FDA Briefing Document

Pediatric Advisory Committee Meeting
September 27, 2019

Neuropsychiatric Events with Use of Montelukast in Pediatric Patients

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought information and data regarding montelukast to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Division Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
M E M O R A N D U M

Date:	September 4, 2019
From:	Sally Seymour, MD Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Stacy Chin, MD Clinical Team Leader, DPARP Katherine Clarridge, MD Clinical Reviewer, DPARP
To:	Pediatric Advisory Committee (PAC) and Drug Safety and Risk Management Advisory Committee (DSaRM)
Subject:	Overview of the September 27, 2019, Joint PAC and DSaRM meeting

1.1. Introduction

Thank you for your participation in the upcoming joint meeting of the Pediatric Advisory Committee (PAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee, to be held September 27, 2019. As members of FDA Advisory Committees (AC), we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision-making processes. The objective of the upcoming meeting is to discuss a pediatric-focused safety review of neuropsychiatric events with the use of montelukast.

The safety concerns regarding neuropsychiatric events with montelukast (and other leukotriene modifiers) date back to 2007 when FDA initiated an investigation following a request by Merck to update the montelukast package insert with neuropsychiatric events, namely tremor, depression and suicidal behavior, as well as a suicide report in a 15-year-old male taking montelukast. The subsequent review resulted in FDA requiring a Precaution (currently Warnings and Precautions) for neuropsychiatric events in the prescribing information and patient information leaflet. Since that time, there have been additional updates to the existing Warnings and Precautions as described in the Background - Regulatory History section. In addition, there has been continued interest and discussion with stakeholders regarding this safety issue, including discussion at the Nonprescription Drugs Advisory Committee (NDAC) meeting in May 2014 followed by a PAC meeting in September 2014.

In November 2017, stakeholders requested FDA re-evaluate the risk of neuropsychiatric events with montelukast (Appendix, Section 6.2). FDA initiated another review of data in the FDA Adverse Event Reporting System (FAERS) database, drug utilization databases, and recent literature. In addition, FDA conducted a study in the Sentinel Distributed Database system to evaluate the risk of serious depression, self-harm, and suicide in montelukast users. Detailed reviews are provided in this background package. The purpose of this PAC meeting is to present our findings and recommendations. We ask for your input on regulatory options for labeling and recommendation for communication strategies as it relates to the risk of neuropsychiatric side effects of montelukast in pediatric patients.

Although all the leukotriene modifier products (montelukast, zafirlukast, zileuton) have had neuropsychiatric events added to the Warnings and Precautions section of the label, this discussion will focus on montelukast which accounts for the majority of the market share amongst the leukotriene modifier products.

1.2. Product Information

1.2.1. Approval History

Montelukast sodium (Singulair) is a specific cysteinyl leukotriene type-1 receptor antagonist (CYSLT-1) that was first approved in 1998 for patients with asthma ≥ 15 years of age. Over the years, the indication has been expanded to include seasonal allergic rhinitis (SAR) in 2002,

perennial allergic rhinitis (PAR) in 2005, and prevention of exercise-induced bronchoconstriction (EIB) in 2007. Montelukast is available in multiple dosage forms and strengths by prescription only. The currently approved indications and prescription dosing by indication and patient age are summarized in Table 1.

Table 1. Approved Montelukast Prescription Dosing by Indication and Age

Indication/Age	**Dose**
Asthma	
≥ 15 years	10 mg
6-14 years	5 mg
12 months - 5 years	4 mg
Seasonal Allergic Rhinitis (SAR)	
≥ 15 years	10 mg
6-14 years	5 mg
2-5 years	4 mg
Perennial Allergic Rhinitis (PAR)	
≥ 15 years	10 mg
6-14 years	5 mg
6 months - 5 years	4 mg
Exercise-Induced Bronchoconstriction (EIB)	
≥ 15 years	10 mg
6-14 years of age	5 mg

Source: Singulair Prescription Package Insert

Montelukast is available in multiple formulations in the United States (film coated tablet, chewable tablets, and oral granules). Three NDA applications for Singulair have been approved and are currently marketed.

- Singulair (NDA 20-829; approved February 20, 1998): Tablets 10 mg
- Singulair (NDA 20-830; approved February 20, 1998): Chewable Tablets 4 mg, 5 mg
- Singulair (NDA 21-409; approved July 26, 2002): Oral Granules 4 mg

Generic montelukast has also been marketed under numerous ANDAs for all formulations (4 mg, 5 mg, and 10 mg, and oral granules) beginning on August 3, 2012. Per the NDA holder, Merck, generic montelukast products now account for the majority (>99%) of the market share in the United States.

1.2.2. Clinical Trials to Support Approval

To provide some context for the discussion at hand, this section lists the pivotal clinical trials and the corresponding National Clinical Trial (NCT) Identifier number which provided evidence of safety and effectiveness and served as the basis for approval of montelukast for each indication and age group (Table 2).

Data from numerous clinical trials have been reviewed by the Agency to support dose selection, efficacy, and safety of montelukast for the treatment of the aforementioned indications and to inform the current product label. Because efficacy is often extrapolated from adults to children when the disease process and systemic exposure are the same, pediatric trials were primarily designed to evaluate safety. Although the clinical trial database for montelukast is sizeable, most trials were relatively short in duration given the indications being studied.

