Neuropsychiatric Events Associated with Montelukast: Postmarketing Experience

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Outline

- Purpose
- Overview of postmarketing adverse event reports associated with montelukast to date
- Fatal neuropsychiatric events
- Select non-fatal neuropsychiatric events
- Summary

Purpose

- Analyze adverse event reporting trends associated with montelukast using information from the FDA Adverse Event Reporting System (FAERS)
- Characterize cases of select neuropsychiatric events associated with montelukast in the post-marketing setting

Background

- Office of Surveillance and Epidemiology has completed an extensive number of reviews regarding neuropsychiatric events associated with montelukast
- Most recent review (2018) was completed in response to the Patient Advocacy groups letter to the Office of Pediatric Therapeutics

FDA Adverse Event Reporting System

- Computerized database of spontaneous reports
  - Voluntary communication from an individual (e.g., healthcare professional, consumer) describing one or more suspected adverse events
- Contains human drug and therapeutic biologic reports
- As of May 2019
  - ~18 million reports received since 1969
- Over 2 million new reports received in 2018

Limitations

- Spontaneous adverse event reporting does not require a causal relationship
- Under-reporting
- Lack of clinical detail
- Cannot calculate an incidence rate
- Reporting bias – more likely to report severe cases
- Stimulated reporting – increases in reports due to heightened public awareness

Strengths

- Detection of events not seen in clinical trials (“signal generation”)
- Detection of events with rare background rate
- Identification of possible risk factors, populations, and other clinically significant emerging safety concerns
- Conduit for the general public to directly communicate safety concerns to the FDA in terms of specific patient experiences

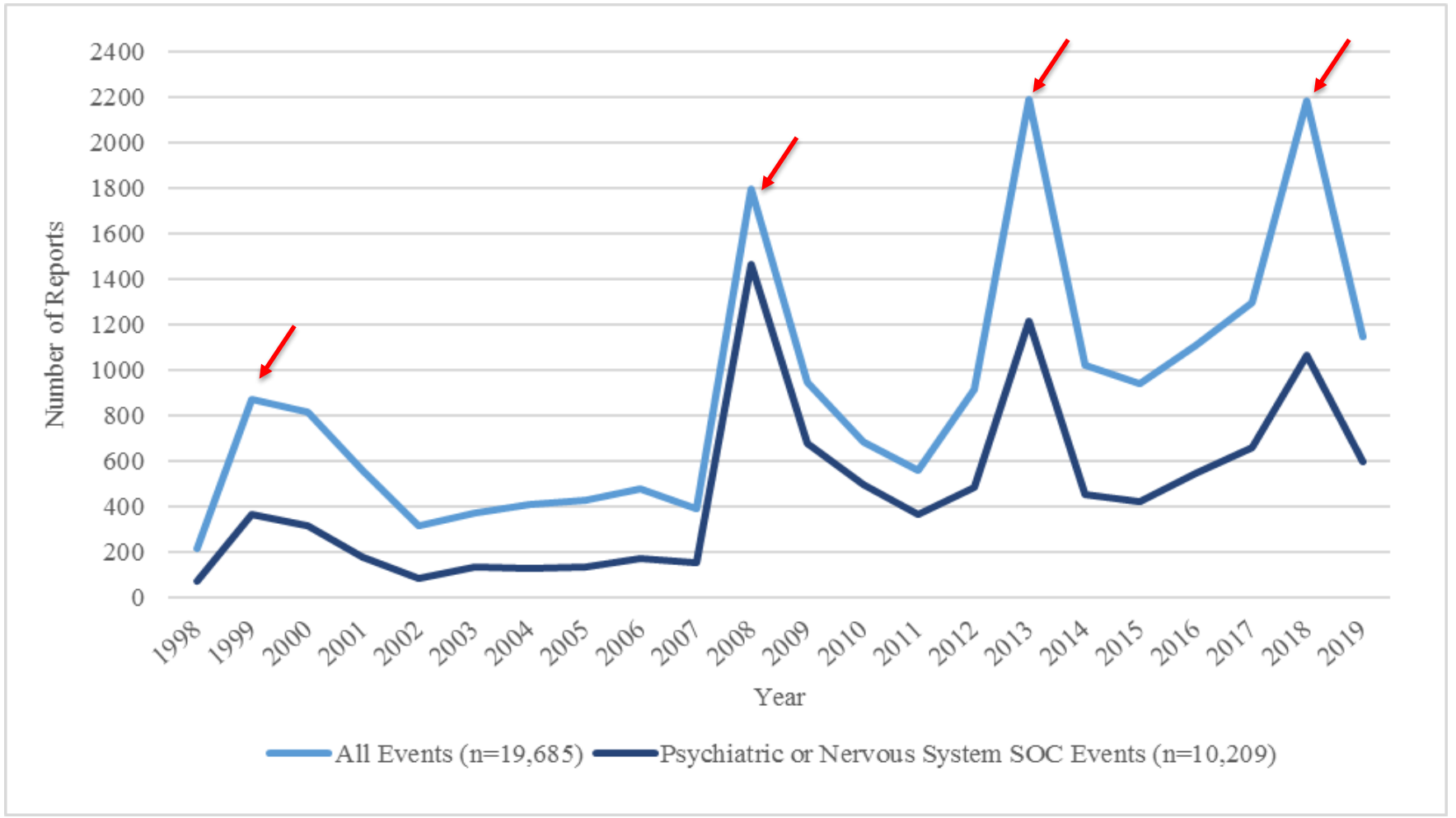
High-Level Overview of Neuropsychiatric Adverse Events Reported to FAERS

