC-20080900040	Expedited
6876919	1	DS	12	Male	Saudi Arabia	SA-JNJFOC-20090100373	Expedited
6957992	2	HO	9	Male	Spain	ES-JNJFOC-20090306438	Expedited
6986018	1	OT	9	Male	USA		Direct
7269879	1	OT	11	Male	USA	US-B.I. PHARMACEUTICALS,INC./RIDGEFIELD-2010-DE-00374GD	Expedited

FAERS Case #	Version	Outcome*	Age (Years)	Sex	Country	Manufacturer Control #	Case Type
7476786	1	OT	10	Male	Netherlands	NL-BRISTOL-MYERS SQUIBB COMPANY-15191075	Expedited
7850115	3	OT	7	Male	India	PHHY2011IN15300	Expedited
7854736	1	HO	10	Male	Taiwan	TW-JNJFOC-20110302680	Expedited

*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. A case can have more than one serious outcome.
HO=hospitalization, DS=disability, OT=other medically significant
†Two cases were obtained from the medical literature but were not submitted to FAERS.

8.6 APPENDIX F. ADDITIONAL CLINICAL DETAILS OF FAERS CASE SERIES (N=36)

FAERS Case #/ Publication	Demographics	AE Clinical Description	ADHD Stimulant/Dose (if reported)	Antipsychotic/Dose (if reported)	Drug-Drug Interaction Permutation	Latency	Anticholinergic Treatment	Outcome	Causality Assessment
12578402	7 y/o male	Very extreme restlessness, dyskinesia, does not want to eat anymore, speech disturbed, sleeps late, tongue thickened	Lisdexamfetamine 20 mg daily	Risperidone 0 25 mg daily	1	1 day	Not reported	AE resolved after discontinuation of both medications	Possible
15988137	9 y/o male	Abnormal involuntary movements including lip smacking, eye blinking, body rocking and shakes, and writhing movements of the neck	Dexmethylphenidate 20 mg daily	Risperidone 4 mg daily	4	5 days	Yes	AE resolved after reintroduction of risperidone	Possible
3931499	16 y/o female	Acute dystonia/ strange things with tongue	Atomoxetine	Olanzapine	1	2 days	Yes	AE resolved after treatment	Possible
6180809	6 y/o male	Acute dystonia	Methylphenidate transdermal system	Olanzapine 7.5 mg daily	2	1 day	Yes	AE resolved with treatment	Possible
11166157	9 y/o male	Licking tongue protrusion and tension with difficulty closing mouth	Methylphenidate extended release 54 mg daily	Risperidone 1.5 mg bid	2	6-7 hours	Not reported	AE resolved when both medications were taken together with no missed methylphenidate doses	Probable
11393483	9 y/o female	Dystonic reaction with left jaw muscle contraction resulting in difficult eating	Methylphenidate extended release 50 mg every morning/ Methylphenidate 5 mg after school	Aripiprazole 1 mg bid	2	>24 hours - 7 days	Yes	AE resolution with anticholinergic treatment	Possible
11393486	7 y/o male	Neck spasms and dystonic neck contractions	Dextroamphetamine racemic 30 mg daily	Aripiprazole 2 mg daily	2	>24 hours - 7 days	No	AE resolved with restarting of dextroamphetamine	Possible
11882362	6 y/o male	Involuntary jaw movements, tongue rolling, and repetitive chewing-like behaviors, irregular counting-like movements of the fingers and serial blinking	Methylphenidate 5 mg daily	Risperidone 1 mg daily	6	3 hours	No	AE resolved after methylphenidate discontinuation	Probable
12319295	13 y/o male	Severe, painful cervical dystonia and dyskinesia consisting of intense, repetitive, involuntary movements of the upper extremities, as well as an uncontrollable sense of restlessness and agitation	Methylphenidate	Risperidone 1.5 mg BID	5	>24 hours - 7 days	Yes	AE resolved after risperidone reintroduction at initial dose	Possible
12395574	13 y/o male	Difficulties swallowing and contractions in and around her mouth	Atomoxetine 80 mg daily	Aripiprazole 5 mg daily	5	16 hours	Yes	AE resolved after treatment with anticholinergic	Probable

