# 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**
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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 |
|---|---|
| **Mydayis**<br>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 |
| **Adzenys ER**<br>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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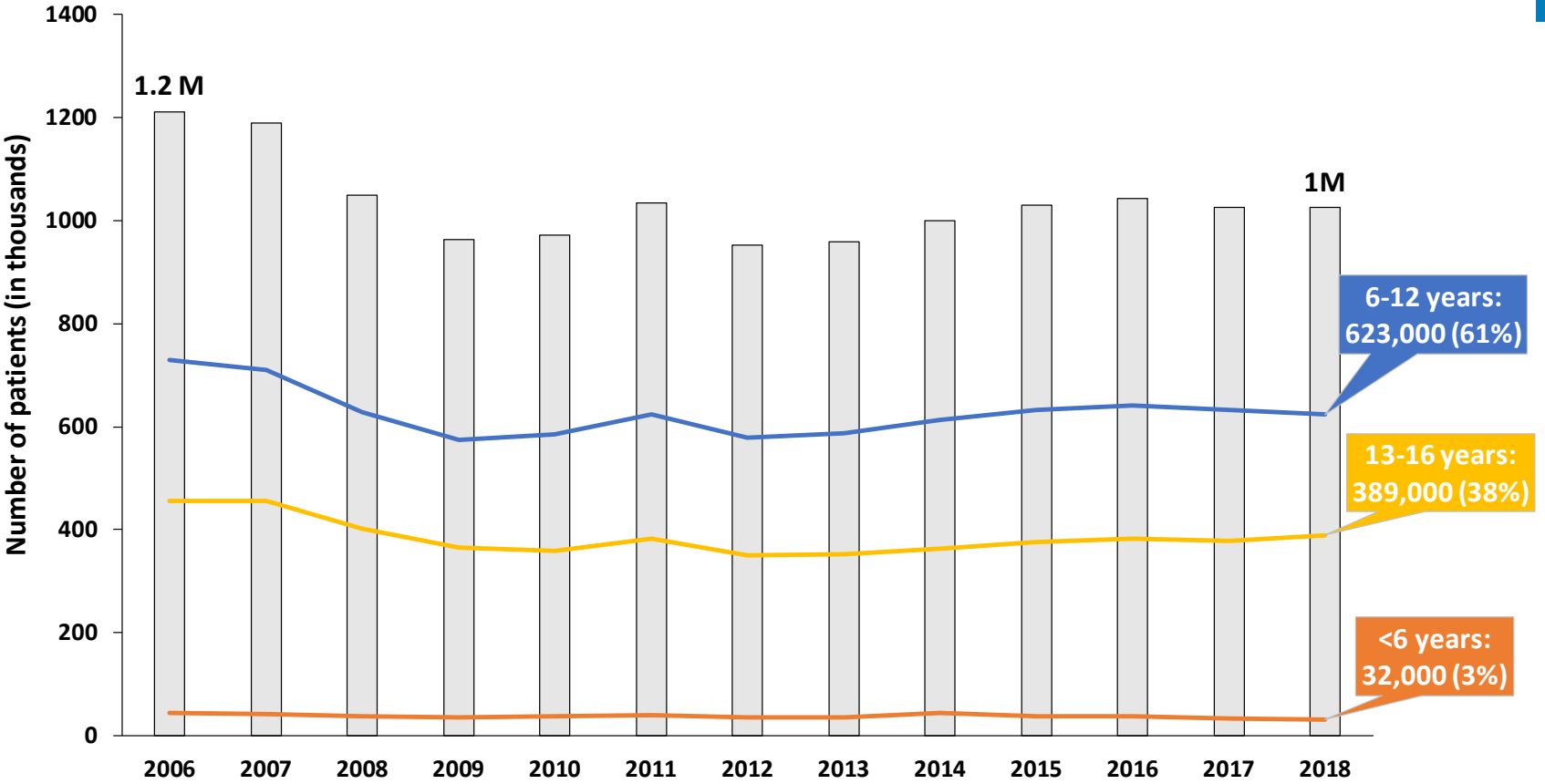
# Amphetamine Use in Pediatrics Patients




