



**Pediatric Focused Safety Review**  
**Mydayis (mixed salts of single entity amphetamine)**  
**Adzenys ER (amphetamine extended release)**  
**Pediatric Advisory Committee Meeting**  
**September 15, 2020**

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# Outline

- Background Information
- Previous Pediatric Advisory Committee (PAC) Meetings
- Relevant Safety Labeling
- Drug Use Trends
- Pediatric Adverse Events
- Newly Identified Safety Signal
- Summary

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# Background Information



- **Drug:** Mydayis (mixed salts of a single entity amphetamine)
- **Original market approval:** June 20, 2017
- **Applicant:** Takeda (formerly Shire US)
- **Therapeutic category:** Central nervous system (CNS) stimulant
- **Indication:** Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 13 years and older
- **Formulation:** Extended release capsule (available as 12.5 mg, 25 mg, 37.5 mg, 50 mg)



# Background Information

- **Drug:** Adzenys ER (amphetamine extended release)
- **Original market approval:** September 15, 2017
- **Applicant:** Neos Therapeutics
- **Therapeutic category:** CNS stimulant
- **Indication:** Treatment of ADHD in patients 6 years and older
- **Formulation:** Extended release oral suspension (concentration 1.25 mg amphetamine per mL in 450 mL bottles)

# Pediatric Labeling Change



Date	Labeling Change
<b>Mydayis</b> June 20, 2017	Safety and effectiveness in pediatric patients with ADHD ages 13 to 17 years have been established in two placebo-controlled clinical trials
<b>Adzenys ER</b> September 15, 2017	Safety and effectiveness have been established in pediatric patients with ADHD ages 6 to 17 years of age in two placebo-controlled clinical trials

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# Previous PAC Meetings

- **PAC Meeting March 2006**
  - Adderall IR and Adderall XR
  - Psychiatric and cardiovascular events as safety concerns
- **PAC Meeting April 2018**
  - Dyanavel XR and Adzenys XR-ODT
  - No new safety concerns identified
  - Recommended routine monitoring