FAERS Search Strategy

- Received from February 20, 1998*, to May 31, 2019
- All reports, foreign and domestic, all events for montelukast or montelukast sodium†

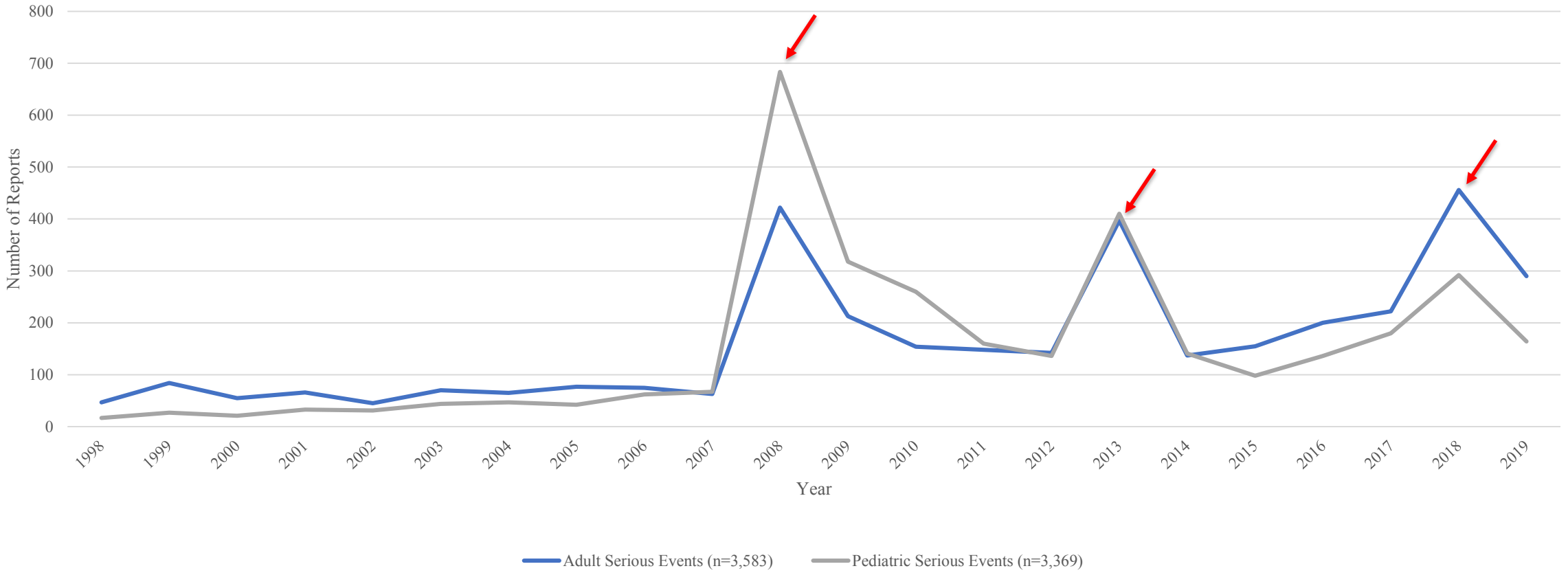
*Date of U.S. drug approval
†Includes reports for Singulair

