Pediatric Focused Safety Review Vyvanse (lisdexamfetamine)

Pediatric Advisory Committee

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Outline

- Background Information
- Relevant Pediatric Labeling
- Drug Use Trends
- Safety Data
- Acute Dystonia Signal Evaluation

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Background Information

- **Drug:** Vyvanse (lisdexamfetamine)
- **Original Market Approval:** February 23, 2007
- **Applicant:** Shire
- **Therapeutic Category:** Central nervous system (CNS) stimulant
- **Current Indications:**
  1. Attention Deficit Hyperactivity Disorder (ADHD)
  2. Moderate to severe Binge Eating Disorder (BED) in adults
- **Formulations:** Oral capsule, chewable tablet

Pediatric Labeling History

Date	Labeling Change
February 23, 2007	Lisdexamfetamine oral capsules approved for the treatment of ADHD in children 6 to 12 years of age
November 10, 2010	Lisdexamfetamine approved for ADHD to adolescents 13 to 17 years of age
April 26, 2013	Lisdexamfetamine approved for the maintenance of treatment ADHD in pediatric patients 6 to 17 years of age
January 28, 2017	Lisdexamfetamine chewable tablets approved for the treatment of ADHD in patients 6 years and above and moderate to severe BED in adults

2012 PAC Presentation

- September 2012
  - FDA's evaluation did not identify any new safety concerns
  - Committee recommendation:
    - Return to standard, ongoing monitoring for adverse events

2016 PAC Presentation

- April 2016
  - FDA identified a safety signal with alopecia reported in association with lisdexamfetamine and recommended review of this safety signal
  - Committee recommendations:
    - Continue ongoing safety monitoring
    - Review safety signal for alopecia
    - Although no suicidality signal identified, explore claims database to obtain information regarding suicidality

2016 PAC Presentation Follow Up

- A safety review of alopecia was completed in select amphetamine products that were previously not labeled for alopecia
- May 19, 2017 – alopecia added to the ADVERSE REACTIONS Postmarketing Experience section of the labeling for lisdexamfetamine and select amphetamine products

2016 PAC Presentation Follow Up

- Division of Epidemiology (DEPI) exploring use of administrative claims databases to evaluate suicide-related outcomes
  - Data Sources for Suicide Outcomes Project
    - Study intentional self-harm in association with drug exposures
    - Includes systematic review of suicidal outcome definitions used in observational studies (Swain et al.)
  - Methodology for study of suicide and self-harm is currently not well-established
  - Low event rates present challenges regarding statistical power

Swain RS et al. A systematic review of validated suicide outcome classification in observational studies. *Int J Epidemiol*. 2019;48(5):1636-1649.

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Labeling: Warnings and Precautions

5.1 Potential for Abuse and Dependence
5.2 Serious Cardiovascular Reactions
5.3 Blood Pressure and Heart Rate Increases
5.4 Psychiatric Adverse Reactions
5.5 Suppression of Growth
5.6 Peripheral Vasculopathy, including Raynaud's Phenomenon
5.7 Serotonin Syndrome

Labeling: Adverse Events - Pediatric

6.1 Clinical Trials Experience

- The most common adverse reactions were similar for children, adolescents, and/or adults
- Frequently reported adverse reactions (≥5%)
  - Anorexia
  - Anxiety
  - Decreased appetite
  - Decreased weight
  - Diarrhea
  - Dizziness
  - Dry mouth
  - Irritability
  - Insomnia
  - Nausea
  - Upper abdominal pain
  - Vomiting