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# Relevant Safety Labeling

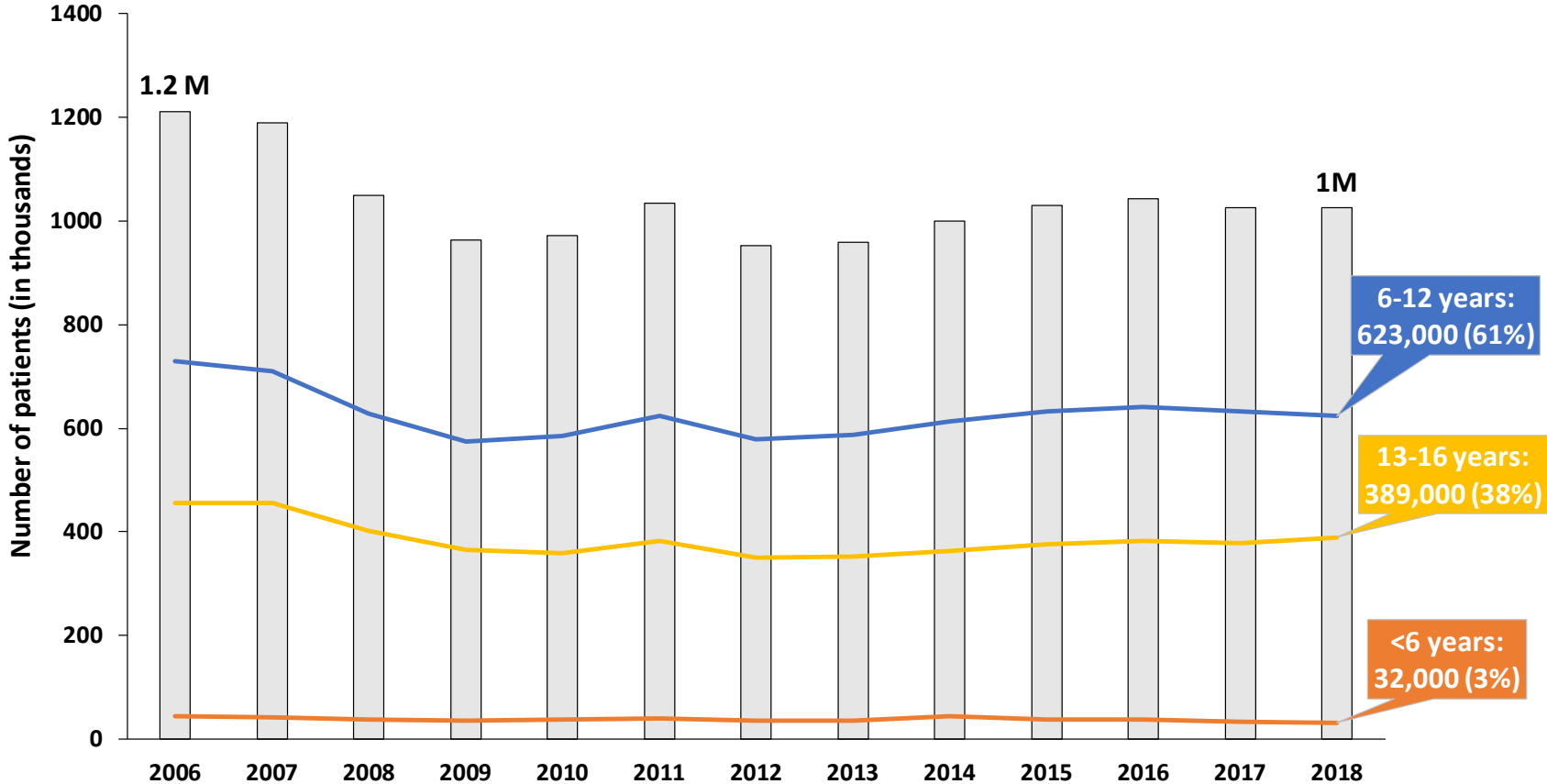
- **Boxed Warning**
  - Abuse and Dependence
- **Warnings and Precautions**
  - Serious Cardiovascular Reactions
  - Blood Pressure and Heart Rate Increases
  - Psychiatric Adverse Reactions
  - Long-Term Suppression of Growth
  - Peripheral Vasculopathy including Raynaud’s phenomenon
  - Seizures
  - Serotonin Syndrome
- **Adverse Reactions**
  - In general, the adverse events in pediatric patients were similar in frequency and type to those seen in adult patients
    - Mydayis categorized by pediatric age 13 to 17 years
    - Adzenys ER categorized by pediatric age (6 to 12) and (13 to 17) years old



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# Amphetamine Use in Pediatrics Patients