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

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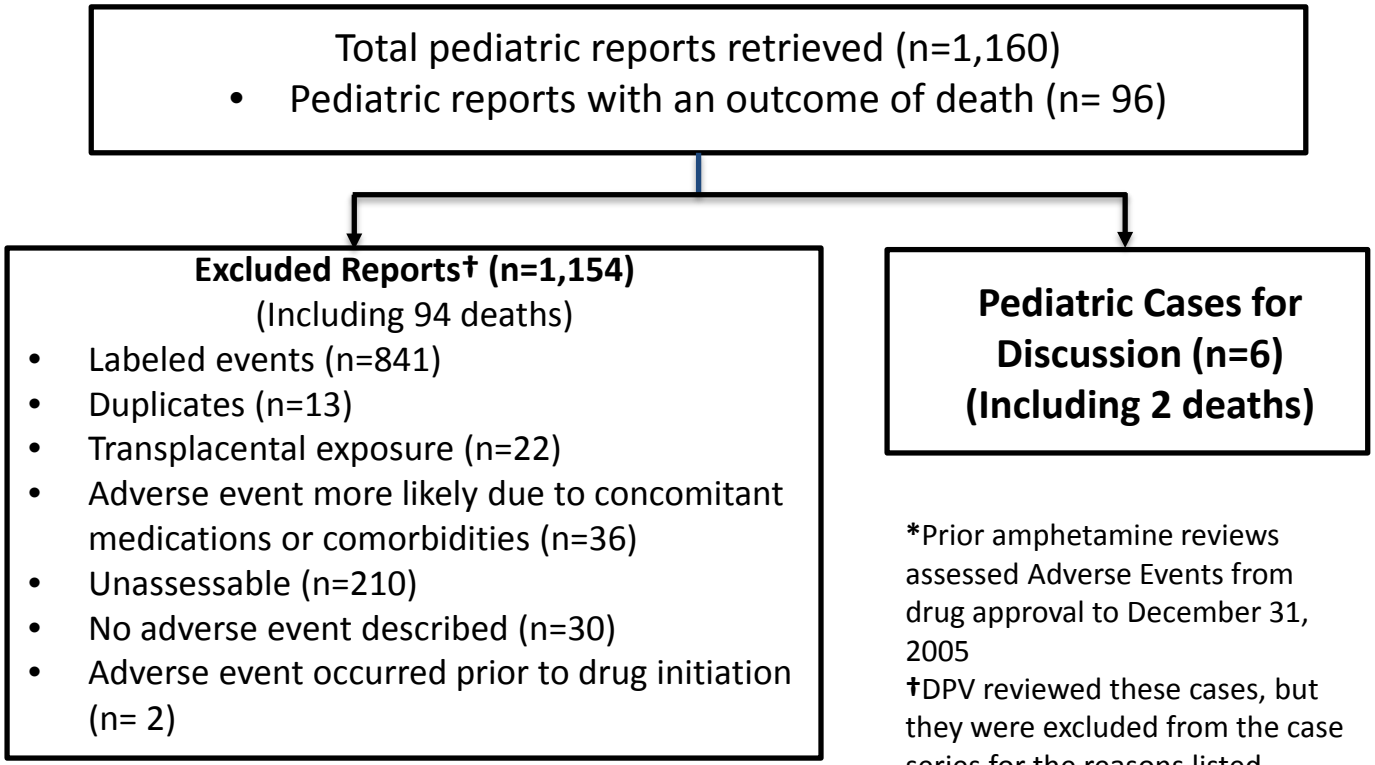
# FAERS Pediatric Case Selection Jan 1, 2006* to May 15, 2019




*Prior amphetamine reviews assessed Adverse Events from drug approval to December 31, 2005

†DPV reviewed these cases, but they were excluded from the case series for the reasons listed

# 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

Unlabeled events are underlined

# 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

Unlabeled events are underlined

# 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

Unlabeled events are underlined

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# FAERS Search Strategy

| **DDI between ADHD Stimulants or Atomoxetine and Antipsychotics resulting in Acute Hyperkinetic Disorders** | |
|---|---|
| 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<br>Group 1 Product List – Antipsychotics [(First (FGA) and Second generation (SGA)]<br>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 | 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<br>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 |