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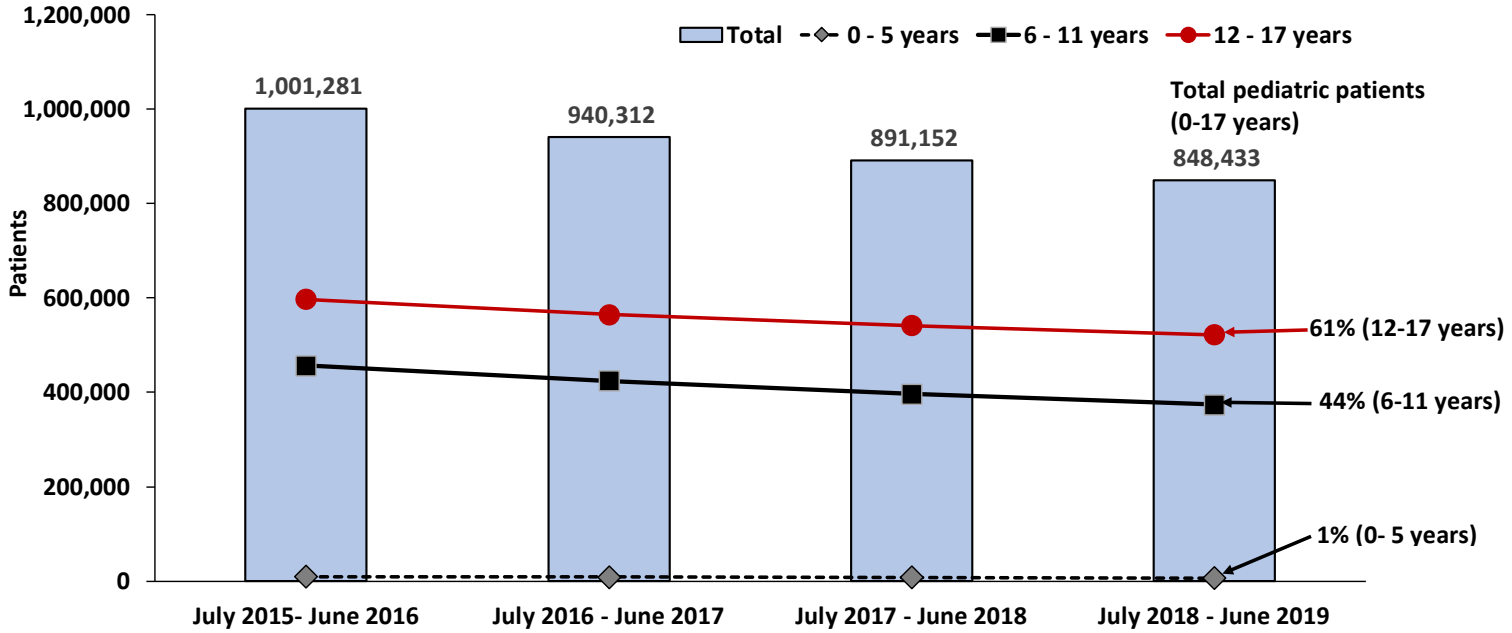
Lisdexamfetamine: Pediatric Utilization



Estimated number of pediatric patients (0-17 years) with dispensed prescriptions for lisdexamfetamine from U.S. Outpatient retail pharmacies, stratified by patient age, July 2015- June 2019, yearly

Source: IQVIA Total Patient Tracker™ Data extracted December 2019

Unique patient counts may not be added across time periods or age groups due to the possibility of double counting those patients who are receiving treatment over multiple time periods or age into the next age group during the time period.

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Selection of Serious Unlabeled U.S. Pediatric FAERS Cases with Lisdexamfetamine

Total pediatric reports with a serious outcome (n=202)
Pediatric reports with the outcome of death (n=13)

Excluded Reports* (n=179)
(Including 10 deaths)

- Duplicates (n=19, including 9 deaths)
- Labeled adverse event for lisdexamfetamine (n=89)
- Unassessable (n=45)
- Transplacental exposure (n=3)
- No adverse event described (n=8)
- Adverse event more likely associated with concomitant medications or comorbidities (n=7, including 1 death)
- Drug ineffective and indication-related adverse events (n=6)
- Miscoded age (n=2)

Pediatric cases for discussion (n=23)
(Including 3 deaths)

* Reviewed and excluded for stated reasons

Lisdexamfetamine Summary of FAERS Cases with Serious Unlabeled Adverse Events (n=23)

- Cases with fatal outcome (n=3)
  - Completed suicide in adolescent patients
    - Insufficient information of a causal association with lisdexamfetamine

Lisdexamfetamine Summary of FAERS Cases with Serious Unlabeled Adverse Events (n=23)

- Cases with nonfatal outcomes (n=20)
  - Suicide-related events (n=11) or self-injury events (n=3)
    - Insufficient evidence to support a signal
      - Cases with were limited or confounded
    - Findings from past evaluations did not support a signal
      - Placebo-controlled trials with lisdexamfetamine and other ADHD stimulants did not provide evidence of increased risk for suicide-related event
      - Applicant reviews for suicide-related events with lisdexamfetamine did not identify increased risk relative to background risk for in general population and ADHD population
      - FDA reviews evaluating suicide-related events for lisdexamfetamine and other ADHD drugs did not support a signal

Lisdexamfetamine Summary of FAERS Cases with Serious Unlabeled Adverse Events (n=23)