Table 2. Key Pivotal Efficacy and Safety Studies

Trial (NCT#)	Age Range (years)	Design	Treatment Arms (N)	Treatment Duration	Primary Outcome
Seasonal Allergic Rhinitis (SAR)					
117 (00963599)	15-82	P3, R, DB, PC, AC, PG, MC	Montelukast + Loratadine 10mg (302) Montelukast 10mg (155) Loratadine 10mg (301) Placebo (149)	2 weeks	DNSS
162 (00979901)	15-81	P3, R, DB, PC, AC, PG, MC	Montelukast 10mg (348) Loratadine 10mg (602) Placebo (352)	2 weeks	DNSS
192 (00960141)	15-82	P3, R, DB, PC, AC, PG, MC	Montelukast 10mg (326) Loratadine 10mg (170) Placebo (333)	2 weeks	DNSS
219 (00968149)	2-14	P3, R, DB, PC	Montelukast 4mg (100) Montelukast 5mg (180) Placebo (133)	2 weeks	ASS
235 (00972738)	15-82	P3, R, DB, PC, AC, PG, MC	Montelukast 10mg (522) Loratadine 10mg (171) Placebo (521)	2 weeks	DNSS
240 (00963469)	15-82	P3, R, DB, PC, AC, PG, MC	Montelukast 10mg (448) Loratadine 10mg (180) Placebo (451)	4 weeks	DNSS
Perennial Allergic Rhinitis (PAR)					
246 (00974571)	15-82	P3, R, DB, PC, AC, PG, MC	Montelukast 10mg (630) Cetirizine 10mg (122) Placebo (613)	6 weeks	DNSS
265 (00092118)	15-81	P3, R, DB, PC, PG, MC	Montelukast 10mg (1002) Placebo (990)	6 weeks	DNSS
Exercise Induced Bronchospasm (EIB)					
270 (00092131)	16-39	P3, R, DB, PC, CO, MC	Montelukast 10mg → placebo (25) Placebo → Montelukast 10mg (26)	2 days x 2	ΔFEV_1

275 (00090142)	15-41	P3, R, DB, PC, CO, MC	Montelukast 10mg → placebo (31) Placebo → Montelukast 10mg (31)	2 days x 2	ΔFEV_1
316 (00245570)	15-44	P3, R, DB, PC, AC, CO, MC	Montelukast 10mg Salmeterol 50mcg Placebo Total subjects (47) randomized evenly to each sequence	1 day x 4	ΔFEV_1
377 (00534976)	6-14	P3, R, DB, PC, CO, MC	Montelukast 5mg → placebo (28) Placebo → Montelukast 5mg (37)	2 days x 2	% fall in FEV_1
Asthma					
020	15-85	P3, R, DB, PC, PG, MC	Montelukast 10mg (387) Placebo (257) Beclomethasone 2 puffs BID (251)	12 weeks	ΔFEV_1
031	15-85	P3, R, DB, PC, PG, MC	Montelukast 10mg (408) Placebo (273)	12 weeks	ΔFEV_1
049	6-14	P3, R, DB, PC, PG, MC	Montelukast (201) Placebo (135)	8 weeks	ΔFEV_1
072 (00968201)	2-5	P3, R, DB, PC, PC, MC	Montelukast (461) Placebo (228)	12 weeks	safety

(N): number of patients, P: phase, R: randomized, DB: double blind, PC: placebo controlled, AC: active control, PG: parallel group, CO: Crossover, MC: Multicenter, DNSS: daytime nasal symptom score, ASS: Average Symptoms Score, C: cetirizine, FEV_1: forced expiratory volume in 1 second

Source: Sponsor submitted Clinical Study Reports.

1.2.3. Product Label

The current montelukast product label (last updated 08/2019) contains information regarding neuropsychiatric events in the Warnings and Precautions, Adverse Reactions - Post-marketing Experience, and Patient Counseling Information sections. Select labeling sections regarding neuropsychiatric events with montelukast are shown below.

----------**5 WARNINGS AND PRECAUTIONS**----------

5.4 Neuropsychiatric Events

Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include, but are not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.
Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur [*see Adverse Reactions (6.2)].*

----------**6 ADVERSE REACTIONS**----------

6.2 Post-Marketing Experience

Psychiatric disorders: including, but not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor [*see Warnings and Precautions (5.4)].*

----------**17 PATIENT COUNSELING INFORMATION**----------

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Information for Patients:

- Patients should be instructed to notify their physician if neuropsychiatric events occur while using SINGULAIR.

These events are also described in the FDA approved Patient Information Leaflet for Singulair below.

SINGULAIR may cause serious side effects:

- Behavior and mood-related changes. Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - memory problems
  - obsessive-compulsive symptoms
  - attention problems
  - restlessness
  - bad or vivid dreams
  - sleep walking
  - depression
  - stuttering
  - disorientation (confusion)
  - suicidal thoughts and actions (including suicide)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - tremor
  - trouble sleeping
  - irritability
  - uncontrolled muscle movements

1.3. Regulatory History Related to Neuropsychiatric Findings

1.3.1. Original Safety Review 2007 – 2009

In 2007, Merck submitted labeling supplements to add "tremor", "depression", and "suicidal thinking and behavior (suicidality)" to the Adverse Reactions Post-Marketing Experience section of the montelukast prescribing information. Because of the nature of these events and outside inquiries regarding an index case of suicide in a 15-year-old male taking montelukast in August 2007, FDA initiated a safety review of drugs that act via the leukotriene pathway and the potential association of neuropsychiatric events, including suicide. FDA requested that Merck along with sponsors for zafirlukast and zileuton provide an analysis of neuropsychiatric adverse events and suicide and suicide-related adverse events from their clinical trial databases. As part of the review, FDA also evaluated safety data from literature and FDA post-marketing adverse event reports (FAERS). FDA posted an Early Communication outlining the ongoing safety review of montelukast and other leukotriene modifying agents (LMTA).[1]