Source: IQVIA, Total Patient Tracker (TPT)™. 2006-2018. Accessed November 2019

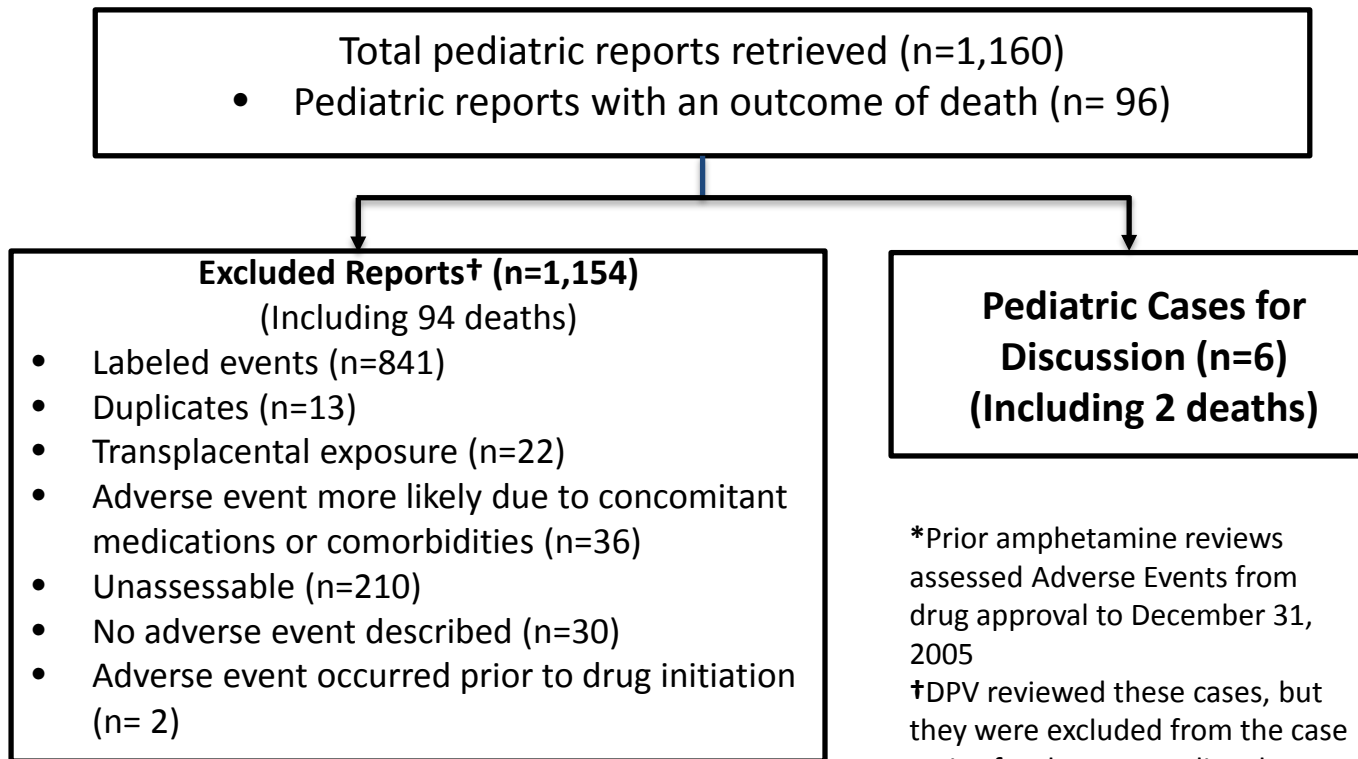


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# FAERS Pediatric Case Selection

## Jan 1, 2006\* to May 15, 2019



# Fatal Adverse Events in Pediatric Patients



- Cases with fatal outcome (n=2)
  - 15 year-old boy developed exertional heat stroke during football training while on amphetamine for an unknown dose or duration and died from complication of heat stroke
  - 13 year-old boy committed suicide a week after being switched from Vyvanse to Adderall for ADHD after uncharacteristic aggressive outburst
  - In both cases the extent of the causal association was difficult to determine given the available information

# Serious Non-fatal Unlabeled Adverse Events in Pediatric Patients



- **Eye disorders**
  - Glaucoma/borderline glaucoma (n=2)
- **Vascular disorders**
  - Vasculitis (n=1)
- Cases reported a long latency
- No additional cases of glaucoma or vasculitis were reported with the use of amphetamines in pediatric patients



# Serious Non-fatal Unlabeled Adverse Events in Pediatric Patients



- **Nervous system disorders**
  - Dystonia (n=1)
    - 7-year-old boy with a history of ADHD developed acute cervical dystonia after the withdrawal of dextroamphetamine while on aripiprazole.
    - Reintroduction of dextroamphetamine resulted in the resolution of the dystonic episode
    - Additional cases identified in FAERS in pediatric patients
    - Newly identified safety signal

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# FAERS Search Strategy

<b>DDI between ADHD Stimulants or Atomoxetine and Antipsychotics resulting in Acute Hyperkinetic Disorders</b>	
Date of Search	December 7, 2019
Time period of search	All reports through December 6, 2019
Search Type	FDA Business Intelligence System (FBIS) Drug interaction Quick Query
Product Terms	Includes reports listing either product groups as suspect only Group 1 Product List – Antipsychotics [(First (FGA) and Second generation (SGA))] Group 2 Product List – ADHD stimulants & atomoxetine
MedDRA search terms (version 22.0)	Preferred Terms: 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

# Literature Search Strategy

Date of Search	January 13, 2020
Database	PubMed (National Library of Medicine, Bethesda, MD), Embase (Reed Elsevier PLC, Amsterdam, Netherlands)
Search terms	<p>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</p> <p>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)</p>
Years included in search	All years
Limits	English, humans