Figure 1. All Montelukast FAERS Reports and Neuropsychiatric Adverse Event Reports by FDA Received Year between 1998-2019*



*May include duplicates and not assessed for causality. Data lock date May 31, 2019.

Figure 2. Adult versus Pediatric Serious Neuropsychiatric Events Reported by Year*



*May include duplicates and not assessed for causality. Only includes reports with age in the coded field. Data lock date May 31, 2019.

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Review of Domestic Fatal Neuropsychiatric Adverse Events Associated with Montelukast Use

FAERS Search Strategy

- Received from February 20, 1998*, to May 31, 2019, montelukast or montelukast sodium†
- Domestic, fatal events containing Preferred Terms (PTs) within Nervous System Disorders or Psychiatric Disorders System Organ Classes (SOC)

*Date of U.S. drug approval
†Includes reports for Singulair

FAERS Search Results

- 296 crude reports; 214 excluded for the following reasons
  - 135 were duplicates,
  - 44 were reported by a poison control center and described a multi-substance overdose,
  - 20 contained a cause of death other than a neuropsychiatric event (e.g., asthma exacerbation, sepsis, motor vehicle accident, myocardial infarction, choking),
  - 7 were entered for groups with data reported in aggregate (i.e., data for individual patients was not reported),
  - 4 were miscoded and did not report fatalities,
  - 2 described transplacental exposure, and
  - 2 described illicit drug overdoses
- 82 unique cases of completed suicide

FAERS Case Characteristics (n=82)

Descriptive Characteristics of Domestic Cases of Completed Suicide Associated with Montelukast Use, Received by FDA from February 20, 1998, to May 31, 2019					
		Total (n=82)	Adult (≥17 years) (n=45)	Pediatric (0-16.99 years) (n=19)	Age not reported (n=18)
Year reported	1998-2004	1	1	--	--
	2005-2009	52	33	12	7
	2010-2014	14	5	6	3
	2015-2019	15	6	1	8
Sex	Male	54	30	13	11
	Female	22	14	6	2
	Not reported	6	1	--	5
Age (years)	Less than 10	2	--	2	--
	11-13	5	--	5	--
	14-16	12	--	12	--
	17-19	12	12	--	--
	20-24	6	6	--	--
	25-29	3	3	--	--
	30-39	1	1	--	--
	40-49	6	6	--	--
	50-64	12	12	--	--
	65 and older	5	5	--	--
	Not reported	18	--	--	--

Patient Characteristics

- Patient demographics
  - Majority of cases (35/64;55%)* occurred in patients 11-24 years of age
  - Majority of cases (54/76;71%)* occurred in male patients
- Psychiatric history
  - 11/82 confirmed a psychiatric history
  - Only 2 cases contained sufficient information to determine the psychiatric condition preceded montelukast initiation

*64 cases reported age; 76 cases reported sex

Miron O, Yu KH, Wilf-Miron R, Kohane IS. Suicide Rates Among Adolescents and Young Adults in the United States, 2000-2017. *JAMA.* 2019;321(23):2362-2364.