FAERS Case #/ Publication	Demographics	AE Clinical Description	ADHD Stimulant/Dose (if reported)	Antipsychotic/Dose (if reported)	Drug-Drug Interaction Permutation	Latency	Anticholinergic Treatment	Outcome	Causality Assessment
12395579	17 y/o male	Torticollis painful contraction of the neck	Atomoxetine	Aripiprazole	5	36 hours	Yes	AE resolved after treatment with anticholinergic	Possible
12658918	7 y/o male	Twitching movements of his hands and feet, together with repeated throat clearing (1st episode). Mouth movements, tongue protrusion, shoulder shrugging, and sustained flexion of the wrist and finger joints (2nd episode) but he was not unwell as before	Methylphenidate extended release 36 mg daily	Risperidone 1.5 mg daily	6	8 hours	Not reported	AE resolution within a few hours of reintroducing risperidone	Probable
13383618	9 y/o male	Agitation, severe choreoathetoid movements, oral dyskinesias, and insomnia	Methylphenidate	Risperidone	3	>24 hours - 7 days	Yes	AE resolved after risperidone reintroduction.	Possible
16377995	8 y/o female	Involuntary movements including tongue protrusion and jerking movements of her shoulders and neck	Lisdexamfetamine	Quetiapine	6	>24 hours - 7 days	Yes	AE resolved after risperidone reintroduction	Possible
5837897	13 y/o male	Arched back and neck, generalized body stiffness	Methylphenidate 54 mg	Risperidone 0.5 mg TID	2	1 day	Not reported	AE resolution after methylphenidate reintroduction	Probable
5913995	9 y/o male	Thick tongue, dysarthria, limbs stiffness	Dextroamphetamine-racemic 10 mg TID	Risperidone 1 mg BID	2	1 day	Yes	AE resolution after anticholinergic treatment	Probable
5952421	9 y/o male	Stiff, twisted neck and shoulder	Methylphenidate 15 mg TID	Risperidone 1.5 mg TID	2	1 day	Yes	AE resolution after anticholinergic treatment	Probable
14303348	12 y/o male	Acute dystonia	Methylphenidate	Aripiprazole 5 mg daily	3	1 day	Not reported	Not reported	Possible
14541267	10 y/o male	Acute dystonia	Dextroamphetamine	Aripiprazole	5	1 day	Not reported	Not reported	Possible
3820584	12 y/o male	Difficulty in talking, shortness of breath and difficulty moving because of stiffness. His mother noticed that his speech was slurred, and he was unable to close his mouth twitching in his hands, shoulder, neck and head, which progressed to jerking movements of his jaw and arms	Methylphenidate 10 mg daily	Risperidone 1 mg BID	3	30 hours	Yes	AE resolution after anticholinergic treatment	Possible
3906986	10 y/o male	Acute dystonia	Atomoxetine	Risperidone	1	>24 hours - 7 days	Not reported	Not reported	Possible

FAERS Case #/ Publication	Demographics	AE Clinical Description	ADHD Stimulant/Dose (if reported)	Antipsychotic/Dose (if reported)	Drug-Drug Interaction Permutation	Latency	Anticholinergic Treatment	Outcome	Causality Assessment
5820458	5 y/o male	Dystonic could not hold his head up, his head bobbing around, could not control arm and leg movements and could not speak in sentences	Methylphenidate extended release 36 mg daily	Risperidone	3	1 day	Yes	AE resolution after anticholinergic treatment	Possible
5821770	5 y/o male	Tongue movements and possibly movements involving the neck as well	Methylphenidate	Risperidone 1.2 mg daily	5	1 day	Yes	AE resolution after anticholinergic treatment	Possible
6073459	45 y/o male	Acute dystonia and difficulty breathing	Single-entity mixed amphetamine	Ziprasidone	3	1 day	Yes	AE resolution after anticholinergic treatment	Possible
6332221	11 y/o female	Generalized dystonia and torsion movements of trunk and axial muscles, and torticollis	Methylphenidate 30 mg daily	Risperidone 2 mg daily	2	1 day	Yes	AE resolution after anticholinergic treatment	Probable
6588851	18 y/o male	Torticollis	Dextroamphetamine 10 mg daily	Risperidone 4 mg daily	2	1 day	Yes	AE resolution after anticholinergic treatment	Probable
6748881	8 y/o male	Oromandibular dystonia and dystonia (dystonic movements in the mouth and extremities)	Methylphenidate extended release 36 mg	Risperidone 0 25 mg daily	1	3 hours	Yes	AE resolution after anticholinergic treatment	Possible
6876919	12 y/o male	Choreoathetosis	Methylphenidate extended release 36 mg	Risperidone 1.5 mg daily	4	>24 hours - 7 days	Not reported	AE resolved with reintroduction of risperidone	Possible
6957992	9 y/o male	Acute dystonia	Methylphenidate extended release 36 mg	Paliperidone 3 mg daily	3	2 days	Yes	AE resolution after anticholinergic treatment	Possible
6986018	9 y/o male	Acute dystonia	Methylphenidate	Aripiprazole 10 mg daily	3	2 days	Not reported	AE resolution after aripiprazole discontinuation	Possible
7269879	11 y/o male	Forceful jaw closure, difficulty opening his mouth	Methylphenidate 108 mg daily	Aripiprazole 15 mg BID	2	33 hours	Yes	AE resolution after anticholinergic treatment	Probable
7476786	10 y/o male	Acute dystonia	Dextroamphetamine	Aripiprazole 5 mg daily	5	1 day	No reported	Not reported	Possible
7850115	7 y/o male	Tongue protrusion; restlessness/akathisia	Methylphenidate sustained release 10 mg	Risperidone 2mg daily	1	7 days	Not reported	Resolution within 2 days methylphenidate discontinuation	Possible