# Case Selection Criteria

- **Acute Hyperkinetic Movement Disorder**
  - **Inclusion Criteria**
    - Case reports a diagnosis of acute\* dystonic reaction or acute dystonia by a physician
    - In absence of diagnosis by a physician, case describes signs or symptoms consistent with acute\* onset involuntary sustained muscle contractions or involuntary movements of the face, neck, trunk or extremities.
  - **Exclusion Criteria**
    - Duplicate reports
    - 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)
    - Other isolated hyperkinetic movement disorder (e.g., tics, akathisia, myoclonus)

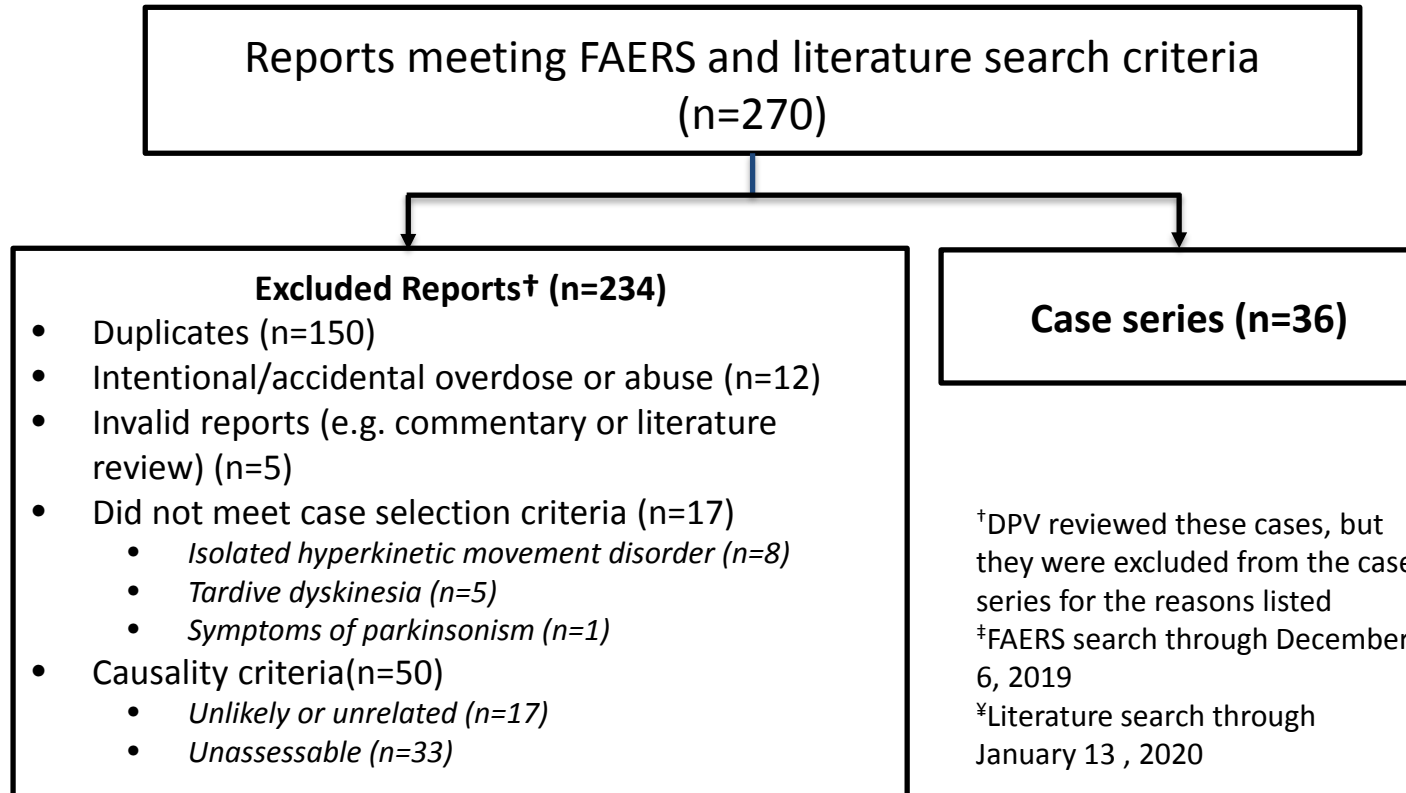
\*Acute refers to the onset and progression of the symptoms or signs over a period of minutes to hours