# 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

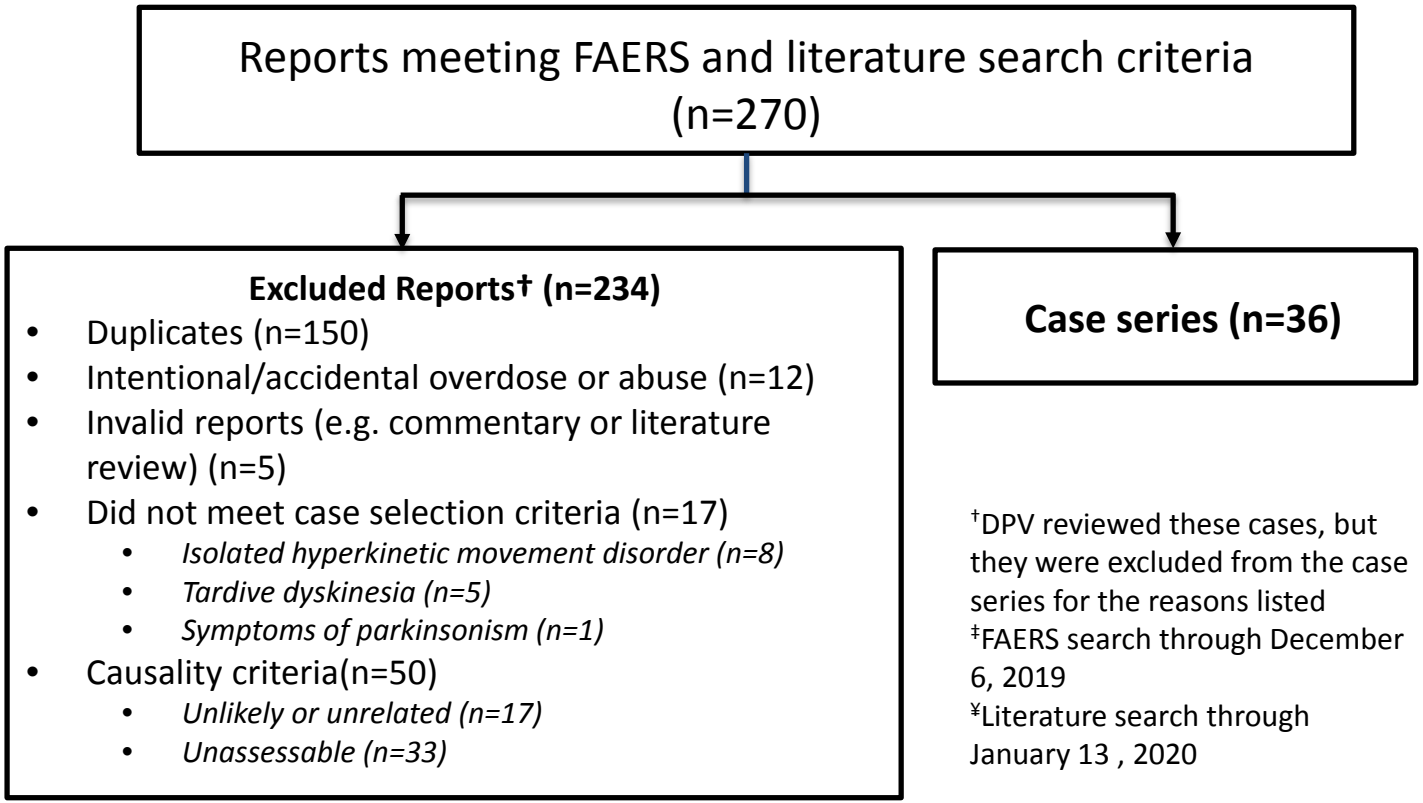
# DDI Permutations

| 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 ether drug

ADHD=Attention Deficit Hyperactivity Disorder, DDI=Drug-Drug interaction

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




†DPV reviewed these cases, but they were excluded from the case series for the reasons listed