Review of Data from Clinical Trials
To assess suicide and suicidal behavior, Merck submitted data from 41 trials in patients 6 years of age and older, of which 9929 subjects were treated with montelukast, 7780 were treated with placebo, and 4724 were treated with an active control for a total population of 22,433 subjects. These trials included patients with asthma, SAR, PAR, and migraine headaches. The duration of randomized treatment ranged from ≤ 2 weeks to 56 weeks. One adult patient (0.01%) out of 9929 patients treated with montelukast had suicidal ideation and there were no completed suicides. No patients in the placebo or active control groups had suicidal ideation or suicide.

FDA also requested that manufacturers of other leukotriene modifiers submit controlled trial data for suicidality. AstraZeneca submitted results from 45 placebo-controlled clinical trials in patients 5 years of age and older, of which 7540 were treated with zafirlukast and 4659 were treated with a placebo. No patients treated with zafirlukast had suicidal ideation or completed suicide. Two patients in the placebo group (0.04%) had suicidality (one suicide attempt and one suicidal ideation). Cornerstone Therapeutics submitted results from 11 placebo-controlled clinical trials in patients 12 years of age and older, of which 1745 were treated with zileuton and 1063 were treated with a placebo. No patients treated with zileuton or placebo had suicidal ideation or completed suicide.

In addition to suicidality, FDA reviewed data for other neuropsychiatric events[a] from controlled clinical trials in patients 3 months of age and older. The montelukast safety database included 10,402 montelukast treated patients, 8017 placebo patients and 4724 active control patients. Of these, 2735 (13%) were < 6 years of age, 1919 (9%) were 6 to 11 years, and 1624 (8%) were 12 to 17 years. In

[a] Included all MedDRA (v11.0) Preferred Terms within the Psychiatric Disorders Systems Organ Class, as well as akathisia, extrapyramidal disorder, hyperkinesia, hyperkinesia neonatal, motor dysfunction, movement disorder, psychomotor hyperactivity, restlessness, asthenia, chronic fatigue syndrome, fatigue, feeling abnormal, feeling jittery, irritability, and malaise

general, neuropsychiatric events were not common in the clinical trials, but ascertainment was a concern because of the low frequency of events and because the trials were not designed to specifically examine neuropsychiatric events. The overall rate of neuropsychiatric events was low - the frequency for all events was 2.8% and 2.4% for montelukast and placebo treatment, respectively. Though rare, the number of treatment discontinuations and serious[b] neuropsychiatric events were either the same or lower in the montelukast group. In the pediatric population, sleep disorders were the most common neuropsychiatric event (although only reported in < 1% of patients) and were more common with montelukast treatment in patients ages 6 to 11 years and adolescents. Similarly, sleep disorders were more common with zafirlukast (0.8% vs 0.7%) and zileuton (3.4% vs 1%) compared to placebo. Depressed mood was also more frequent in the montelukast group compared to placebo, both overall (0.17% vs 0.07%) and in pediatric patients.

A review of the clinical trial safety database did not reveal a strong signal for neuropsychiatric events or suicidality for montelukast or other leukotriene modifiers. However, FDA noted the limitations of this review because the clinical trials were primarily short in duration and not designed to specifically examine neuropsychiatric events.

Review of Post-marketing Reports

In addition to controlled clinical trial data, FDA also reviewed post-marketing data in FAERS for neuropsychiatric events. The review identified a broad set of neuropsychiatric adverse event reports, some of which appeared consistent with a drug-induced effect (e.g., positive de-challenge or re-challenge); however, the events were typically non-serious and reversed with the cessation of therapy. Based upon the review of post-marketing adverse event reports, FDA recommended a Precaution in the product labeling to describe the variety of neuropsychiatric events reported.

Labeling and Communications

FDA updated the labeling for montelukast, zafirlukast, and zileuton to reflect the findings of the FDA reviews and posted several Drug Safety Communications (DSCs) on the FDA website to inform healthcare professionals and patients of the new safety information.[1-3] Following FDA's DSCs, Merck communicated the information to health care providers and patients via several mechanisms including distribution of hard copies of all FDA statements along with a Dear Health Care Provider (DHCP) letter to specialists and primary care physicians. Merck also sent communications containing the FDA updates to pharmacies and professional societies and posted the FDA statements to their website. AstraZeneca sent a similar DHCP letter shortly thereafter.

Post-marketing Trial Considerations

Upon completing the review, FDA considered the appropriateness of requiring a post-marketing safety trial. Given the low rate of neuropsychiatric events in the clinical trials, the wide variety of event reports (e.g., depression, anxiety, sleep disorders), and the fact that the more serious adverse events of

[b] Under 21§CFR312.32 an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

concern, such as suicidality, were expected to be quite rare, a post-marketing safety trial was not required due to feasibility concerns.