# DDI Permutations

Antipsychotics		ADHD Stimulants
Scenario 1	Stable dose	Introduction or dose titration
Scenario 2	Stable dose	Withdrawal or dose taper
Scenario 3	Introduction or dose titration	Stable dose
Scenario 4	Withdrawal or dose	Stable dose
Scenario 5	Switched to*	Switched from*
Scenario 6	Switched from*	Switched to*

\*Regardless of whether there is an overlapping/concurrent administration, or titration/taper of either drug  
 ADHD=Attention Deficit Hyperactivity Disorder, DDI=Drug-Drug interaction

# FAERS<sup>‡</sup> & Literature<sup>¥</sup> Case Selection: DDI between ADHD Stimulants or Atomoxetine & Antipsychotics



**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)**



<b>Selected Characteristics</b>	<b>Methylphenidate products (n=23)</b>	<b>Amphetamine products (n=9)</b>	<b>Atomoxetine (n=4)</b>
<b>Age ( years)</b>			
0-5	2	-	-
6-12	19	7	1
13-17	2	-	3
18-65	-	2	-
<b>Sex</b>			
Male	21	7	3
Female	2	2	1
<b>Country of reporter</b>			
USA	15	5	2
Foreign	8	4	2
<b>Year received/published</b>			
2001-2005	5	1	2
2006-2010	11	4	-
2011-2015	3	1	-
2016-2020	4	3	2





**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)**

<b>Selected Characteristics</b>	<b>Methylphenidate products (n=23)</b>	<b>Amphetamine products (n=9)</b>	<b>Atomoxetine (n=4)</b>
<b>Time-to-onset</b>			
Within 24 hours of drug change	12	6	1
More than 24 hours up to 7 days of drug change	11	3	3
<b>Hyperkinetic movement disorder</b>			
Acute dystonic reaction features	15	7	4
Withdrawal emergent dyskinesia features	6	1	-
Mixed movement disorder features/unclassifiable	2	1	-
<b>Antipsychotic product</b>	Risperidone (15) Aripiprazole (6) Olanzapine (1) Paliperidone (1)	Risperidone (4) Aripiprazole (3) Quetiapine (1) Ziprasidone (1)	Aripiprazole (2) Risperidone (1) Olanzapine (1)
<b>DDI permutation</b>	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)



**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)**

<b>Selected Characteristics</b>	<b>Methylphenidate products (n=23)</b>	<b>Amphetamine products (n=9)</b>	<b>Atomoxetine (n=4)</b>
<b>Treatment of adverse event<sup>†</sup></b>			
Treatment with anticholinergic/benzodiazepine	11	2	3
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
<b>Relevant concomitant medications<sup>†</sup></b>	(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)

<sup>†</sup>More than one treatment of adverse event, concomitant medication, or serious outcome may have been reported per case