FAERS Case #/ Publication	Demographics	AE Clinical Description	ADHD Stimulant/Dose (if reported)	Antipsychotic/Dose (if reported)	Drug-Drug Interaction Permutation	Latency	Anticholinergic Treatment	Outcome	Causality Assessment
7854736	10 y/o male	Acute dystonia reported to have soreness of back, could not stretch his back and could not stand steadily	Methylphenidate	Aripiprazole 2.5 mg daily	3	7 days	Yes	AE resolution after anticholinergic treatment	Possible
Levine et al 2007[34]	9 y/o female	Bilateral blepharospasm	Dextroamphetamine ER 10 mg	Risperidone 0.5 mg BID	3	7 days	Not reported	AE resolution with dose reduction of both medications	Possible
Sharp et al 2007[35]	11 y/o male	Torticollis, dysarthria, and rigidity of his extremities	Methylphenidate extended release 18 mg	Aripiprazole	1	1 day	Not reported	AE resolved 2 days after MPH discontinuation	Probable

ADHD=Attention Deficit Hyperactivity Disorder, AE=adverse event, BID=twice a day, DDI=drug-drug interaction, TID=three times a day, y/o=year-old

8.7 APPENDIX G. DRUG UTILIZATION TABLES

Table A. Estimated number of patients with prescriptions for ADHD stimulants* alone, or concurrently with *SGAs*, stratified by drug group and patient age, from U.S. outpatient retail pharmacies, 2015-2018, yearly

	2015			2016			2017			2018		
	Patient Counts	Concurrent Patients	Concurrency %	Patients Counts	Concurrent Patients	Concurrency %	Patients Counts	Concurrent Patients	Concurrency %	Patients Counts	Concurrent Patients	Concurrency %
ADHD Stimulants	9,945,909	980,070	10%	10,643,095	1,222,857	11%	10,794,386	1,274,385	12%	10,938,173	1,303,764	12%
0-5 years	118,600	13,112	11%	160,246	22,955	14%	197,131	31,345	16%	230,716	39,397	17%
6-11 years	2,162,770	194,858	9%	2,443,992	249,167	10%	2,634,526	272,127	10%	2,783,752	288,592	10%
12-17 years	1,959,828	225,092	11%	1,915,696	246,138	13%	1,775,858	226,709	13%	1,630,719	202,788	12%
18-64 years	5,508,936	523,872	10%	5,921,784	676,367	11%	5,989,812	715,564	12%	6,102,970	745,175	12%
65 yrs and older	196,629	23,241	12%	203,615	28,569	14%	200,177	29,015	14%	195,627	28,442	15%
Unspecified age	230	26	11%	232	33	14%	224	28	12%	220	24	11%
ADHD Stimulant Drug Groups												
Amphetamines	6,668,107	604,079	9%	7,257,218	776,403	11%	7,434,013	822,880	11%	7,616,652	853,073	11%
Methylphenidate Products	3,581,119	363,824	10%	3,681,644	428,676	12%	3,623,037	427,880	12%	3,539,668	419,648	12%
Atomoxetine	547,195	99,513	18%	596,648	123,125	21%	617,773	129,323	21%	667,071	139,159	21%
SGAs	7,138,758	980,070	14%	8,862,629	1,222,857	14%	9,341,801	1,274,385	14%	9,579,463	1,303,764	14%
0-5 years	26,825	13,112	49%	40,963	22,955	56%	51,633	31,345	61%	62,141	39,397	63%
6-11 years	309,736	194,858	63%	392,688	249,167	63%	434,059	272,127	63%	468,884	288,592	62%
12-17 years	557,080	225,092	40%	653,726	246,138	38%	663,932	226,709	34%	664,869	202,788	31%
18-64 years	5,156,751	523,872	10%	6,442,683	676,367	10%	6,793,669	715,564	11%	6,951,714	745,175	11%
65 yrs and older	1,090,436	23,241	2%	1,334,922	28,569	2%	1,400,648	29,015	2%	1,436,578	28,442	2%
Unspecified age	235	26	11%	269	33	12%	341	28	8%	365	24	7%