January 2009 Citizen's Petition
On January 30, 2009, during the review of clinical trial data, the Parents United for Pharmaceutical Safety and Accountability submitted a Citizen Petition (CP) requesting FDA remove the indication for montelukast use in children and update the adverse events to include seizures, neurological damage, neuropsychiatric events, and Churg-Strauss Syndrome. FDA conducted a safety review to address the CP requests but did not find evidence to support removal of the indication for use in children. However, Henoch-Schonlein purpura was added to the Adverse Reactions Post-Marketing Experience section of the label.[4,5]

1.3.2. FDA Advisory Committee Meetings - 2014

In 2013, Merck proposed a partial over-the-counter (OTC) switch for montelukast for the SAR/PAR indications in adults - for temporary relief of symptoms due to upper respiratory allergies in adults. The use in children under 18 years of age and the asthma and EIB indications would remain prescription. On May 2, 2014, FDA convened the Nonprescription Drugs Advisory Committee (NDAC) to discuss the adequacy of the safety and efficacy data submitted by Merck to support the proposed OTC switch. Several issues were discussed including whether the risk/benefit profile of montelukast supported OTC use for the proposed indication. At this meeting, FDA raised concerns regarding off-label use for asthma, potential inappropriate use in the pediatric population, and, notably, the risk of neuropsychiatric events. The review of post-marketing data did not identify any new, previously unrecognized safety issues. However, the FDA acknowledged the lack of well-designed epidemiologic studies to accurately quantify the suicide risk among patients using montelukast. The majority of the committee did not agree that the risk/benefit profile of montelukast supported OTC use, and FDA did not approve the switch.[6]

Following the March 2012 approval of the EIB indication in pediatric patients, the PAC convened on September 23, 2014, to review the current montelukast labeling regarding the risk of neuropsychiatric events. Ultimately, the committee felt that the patient information was clear, but the physician labeling (i.e., Prescribing Information) might be strengthened. Specifically, the committee recommended formatting the label to highlight side effects of interest and communicating this information to healthcare providers so that they may better inform their patients. Following this PAC meeting, FDA contacted the sponsor to consider communication options including a DHCP letter or a DSC. These measures were not felt to be warranted, given the absence of new information to convey regarding this existing safety issue. However, in order to raise awareness amongst health care providers of the association of montelukast with neuropsychiatric events, FDA participated in a Medscape interview to summarize the take-home messages for clinicians prescribing leukotriene modifiers.[7]

1.3.3. Other Relevant Labeling Updates

Since the initial approval in 1998, the montelukast U.S. Prescribing Information (USPI) and Patient Product Information (USPPI) have periodically been updated to communicate post-marketing reports of neuropsychiatric events. The following neuropsychiatric adverse events were added to the post-marketing experience section of the label prior to 2007: dream abnormalities, irritability, and restlessness (1999), insomnia (2000), hallucinations (2001), agitation including aggressive behavior (2002). Since 2007, based upon review of labeling supplements submitted by the sponsor or in response to FDA request, the following terms have been added to the list of neuropsychiatric adverse events in the Warnings and Precautions section of the product label: tremors, depression, suicidal thinking and behavior (including suicide), anxiousness, hostility, somnambulism, disorientation, memory impairment, paresthesia/hypoesthesia, and very rarely seizures, tic, uncontrolled muscle movement, obsessive compulsive symptoms, and dysphemia (See Section 1.2.3).

1.4. Current Review of Montelukast and Neuropsychiatric Events

1.4.1. Correspondence from Patient Advocacy Groups

On November 3, 2017, the Montelukast (Singulair) Side Effects Support and Discussion Group, previously known as Making the Side Effects of Singulair Aware to Parents of Children & Teens, and Parents United for Pharmaceutical Safety and Accountability submitted a letter to FDA stating the incidence of neuropsychiatric side effects with montelukast is more common than suggested by the label and publicly available information. The letter contained an analysis of the FAERS Public Dashboard (citing 30,027 total adverse event cases with Singulair, montelukast, and montelukast sodium from 1998 and 2017 as of August 31, 2017)[c], citations of numerous case reports and studies, and an online survey conducted by the Parents and Facebook Groups. Furthermore, the letter requested the following from the FDA:

1) determine the mechanisms for montelukast's neuropsychiatric side effects,
2) determine the risk factors for neuropsychiatric adverse reactions,
3) determine the appropriate way to discontinue montelukast,
4) evaluate withdrawal symptoms and long-term sequelae of an adverse reaction,
5) reclassify neuropsychiatric side effects of montelukast to be common in children,
6) update labeling to include a warning for the possible delayed-onset of side effects including "excoriation", "hyperkinesia", and "obsessive-compulsive disorder",
7) issue a Medication Guide for montelukast due to the life-threatening potential of its neuropsychiatric side effects, and
8) consider a boxed warning.

To address concerns raised in the letter, FDA initiated the following:

- Reviewed information submitted with the request, including the literature citations and surveys

[c] The total of 30,027 cases is incorrect because searching with the three product terms separately (Singulair, montelukast, and montelukast sodium) retrieves duplicate reports. Therefore, the true total in the FAERS public dashboard through August 31, 2017, was 15,738 reports.