**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)**

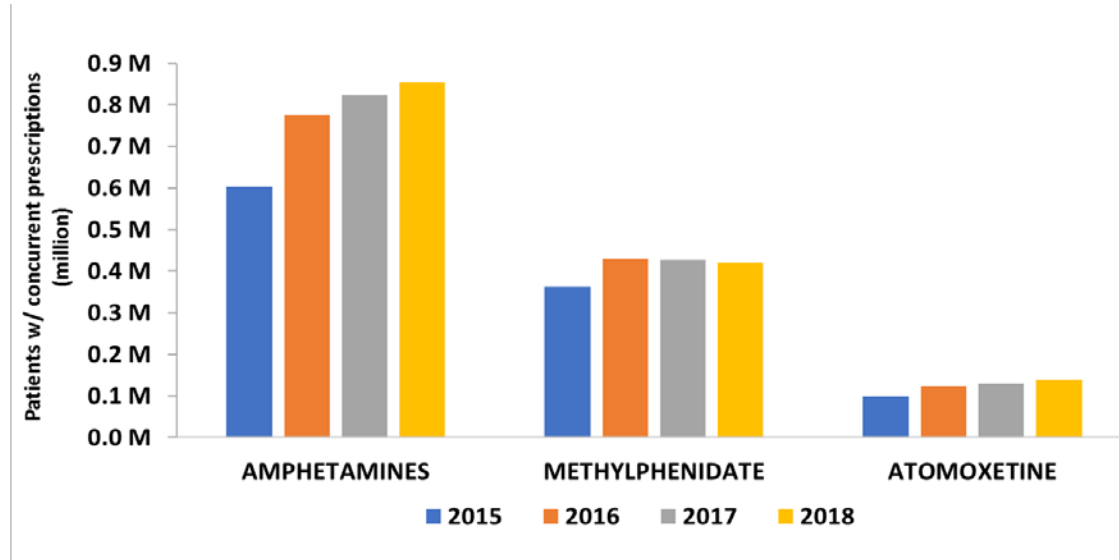
Selected Characteristics	Methylphenidate products (n=23)	Amphetamine products (n=9)	Atomoxetine (n=4)
<b>Causality Assessment</b>			
Probable	8	2	1
Possible	15	7	3
<b>Serious outcome<sup>†,‡</sup></b>			
Hospitalization	11	3	4
Disability	1	-	-
Other serious	12	7	1

<sup>†</sup>More than one treatment of adverse event, concomitant medication, or serious outcome may have been reported per case

<sup>‡</sup>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

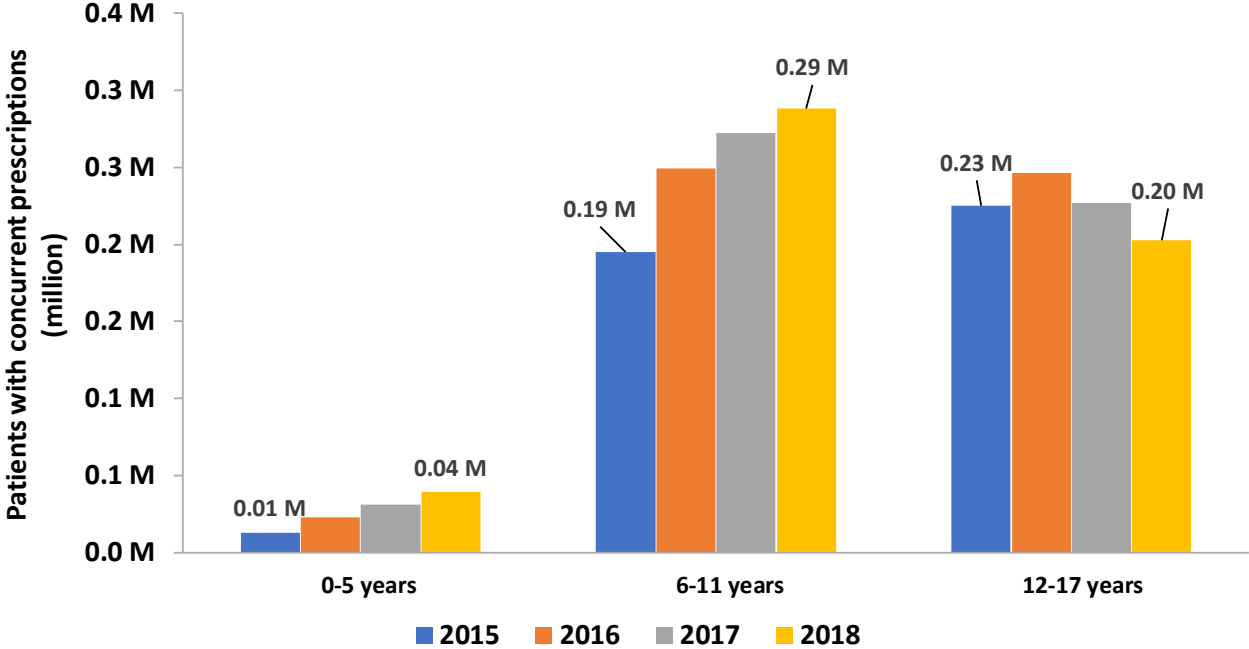
# Patients with Concurrent Therapy: ADHD Stimulants and Second Generation Antipsychotics