- Cases with nonfatal outcomes (n=20)
  - Single reports each of: cerebrovascular accident, macular degeneration, aphthous ulcer, hepatic enzyme increased
  - Acute dystonia (n=2)
    - Potential signal for evaluation
      - Monitored adverse event as part of ongoing surveillance activities for ADHD stimulants
      - Concurrent drug interaction study involving ADHD drugs required evaluation for acute dystonia and ADHD drug

Acute Dystonia Cases

- 26-month-old male with accidental ingestion of lisdexamfetamine developed irritability, gait disturbance, hypertension, tachycardia, and dystonia. He received diphenhydramine and lorazepam in the emergency room and dexmedetomidine in the pediatric intensive care unit. The event outcome was not reported.

- 11-year-old male with ADHD recently restarted lisdexamfetamine after a brief discontinuation for school summer break and developed “hand tightness and inability to relax his hands from the flexed position,” episodes of being “hunched over and hyperventilating,” and “became limp and developed nystagmus.” He was hospitalized and the events resolved after treatment with an unknown medication. Lisdexamfetamine was discontinued with plans to switch to another treatment.

Summary of Pediatric Focused Safety Review

- Acute dystonic reactions was identified as a potential signal
- Adverse events reported in pediatric patients consistent with labeled adverse events
- FDA recommends continuation of ongoing, postmarketing pharmacovigilance for all adverse events with lisdexamfetamine

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Relevant Product Labeling

Mydayis – Section 6.2 Adverse Reactions

- *Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, euphoria, dyskinesia, dysphoria, headache, tics, fatigue, aggression, anger, logorrhea, dermatillomania, and paresthesia (including formication).*

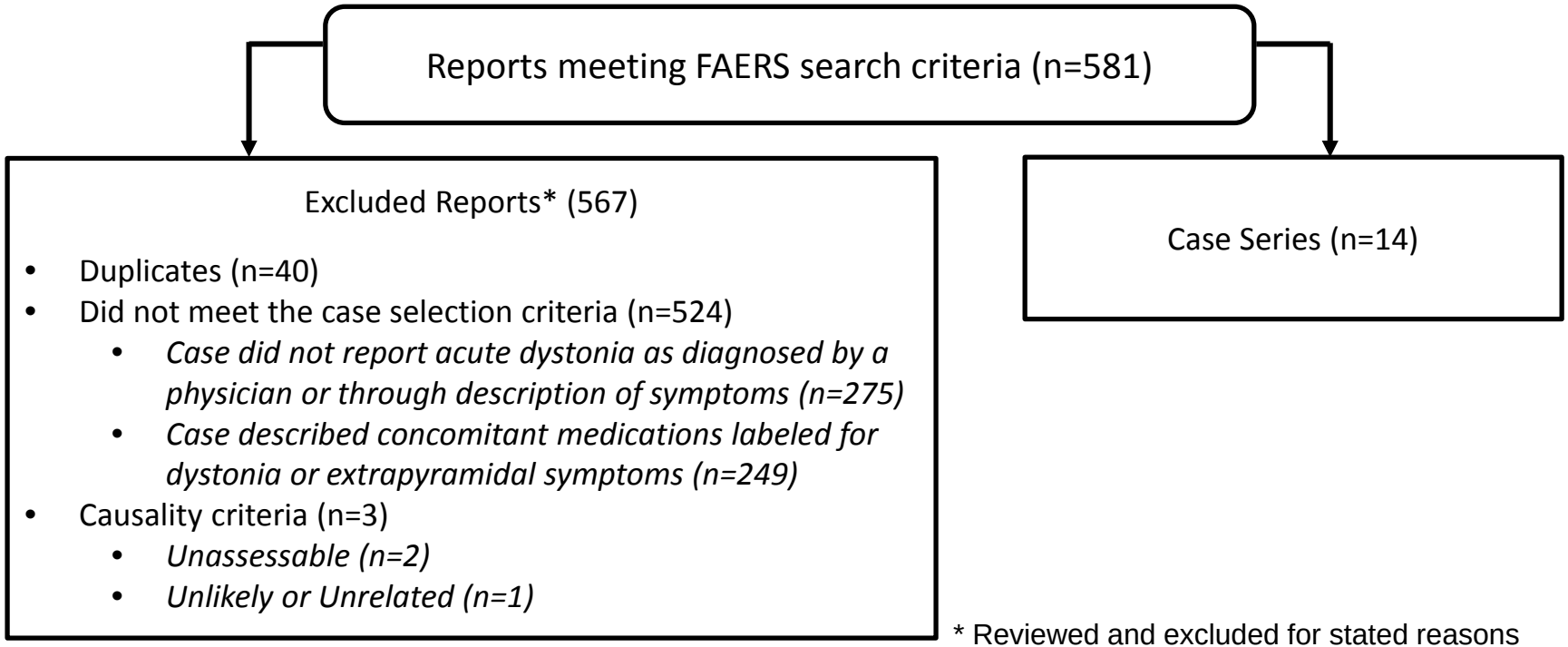
Concerta – Section 6.6 Adverse Reactions