- Updated review of relevant literature related to montelukast and neuropsychiatric events, particularly frequency, risk factors, withdrawal symptoms, and mechanistic information. Findings from the most recent literature review are discussed in Sections 1.4.4 and 5.1
- Reviewed FAERS data for obsessive-compulsive disorder (OCD), excoriation, hyperkinesia, and other neuropsychiatric symptoms following withdrawal associated with montelukast and related LTMA use. An assessment of the most recent review of post-marketing data from FAERS are discussed in Sections 1.4.3 and 4.
- Evaluated the risk of neuropsychiatric adverse events associated with montelukast in the Sentinel Distributed Database. Methods for and results from the Sentinel query for depression, self-harm, suicide and death are discussed in Sections 1.4.5 and 5.2.
- Contacted the Australian Therapeutic Goods Administration (TGA), concurrently investigating the same safety issue. At the April 2008 Advisory Committee on Medicines (ACM) meeting, the members advised that while the evidence of association/causality between montelukast and neuropsychiatric events is not robust, the persistent signal requires vigilance due to the potential impact of serious adverse events.[8]
- Considered labeling options, including Boxed Warning, Medication Guide, and communication opportunities (discussed in Section 1.5).
- Consolidated history and reviews to present findings and recommendations to the PAC.

1.4.2. Drug Utilization

Based on dispensed prescription data from U.S. outpatient retail pharmacies, an estimated total of 2.3 million pediatric patients 0-16 years old (a quarter of the total 9.3 million patients of all ages) were dispensed montelukast in 2018; less than 1000 pediatric patients were dispensed zafirlukast and negligible number of pediatric patients dispensed zileuton. The highest proportion of pediatric montelukast use was among patients ages 6-11 years, followed by patients 12-16 years, 2-5 years and 0-1 year. The number of pediatric patients who received prescriptions dispensed for montelukast remained relatively steady from 2014 through 2018.

As reported by U.S. office-based physician surveys in 2018, the top diagnosis associated with montelukast use in patients ages 2-16 years old was asthma (ICD-10 code J45). Cough (ICD-10 code R05) was the top diagnosis associated with montelukast use in patients 0-1 year old. For all pediatric patients (0-16 years), vasomotor and allergic rhinitis (ICD-10 code J30) was the second most common diagnosis associated with montelukast.

1.4.3. FAERS Analyses

The Division of Pharmacovigilance I (DPV-I) completed two reviews, of which one was integrated with the Division of Epidemiology II (DEPI-II), in response to the safety concerns raised in the November 3, 2017, letter submitted by Parents United for Pharmaceutical Safety and Accountability and the Montelukast (Singulair) Side Effects Support and Discussion Group. This section will summarize the

analyses performed by DPV-I to address the requests in the aforementioned letter to include possible delayed-onset of side effects, excoriation, hyperkinesia, and OCD in the montelukast product label.

The first review completed by DPV-I and DEPI-II, dated September 12, 2018, (see Appendix, Section 6.3) contained an analysis of case reports in the FAERS database and the published medical literature, epidemiologic literature, and sponsor-submitted data for an association between LTMAs and possible delayed-onset of side effects, excoriation, hyperkinesia, and OCD. The FAERS database was searched from February 20, 1998, to January 16, 2018; no case reports involving zafirlukast or zileuton were identified, therefore, those products were excluded from further analysis. After analysis of the data with montelukast, the reviewers concluded that there was sufficient evidence to support the addition of OCD-like symptoms to the montelukast product label, and to add the phrase "including, but not limited to" as a precursor to labeling sections regarding neuropsychiatric events. The reviewers concluded there was insufficient evidence to add the terms excoriation, hyperkinesia, and neuropsychiatric events following montelukast withdrawal to the montelukast label. These labeling changes were incorporated into the current montelukast label, dated December 21, 2018.

The second review completed by DPV-I, dated August 23, 2019, (see Section 4) contains a high-level overview of neuropsychiatric adverse event reports with montelukast in the FAERS database consisting of an analysis of reporting trends and a hands-on review of fatal domestic neuropsychiatric adverse event reports. DPV-I retrieved a total of 19,685 FAERS reports for montelukast from the date of FDA approval, February 20, 1998, to May 31, 2019. Of these, 10,209 (52%) contained Preferred Terms (PTs) in the Nervous system disorder or Psychiatric disorder System Organ Classes (SOCs). Increases in reporting of neuropsychiatric events with montelukast were noted in 1999, 2008, 2013, and 2018. Explanations for the reporting spikes include typical increases in adverse event reporting over the first 2 years of time on the market, heightened awareness of the safety issue after FDA first alerted the public about the possible association between LTMAs and neuropsychiatric events in 2008, duplicate reports received in 2013, and an influx of reports from foreign countries in 2018. With regards to fatal neuropsychiatric events, DPV-I isolated 82 unique cases of suicide, of which 45 were reported in adult patients (age over 17 years), 19 were reported in pediatric patients, and 18 did not report the patient age. The majority of completed suicide cases were reported by someone other than a healthcare professional (e.g., family member, social media) and contained limited information regarding past medical history, past psychiatric history, concomitant medications, and degree of asthma severity.

In addition, this review contains an updated search of the FAERS database and medical literature from January 17, 2018, to May 31, 2019, for case reports of the remaining unlabeled events of excoriation, hyperkinesia, and neuropsychiatric events following montelukast withdrawal. No cases of hyperkinesia or excoriation were identified. Two cases of neuropsychiatric events after montelukast withdrawal were identified; however, the cases were lacking information critical for a robust assessment of causality, such as prior medications, past medical history, and timing and quality of symptomatic improvement. DPV-I concluded that the totality of data regarding the potential phenomena of new-onset or worsening neuropsychiatric events following montelukast withdrawal remains sparse when considering the limited number of cases in the two DPV-I reviews of this safety issue.