Source: Symphony Health IDV® (Integrated Dataverse). Data years 2015-2018. Data extracted Dec 2019. File: CPA_Stimulants_Antipsych_concur_age_tables_1242020 xlsx
* The variation in the total patient counts for ADHD stimulants between Tables A and B in Appendix G is due to the projection factors used to calculate the national estimates in the number of patients. The number of projected patients is calculated separately for each concurrency study, based on the patients who qualify for each specific study. This can cause differences in the number of projected patients when separate studies are compared, even though the definition of a patient with stimulant use is the same.
ADHD=Attention Deficit Hyperactivity Disorder, SGA=second-generation antipsychotic

Table B. Estimated number of patients with prescriptions for ADHD stimulants* alone or concurrently with *FGAs*, stratified by drug group and patient age, from U.S. outpatient retail pharmacies, 2015-2018, yearly

	2015			2016			2017			2018		
	Patient Counts	Concurrent Patients	Concurrency %	Patient Counts	Concurrent Patients	Concurrency %	Patients Counts	Concurrent Patients	Concurrency %	Patients Counts	Concurrent Patients	Concurrency %
ADHD Stimulants	9,718,952	58,286	1%	10,134,007	76,239	1%	10,247,466	76,402	1%	10,411,983	75,035	1%
0-5 years	113,606	188	<1%	146,853	339	<1%	178,631	480	<1%	208,916	620	<1%
6-11 years	2,116,240	3,642	<1%	2,337,739	5,169	<1%	2,515,871	5,807	<1%	2,665,900	6,300	<1%
12-17 years	1,910,487	6,156	<1%	1,818,073	7,521	<1%	1,683,567	7,277	<1%	1,552,679	6,507	<1%
18-64 years	5,386,982	44,023	1%	5,636,959	57,908	1%	5,678,034	57,688	1%	5,798,316	56,907	1%
65 yrs and older	192,832	4,277	2%	195,765	5,299	3%	192,125	5,151	3%	188,715	4,700	2%
Unspecified age	224	0	0%	220	2	1%	212	2	1%	209	0	0%
ADHD Stimulant Drug Groups												
Amphetamines	6,518,511	35,770	1%	6,913,183	48,121	1%	7,056,798	48,798	1%	7,252,264	48,393	1%
Methylphenidate Products	3,499,993	19,833	1%	3,511,587	24,580	1%	3,448,001	24,110	1%	3,376,319	22,691	1%
Atomoxetine	531,194	5,443	1%	555,773	7,069	1%	575,389	7,070	1%	623,081	7,249	1%
FGAs	1,986,027	58,286	3%	2,449,137	76,239	3%	2,431,382	76,402	3%	2,353,415	75,035	3%
0-5 years	971	188	19%	1,268	339	27%	1,443	480	33%	1,556	620	40%
6-11 years	10,726	3,642	34%	14,189	5,169	36%	15,672	5,807	37%	16,730	6,300	38%
12-17 years	36,587	6,156	17%	46,350	7,521	16%	47,664	7,277	15%	47,092	6,507	14%
18-64 years	1,285,948	44,023	3%	1,576,738	57,908	4%	1,555,294	57,688	4%	1,491,527	56,907	4%
65 yrs and older	651,842	4,277	1%	810,499	5,299	1%	811,164	5,151	1%	796,343	4,700	1%
Unspecified Age	45	0	0%	57	2	4%	87	2	2%	102	0	0%

Source: Symphony Health IDV® (Integrated Dataverse). Data years 2015-2018. Data extracted Dec 2019. File: CPA_Stimulants_Antipsych_concur_age_tables_1242020 xlsx
* The variation in the total patient counts for ADHD stimulants between Tables A and B in Appendix G is due to the projection factors used to calculate the national estimates in the number of patients. The number of projected patients is calculated separately for each concurrency study, based on the patients who qualify for each specific study. This can cause differences in the number of projected patients when separate studies are compared, even though the definition of a patient with stimulant use is the same.
ADHD=Attention Deficit Hyperactivity Disorder, FGA=first-generation antipsychotic

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/s/

MOHAMED A MOHAMOUD
03/19/2020 04:24:43 PM

DAVID J CROTEAU
03/19/2020 04:25:35 PM

NILAR Z IORIO
03/19/2020 05:03:14 PM

CORINNE M WOODS
03/19/2020 05:12:46 PM

CARMEN CHENG
03/19/2020 09:54:35 PM

RAJDEEP K GILL
03/20/2020 08:36:04 AM

CINDY M KORTEPETER
03/20/2020 09:03:13 AM