Key Theme: Limited Information

- Majority of cases (48/82, 59%) did not contain sufficient information for appropriate evaluation of the relationship between montelukast and the adverse events
- Missing documentation
  - Time to onset of event
  - Use of concomitant medications
  - Presence of past or current comorbidities including psychiatric illness
- Remaining well-documented cases contained medications or comorbidities that may increase the risk of self-harm

Additional Key Themes

- Stimulated reporting
  - Evidence of stimulated reporting was found in 33% of cases (27/82)
  - Majority of cases (51/82) were reported between 2008 and 2009
- Role of patient/caregiver education
  - 6/82 cases reported the absence of knowledge or lack of patient counseling regarding neuropsychiatric effects of montelukast
    - Four occurred prior to labeling changes to add suicidality to labeling for montelukast

Summary

- FDA continues to receive neuropsychiatric adverse event reports for montelukast
- Frequency of reporting is influenced by multiple factors
- Direct relationship between the completed suicide events and montelukast is difficult to determine
  - Limited data in the cases
  - Presence of potentially contributory comorbidities
  - Concomitant medications
  - Other unmeasurable contributors

Updated Evaluation of Select Unlabeled Neuropsychiatric Events

Background

- Most recent review of postmarketing and literature reports was completed in response to the Patient Advocacy groups letter to the Office of Pediatric Therapeutics
- Select neuropsychiatric events
  - Obsessive-compulsive symptoms
  - Excoriation
  - Hyperkinesia
  - Withdrawal neuropsychiatric events

FAERS Search Strategy

- Received from January 17, 2018,* to May 31, 2019, montelukast or montelukast sodium†
- Events containing Preferred Terms (PTs) Hyperkinesia, Skin abrasion, or the High Level Term (HLT) Withdrawal and rebound effects

*Data lock of previous review was February 20, 1998, to January 16, 2018.
†Includes reports submitted under the brand name Singulair

FAERS Search Results

Number of Cases of Select Neuropsychiatric Events of Interest Associated with Montelukast Isolated From FAERS		
	February 20, 1998 – January 16, 2018	January 17, 2018 - May 31, 2019
Neuropsychiatric Event of Interest	Number of Cases	
Excoriation	0	0
Hyperkinesia	3	0
Withdrawal Neuropsychiatric Events	15	2

Withdrawal Neuropsychiatric Events

- Previous review isolated 15 cases of withdrawal events
  - 6/15: new onset psychiatric events after montelukast discontinuation
  - 9/15: developed symptoms during montelukast treatment which continued or recurred following montelukast cessation
  - Most common symptoms: anxiety, abnormal behavior, aggression, fear, suicidal ideation, crying, feeling abnormal
  - 13/15 cases were of unassessable causality
- Concluded that the lack of consistency among FAERS cases reporting neuropsychiatric events following montelukast withdrawal did not justify additional regulatory action

Withdrawal Neuropsychiatric Events

- Updated review isolated 2 additional cases assessed as possible causality
  - 17-year-old female with worsening of pre-existing anxiety and suicidal urges
  - 10-year-old female with new onset OCD-like behaviors and anger
- Limited information in the cases prevents robust assessment of causality

Limitations

- Variability of clinical detection of events
- Reporter must report as withdrawal event and not progression of neuropsychiatric condition

Conclusion

- Totality of the data provided regarding withdrawal neuropsychiatric events remains sparse
- Continued surveillance regarding withdrawal neuropsychiatric events following montelukast cessation

Summary

- FDA continues to receive reports of neuropsychiatric events associated with montelukast
- Many of these events are currently labeled
- FAERS post-marketing database cannot give information regarding the frequency of these events


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