1.4.4. Animal and Observational Literature Reviews

Animal Studies

The biologic mechanisms underlying the neuropsychiatric events associated with montelukast treatment are currently not well understood. However, evidence from animal studies suggests that montelukast could act directly on cells in the brain.

Orally administered montelukast (10 mg/kg/day, 7 days) was detectable in brain tissue and cerebrospinal fluid (CSF) in rats[9], providing evidence for its ability to cross the blood-brain barrier. This evidence is consistent with experimental data obtained in rats during the nonclinical development of montelukast by Merck. Twenty-four (24)-hours after a single 10 mg/kg (oral) dose of [^{14}C]montelukast, radioactivity in brain exceeded that in plasma.[10]

Montelukast is protective in several animal models of acute CNS injury and stroke; the clinical significance of this data is not known. Eriksson et al.[11] recently showed that montelukast inhibited cellular proliferation and maturation in the hippocampus of the intact juvenile mouse brain. In this study, juvenile mice (postnatal day 19) were treated with montelukast (10 mg/kg/day, intraperitoneal injection) for 14 days. The total number of dividing cells (Ki-67$^+$) was decreased by approximately 50% in the granule cell layer (GCL) of the dentate gyrus of the hippocampus. Total neurons and microglia (Iba1$^+$) in the GCL were also decreased in montelukast treated animals relative to vehicle controls.

Montelukast is a potent competitive antagonist (IC_{50} = 2.3 nM) at its target, the CysLT1 receptor.[12] However, expression of the CysLT1R in the normal human brain is very low/non-existent. Montelukast is also a competitive antagonist of (IC_{50} = ~60 nM) of GPR17, a G-protein coupled receptor which is expressed on neurons and glial cells in the human brain.[13,14] GPR17 is recognized as a regulator of oligodendrocyte development and remyelinating function.[15] Montelukast inhibition of GPR17 function on neurons and/or glial cells may contribute to the biologic processes underlying the observed neuropsychiatric events associated with montelukast treatment.

Observational Studies

The purpose of the observational literature review is to examine the risk of neuropsychiatric adverse events (NAEs) with montelukast and other LTMAs. The full review can be found in Section 5.1. On December 29, 2017, January 5, 2018, and July 1, 2019, the DEPI conducted literature reviews through multiple databases with search terms to identify neuropsychiatric events associated with LTMAs. The reference sections of the studies were reviewed for additional studies. The quality of the studies was evaluated per the Newcastle-Ottawa Scale[d] for cohort and case-control studies, and according to six attributes the reviewer considered critical when assessing montelukast and neuropsychiatric adverse events. After the removal of duplicates, the literature search included 71 publications. Upon review of the articles, abstracts, and titles, we further excluded 67 studies.[16-82] In total, one survey study[83] and

d. Newcastle-Ottawa scale was used to standardize the study quality. The scale has a numeric scoring system, which was not used in this review to avoid quantifying the quality of results.

three nested case-control studies [84-86] provided data analyses germane to the association between montelukast use and neuropsychiatric outcomes.

Although Bénard's survey study was highly publicized for finding a 9- to 12-fold increased risk of neuropsychiatric adverse events with montelukast use as compared to inhaled corticosteroids, the study had substantial recall bias which resulted in an overestimation of the risk.[83] Glockler-Lauf's case-control study found that cases had twice the odds of being exposed to montelukast compared to controls (adj. odds ratio [OR] 1.91; CI: 1.15 - 3.18), but the cases may have included psychiatric diagnosis prior to asthma medication exposure.[71]

Evidence from the two nested-case control studies by Ali (overall OR: 0.96; CI: 0.80–1.14) and Schumock (overall OR: 0.70; CI: 0.36-1.39) using LifeLink healthcare claims data were considered high quality and were used to form the basis of the literature review's conclusions.[84,85] Schumock found a positive association between montelukast exposure and neuropsychiatric adverse events in patients age 19-24 years (OR: 5.15; CI: 1.16 – 22.86). Although, the Ali and Schumock case-control studies do not suggest an association between neuropsychiatric adverse events and montelukast exposure in pediatric patients (≤17 years), these results must be interpreted in the context of the following limitations: 1) The primarily analyses for both studies do not control for concomitant asthma medications which carry their own risk for neuropsychiatric adverse events. 2) The Ali study did not control for multiple comparisons and the positive results may be due to chance. 3) The suicide attempt definition in the Schumock study may not reflect suicidal ideation. 4) The last author of the Schumock study reported a conflict of interest and the positive study result for the 19-24 year old age group was re-evaluated until it was null.

The observational studies do not provide convincing evidence regarding the association between neuropsychiatric adverse events and montelukast exposure in pediatric patients. The Schumock data are suggestive of an increased risk of self-harm in patients aged 19-24 years; however, these results have not been duplicated in other well-conducted studies. We found no observational evidence regarding the safety of withdrawal and the long-term implications of adverse reactions. Due to limited data, FDA conducted an observational study in the Sentinel Distributed Database to examine risk of serious neuropsychiatric events and suicides associated with montelukast exposure.