‡FAERS search through December 6, 2019

¥Literature search through January 13 , 2020

**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 |
| **Year received/published** | | | |
| 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)**

| Selected Characteristics | Methylphenidate products (n=23) | Amphetamine products (n=9) | Atomoxetine (n=4) |
|---|---|---|---|
| **Time-to-onset** | | | |
| Within 24 hours of drug change | 12 | 6 | 1 |
| More than 24 hours up 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 | - |
| **Antipsychotic product** | Risperidone (15)<br>Aripiprazole (6)<br>Olanzapine (1)<br>Paliperidone (1) | Risperidone (4)<br>Aripiprazole (3)<br>Quetiapine (1)<br>Ziprasidone (1) | Aripiprazole (2)<br>Risperidone (1)<br>Olanzapine (1) |
| **DDI permutation** | Scenario 1 (3)<br>Scenario 2 (7)<br>Scenario 3 (7)<br>Scenario 4 (2)<br>Scenario 5 (2)<br>Scenario 6 (2) | Scenario 1 (1)<br>Scenario 2 (3)<br>Scenario 3 (2)<br>Scenario 5 (2)<br>Scenario 6 (1) | Scenario 1 (2)<br>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)**

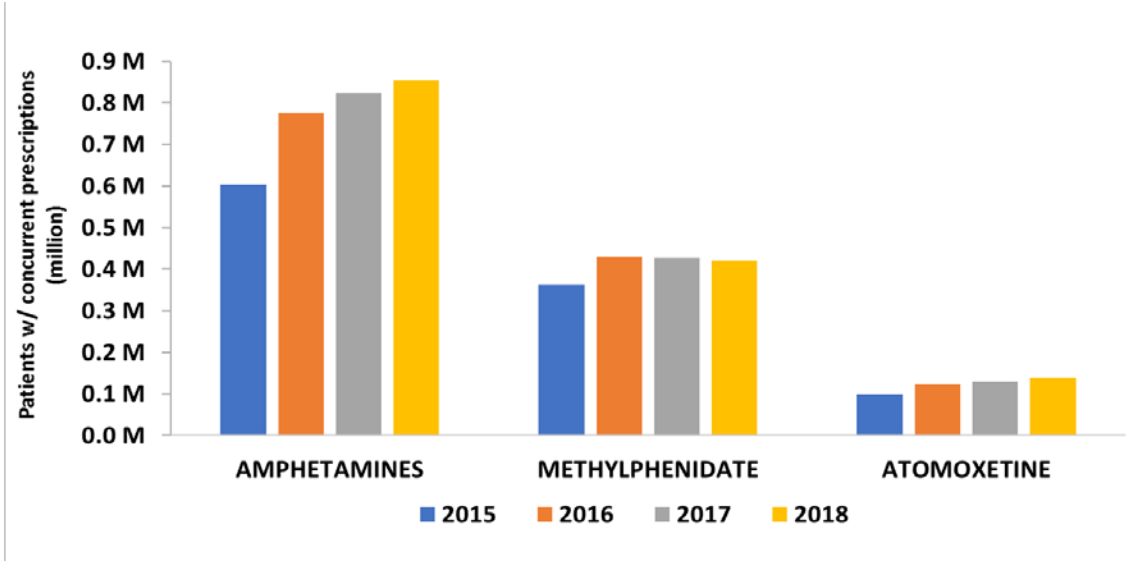
| Selected Characteristics | Methylphenidate products (n=23) | Amphetamine products (n=9) | Atomoxetine (n=4) |
|---|---|---|---|
| **Treatment of adverse event**[†] | | | |
| Treatment with anticholinergic/benzodiazepine | 11 | 2 | 3 |
| ADHD stimulant and/or antipsychotic withdrawal or dose reduction | 12 | 4 | 1 |
| ADHD stimulant and/or antipsychotic introduction or dose increment | 5 | 3 | - |
| Not reported | 2 | 2 | 1 |
| **Relevant concomitant medications**[†] | (n=12)<br>Clonidine (5)<br>Valproic acid (3)<br>Carbamazepine (1)<br>Oxcarbazepine (1)<br>Clobazam (1)<br>Guanfacine (1)<br>Sertraline (1)<br>Fluvoxamine (1)<br>Lithium (1) | (n=2)<br>Clonidine (1)<br>Valproic acid (1)<br>Sertraline (1) | (n=2)<br>Valproic acid (1)<br>Citalopram (1) |