## Estimated number of patients with concurrent prescriptions for ADHD Stimulants and SGAs from U.S. outpatient retail pharmacies by drug groups

Source: Symphony Health Integrated Dataverse®. Data years 2015-2018. Data extracted Dec 2019.  
ADHD=Attention Deficit Hyperactivity Disorder, SGA=second-generation antipsychotic  
Concurrent therapy defined as at least one day overlap between ADHD stimulant and SGA therapy episodes

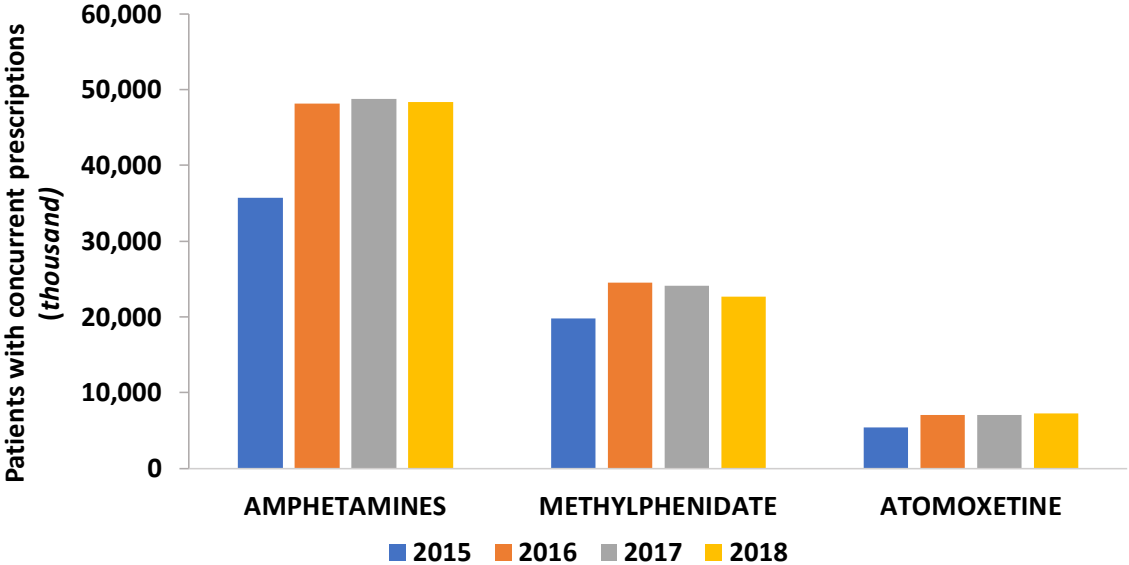
# Pediatric Patients with Concurrent Therapy: ADHD Stimulants and Second Generation Antipsychotics



**Estimated number of patients with concurrent prescriptions for ADHD Stimulants and SGAs from U.S. outpatient retail pharmacies stratified by age**

Source: Symphony Health Integrated Dataverse®. Data years 2015-2018. Data extracted Dec 2019.  
 ADHD=Attention Deficit Hyperactivity Disorder, SGA=second-generation antipsychotic  
 Concurrent therapy defined as at least one day overlap between ADHD stimulant and SGA therapy episodes