1.4.5. Sentinel Study

Using data from the Sentinel Distributed Database (SDD) from January 1, 2000, to September 30, 2015, we investigated if 1) there is an increased risk of depressive disorders, self-harm and suicides associated with montelukast use compared to inhaled corticosteroids (ICS) and 2) if these NAEs with montelukast compared to ICS were modified by the 2008 montelukast labeling changes, age, sex, and psychiatric history. Using data from the SDD from January 1, 2000 to September 30, 2015, we investigated 1) if there is an increased risk of depressive disorders, self-harm and suicides associated with montelukast use compared to ICS use and 2) if the risk of these neuropsychiatric adverse events associated with montelukast compared to ICS was modified by the 2008 Drug Safety Communications (DSC) and montelukast labeling changes, or are modified by age, sex, or psychiatric history. Patients aged 6 years and older with a diagnosis of asthma were included, excluding patients with a diagnosis of chronic obstructive pulmonary disease (COPD). Using a propensity score model, montelukast monotherapy initiators were matched 1:1 to ICS monotherapy initiators based on age, gender, index year, psychiatric

history, medication usage, prior comorbidities, and measures of asthma severity. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

We identified 513,519 and 1,332,531 montelukast and ICS users, respectively. After propensity score matching, 457,377 users were retained in each exposure group, 89.1% and 34.3% of montelukast and ICS initiators, respectively. There were 37,740 with treated outpatient depressive disorder, 647 with inpatient depressive disorder, 219 with evidence of self-harm, and 264 cases identified using the modified self-harm algorithm. Most of the outcomes were NAEs with a previous diagnosis of a psychiatric disorder (94.1%) and occurred in patients exposed to the asthma medications after the 2008 DSC and labeling changes (89.9%).

Exposure to montelukast was significantly associated with a decreased risk of treated outpatient depressive disorder (HR: 0.91; CI 0.89-0.93). This decreased risk was seen in among patients with a history of a psychiatric disorder (HR: 0.89; CI: 0.88-0.91), in patients age 12-17 years (HR: 0.82; CI: 0.76-0.89) and age 18 years and above (HR: 0.90; CI: 0.88-0.92) and in both females (HR: 0.90; CI: 0.88-0.93) and males (HR: 0.93; CI: 0.89-0.97). The overall HR for inpatient depressive disorder with montelukast compared to ICS was 1.06 (CI: 0.90-1.24). There was no significant association between inpatient depressive disorder and montelukast among males (HR: 1.15; CI: 0.84-1.58), females (HR: 1.04; CI: 0.86-1.26), patients 12 years and older, after the 2008 DSC and labeling changes (HR: 1.08; CI: 0.91-1.29) and in patients with a psychiatric history (HR: 1.10; CI: 0.93-1.31). In patients without a psychiatric history, the HR was 0.63 (CI: 0.37-1.07). Exposure to montelukast was also not associated with self-harm (HR: 0.92; CI: 0.69-1.21) and modified self-harm (HR: 0.81; CI: 0.63-1.05). There were 2 suicides in patients exposed to montelukast and 2 in patients exposed to ICS; all occurred in patients over the age of 18 with a psychiatric history.

In summary, our analyses detected a decreased risk of treated outpatient depressive disorder with montelukast use compared to ICS use, but this result should in interpreted with caution. Since most of the exposure occurred after the 2008 DSC and labeling changes, montelukast patients may have been informed to cease treatment should depressive symptoms develop, thus resulting in a decreased risk among montelukast users. We did not find associations between montelukast monotherapy and the more serious outcomes of hospitalizations for depressive disorder, or medical claims for self-harm events when compared to ICS monotherapy.

1.5. Regulatory Considerations

As summarized above and described in greater detail in the subsequent sections of this background memo, FDA initiated a comprehensive safety analyses of available data for montelukast and revisited previous regulatory actions and communication efforts related to neuropsychiatric events in response to a request from outside stakeholders. As we consider the findings from our current review and our recommendations, a brief description of some of the available regulatory options is warranted.

1.5.1. Labeling

Product labeling is FDA's primary tool to convey essential scientific information needed for the safe and effective use of a drug or biological product. Currently, Neuropsychiatric Events is listed in the Warnings and Precautions section of the montelukast label as shown below. Given the outside request to consider a Boxed Warning and Medication Guide, we have provided a brief summary of the regulations regarding both.

Warnings and Precautions
The following is the language in the currently approved montelukast Warnings and Precautions

> **5.4 Neuropsychiatric Events**
> Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include, but are not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, dysphemia (stuttering), hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.
> Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur [*see Adverse Reactions (6.2)].*

Boxed Warning 21§CFR201.57(c)(1)
A Boxed Warning (BW) is used to call attention to serious or life-threatening risks with a product. A BW is ordinarily used to highlight for prescribers one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug
  OR
- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)
  OR
- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) " Risk Evaluation and Mitigation Strategies" Elements to assure safe use).[87]

Medication Guide 21§CFR208.1

A Medication Guide (MG) is FDA required patient labeling. Patient labeling is typically optional. However, FDA may require patient labeling when it is necessary for patients' safe and effective use of the product. An MG has a specific format, and the sponsor is responsible for ensuring that the MG is available for distribution to patients who are dispensed the drug. The FDA may require a MG if one or more of the following circumstances is determined to exist:

- The drug product is one for which patient labeling could help prevent serious adverse effects.
- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.
- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[88]

We will be asking the AC to discuss the current labeling and FDA's recommendations for labeling.

1.5.2. Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. Although all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS. REMS are not designed to mitigate all the adverse events of a medication, these are communicated to health care providers in the medication's prescribing information. Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.

To determine whether a medication needs a REMS, FDA considers whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh the risks. Based upon our review of the risk of neuropsychiatric events with montelukast, we do not recommend a REMS as there are additional labeling options that could be implemented (if appropriate) before considering a REMS.