[†]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)** |
| **Causality Assessment** | | | |
| Probable | 8 | 2 | 1 |
| Possible | 15 | 7 | 3 |
| **Serious outcome[†,‡]** | | | |
| Hospitalization | 11 | 3 | 4 |
| Disability | 1 | - | - |
| Other serious | 12 | 7 | 1 |

[†]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

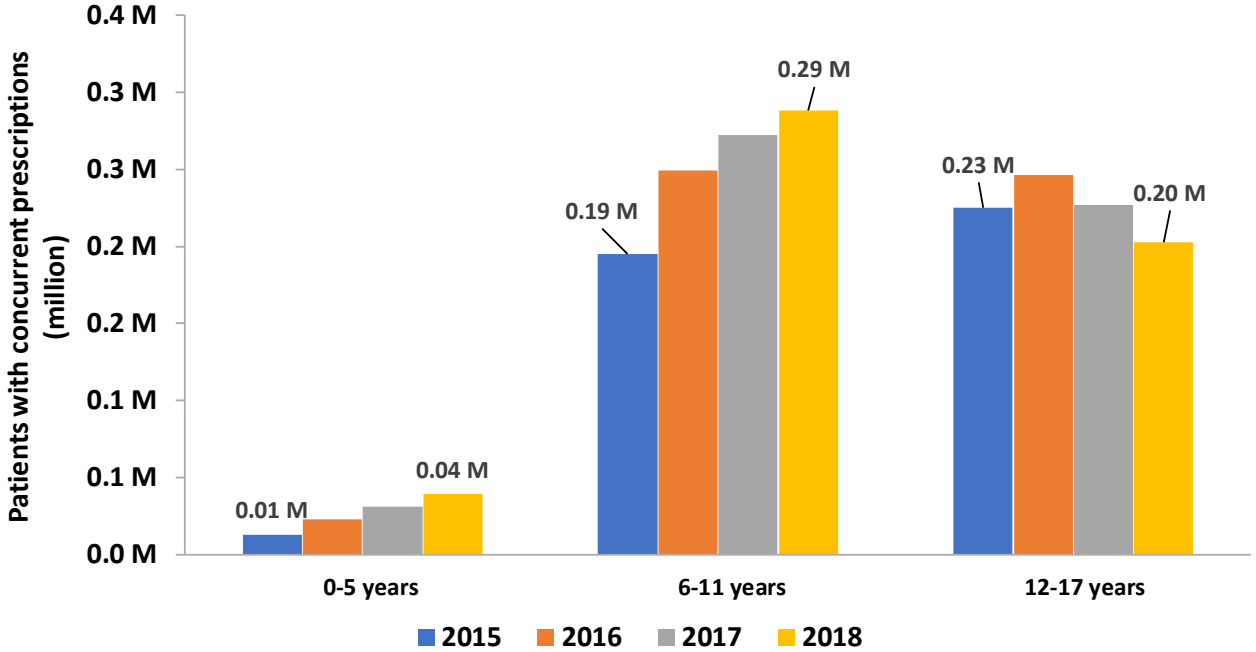
# Patients with Concurrent Therapy: ADHD Stimulants and Second Generation Antipsychotics