- *Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs.*

Acute Dystonia and ADHD Stimulants or Atomoxetine Case Selection Criteria

- **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 dystonic reaction or acute dystonia, i.e., oculogyric crisis, torticollis, opisthotonos, trismus, laryngospasm
- **Exclusion Criteria**
  - Duplicate report
  - Case describes concomitant use of medications labeled for dystonia or extrapyramidal symptoms
  - Case describes non-specific movement abnormality, i.e., muscle twitching, musculoskeletal stiffness
  - Case describes patients with history of primary dystonia or family history of primary dystonia
  - Case describes acute dystonic symptoms occurring prior to exposure to ADHD stimulants or atomoxetine
  - Causality assessment per WHO-UMC scale deemed “unassessable” or “unlikely”

Selection of FAERS Cases with Acute Dystonia and ADHD Stimulants or Atomoxetine Received Through December 12, 2019



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Descriptive Characteristics of Acute Dystonia with ADHD Stimulant Medication or Atomoxetine in FAERS Received by FDA Through December 6, 2019 (N=14)					
Selected Characteristics		Total (n=14)	Amphetamine Products* (n=4)	Methylphenidate Products (n=10)	Atomoxetine* (n=1)
Age (years)	<5	3	0	3	0
	5-9	8	2	6	0
	10-14	2	1	1	0
	15-19	1	1*	0	1*
Sex	Male	8	2	6	0
	Female	6	2*	4	1*
Country	USA	8	3*	5	1*
	Foreign	6	1	5	0
Report Year	'03-'07	2	1*	1	1*
	'08-'12	4	1	3	0
	'13-'18	8	2	6	0

* One case reported both an amphetamine product and atomoxetine. The case is reflected in counts for amphetamine and atomoxetine.

Descriptive Characteristics of Acute Dystonia with ADHD Stimulant Medication or Atomoxetine in FAERS Received by FDA Through December 6, 2019 (N=14)					
Selected Characteristics		Total (n=14)	Amphetamine Products* (n=4)	Methylphenidate Products (n=10)	Atomoxetine* (n=1)
Prescribed indication	ADHD	10	4*	6	1*
	ADD	2	0	2	0
	Hyperactivity	1	0	1	0
	Not prescribed	1	0	1	0
Dechallenge	Positive	4	0	4	0
	Not reported	10	4*	6	1*
Serious outcome†	(Total)	(13)	(4*)	(9)	(1*)
	Other serious	10	3	7	0
	Hospitalization	4	2*	2	1*
	Req intervention	2	1*	1	1*
Causality	Possible	11	3	8	0
	Probable	3	1*	2	1*

* One case reported both an amphetamine product and atomoxetine. The case is reflected in counts for amphetamine and atomoxetine.

† A case may report more than one serious outcome

Division of Epidemiology Literature Search

Article	Objective	Study Design	Conclusion
Meyers, et al., 2018	Assess the risk of dystonia with atomoxetine and with stimulants, in children and adolescents	Retrospective observational cohort study	No difference in risk of dystonia among pediatric patients treated with atomoxetine vs. stimulants
Nutt, et al., 1988	Examine the epidemiology of dystonia (focal or generalized)	Descriptive, retrospective cohort study conducted by chart review	The incidence of focal plus generalized dystonia in this study was approximately 26 per million per year Exposure to stimulants did not appear to be a significant risk factor among these cases
Sharp and Perdue, 2007	Assess abnormal movements among children treated with psychostimulants, atypical antipsychotics, both in combination, or neither	Cross-sectional study of patients in treatment at the authors' clinic	Authors concluded results suggest an interaction between stimulants and atypical antipsychotics resulting in a higher prevalence of abnormal movements in children receiving combined therapy

Acute Dystonia and ADHD Stimulants or Atomoxetine Conclusion

- Insufficient evidence to support the postmarket safety signal of acute dystonia associated with ADHD stimulants or atomoxetine

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