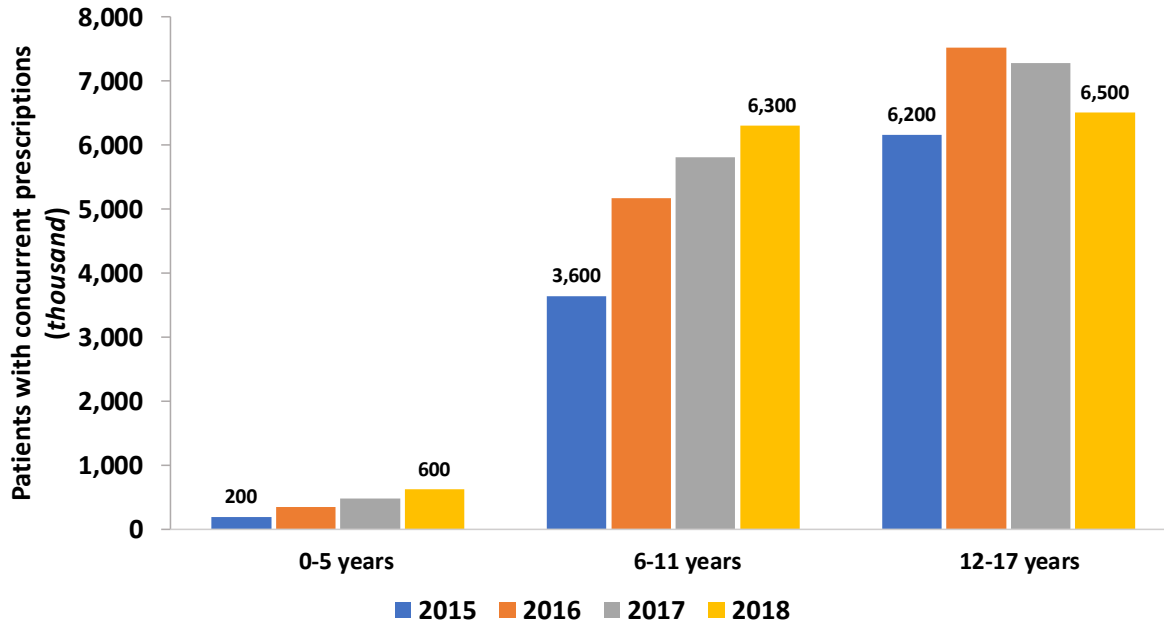
# Patients with Concurrent Therapy: ADHD Stimulants and First Generation Antipsychotics



## Estimated number of patients with concurrent prescriptions for ADHD Stimulants and FGAs from U.S. outpatient retail pharmacies by drug groups

Source: Symphony Health Integrated Dataverse®. Data years 2015-2018. Data extracted Dec 2019.  
 ADHD=Attention Deficit Hyperactivity Disorder, FGA= first-generation antipsychotic  
 Concurrent therapy defined as at least one day overlap between ADHD stimulant and FGA therapy episodes

# Pediatric Patients with Concurrent Therapy: ADHD Stimulants and First Generation Antipsychotics



**Estimated number of patients with concurrent prescription claims for ADHD Stimulants and FGAs from U.S. outpatient retail pharmacies by age**

Source: Symphony Health Integrated Dataverse®. Data years 2015-2018. Data extracted Dec 2019.

ADHD= Attention Deficit Hyperactivity Disorder, FGA= first-generation antipsychotic

Concurrent therapy defined as at least one day overlap between ADHD stimulant and FGA therapy episodes

# Discussion

- No reported DDI cases with ADHD stimulants/atomoxetine and FGAs
- Most cases reported in children and adolescents; children are more sensitive to dopamine changes
- Risperidone and methylphenidate DDI reported highest number of cases with a probable causal association
- Small number of DDI cases of amphetamine and SGA despite higher concurrent utilization
- Risperidone has the strongest binding affinity to D2 receptors among SGAs, therefore risperidone dissociation from D2 receptor is slower
- Aripiprazole does not have distinct pharmacological profile to suggest higher potential for DDI
- Methylphenidate may competitively bind to DA receptor with a higher potency than amphetamine



# Conclusion

- Totality of the evidence supports DDI between methylphenidate and risperidone
- Evidence was not as strong for a DDI between amphetamines & atomoxetine and other antipsychotics



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- FDA will incorporate DDI of acute hyperkinetic movement disorder into all risperidone and methylphenidate product labelings in Drug Interaction section.
- FDA recommends continuing routine, ongoing postmarket safety monitoring of Mydayis and Adzenys ER.

# Acknowledgements

## OSE-DPV-I

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# Mydayis & Adzenys ER: Voting

- FDA will incorporate DDI of acute hyperkinetic movement disorder into all risperidone and methylphenidate product labelings in Drug Interaction section.
- FDA recommends continuing routine, ongoing postmarket safety monitoring of Mydayis and Adzenys ER.
- Does the Pediatric Advisory Committee concur?