**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

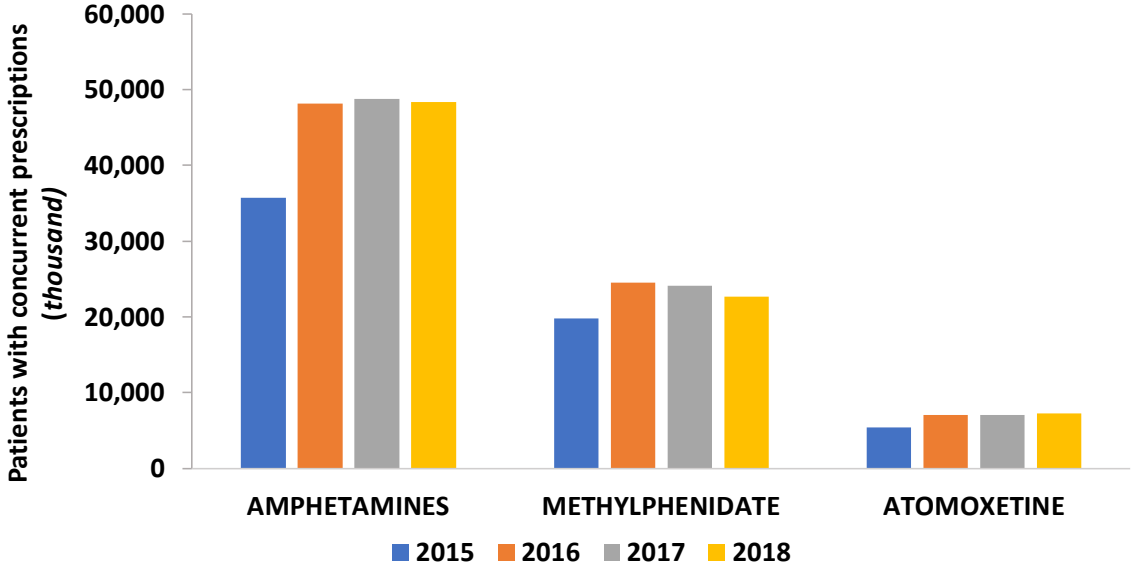
# Pediatric Patients with Concurrent Therapy: ADHD Stimulants and Second Generation Antipsychotics




**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

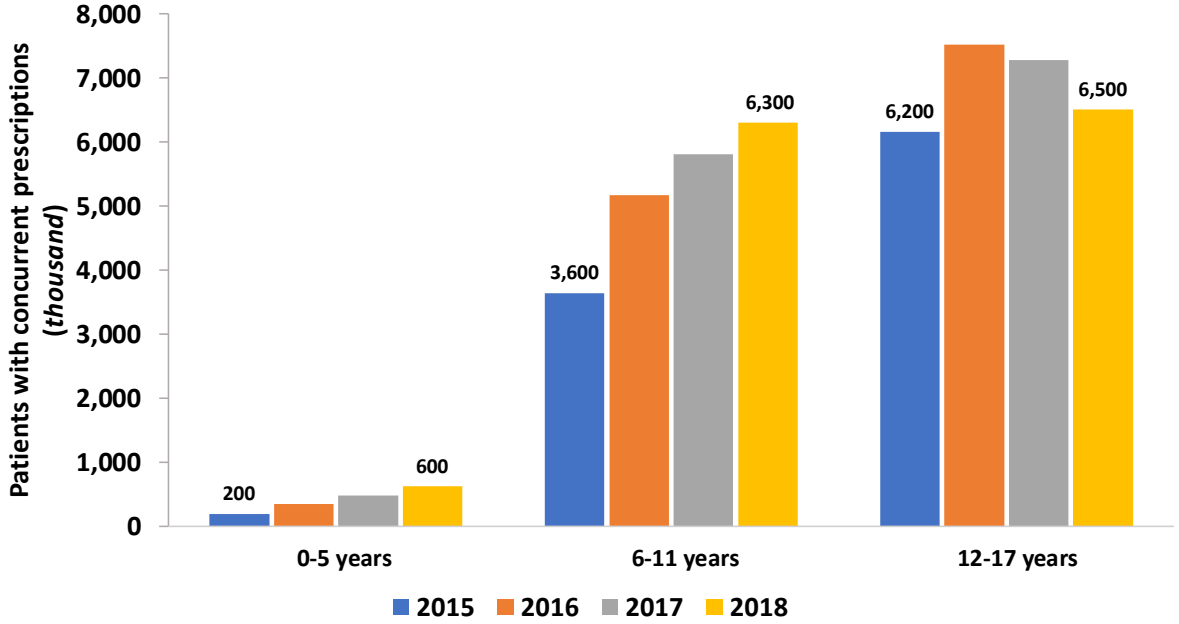
# Patients with Concurrent Therapy: ADHD Stimulants and First Generation Antipsychotics




**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

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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?