1.5.3. Post-marketing Required Safety Trial/Study

FDA has previously considered the appropriateness of requiring a post-marketing safety trial but has determined that a trial is not feasible for reasons described above. To evaluate the serious outcomes of severe depression and suicidality, FDA conducted a study in the Sentinel Distributed Database to evaluate this safety issue.

1.5.4. Communication

To augment labeling changes, FDA has utilized a number of communication tools over the years to disseminate information regarding the risk of neuropsychiatric events with montelukast. A timeline of various communication efforts is provided below.

- March 23, 2008 – Early Communication posted to FDA website alerting health care professionals about a possible association between use of leukotriene modifiers and announcing the ongoing safety review of montelukast, as well as the potential review of other leukotriene modifying drugs.[1]
- January 13, 2009 – Early Communication updated with results of the suicidality safety review and notation that a review of other neuropsychiatric adverse events was ongoing.[2]
- June 12, 2009 – FDA website (Drug Safety Information for Healthcare Professionals) updated with information regarding neuropsychiatric adverse events.
- June 15, 2009 – DHCP letter from Merck agreed upon for distribution
- August 28, 2009 – FDA website (Drug Safety Information for Healthcare Professionals) announced addition of neuropsychiatric adverse events to the Precautions section of the prescribing information.[3]
- Following the FDA's posting of updated information regarding neuropsychiatric adverse events, Merck and Astra Zeneca issued a DHCP letter to prescribers.
- Merck instructed sales representatives to download the new USPI/USPPI to their electronic sales aid, provide the updated USPI/USPPI at the conclusion of every promotional discussion, and distribute the new USPI/USPPI with promotional resources and samples left with health care providers.
- March 2, 2015 –Medscape interview given to raise awareness among healthcare providers of the potential risk of neuropsychiatric adverse events with montelukast following the recommendation of the PAC meeting in September 2014.[7]
- April 2015 – The American Academy of Pediatrics News published an FDA Update entitled, "Neuropsychiatric events linked to asthma medication."[89]

Although FDA has made efforts to communicate the risk of neuropsychiatric events with montelukast, we acknowledge concerns raised by stakeholders regarding the need to raise awareness of this safety issue. Other communication strategies we have considered include the following:

- Engage professional societies (e.g., AAP, AAFP, ACP, AANP) to remind members about this safety issue when prescribing montelukast
- Communications targeted to physicians, pharmacists, nurse practitioners, physician assistants, school nurses
- Online communications through FDA, e.g., FDA Consumer Update, Twitter, Facebook
- Online communications through other parties, e.g., WebMD, Medscape
- Continuing Education activities through other parties
- Submission of a manuscript intended for primary care physicians
- Include information about this safety issue in relevant treatment guidelines

While we have considered a number of outreach strategies listed above, we note that many of these would need to be operationalized by groups outside the FDA. Hence one of the primary challenges in disseminating information is that we cannot guarantee that the groups would be interested in this safety issue, particularly since it is not new. Another challenge is finding a strategy that will ensure this safety issue becomes common knowledge. We will be asking the panel to provide recommendations

for successful strategies to communicate this safety issue and to engage outside parties in order to garner their support and assistance.

1.6. Conclusions

For over a decade, the risk of neuropsychiatric adverse events with montelukast use has been a continuing concern. FDA has completed numerous reviews over the years to evaluate this safety issue and issued communications intended to disseminate information to healthcare providers and patients. Despite FDA's communication efforts and information in the product label, stakeholders have raised concerns that many physicians and patients are not aware of the risk for neuropsychiatric events nor what to do if symptoms occur. During the course of FDA's most recent review, prompted by a request from external stakeholders, additional neuropsychiatric adverse event terms were added to the existing Warnings and Precautions section of the label. Although adding new adverse event terms to the existing label is important to provide the most current safety information to healthcare providers, this will not address broader concerns related to lack of awareness of this long-standing safety issue. Our review, which includes new data from a query of the Sentinel Distributed Database, has not revealed new information that changes the benefit/risk of montelukast nor sheds light on potential mechanisms, risk factors, or long-term sequelae.

Based upon our review, we do not believe that there is new information to elevate the risk of neuropsychiatric events associated with montelukast to a Boxed Warning. However, based upon the criteria for a Medication Guide, requiring a Medication Guide may be appropriate. Another labeling strategy to consider would be to make the current Warning and Precaution more prominent by moving it to section 5.1 in the label. We will be asking for your input on the montelukast labeling.

The major concern voiced by external stakeholders is the lack of awareness in both patients/caregivers as well as healthcare providers/prescribers of the potential risk of neuropsychiatric events with montelukast. Although FDA has communicated this safety issue in a variety of ways in the past, we are interested in additional communication strategies that you deem effective and appropriate in this situation.

2 Draft Discussion Topics for the Committee

- Discuss the safety update provided today for montelukast.

- Discuss the current labeling for montelukast, including the current Warning and Precaution, and stakeholder request for Boxed Warning and Medication Guide.

- Discuss recommendations for successful strategies to communicate the risk of neuropsychiatric events with montelukast. Include the following in your discussion:
    - groups you recommend we target (e.g., providers, pharmacists, patients, school nurses);
    - organizations you recommend we target;
    - modalities of communication (e.g., specific websites, social media, journal article, continuing education).

3 Drug Utilization

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Utilization Review

Date:	August 27, 2019
Reviewer:	Ibrahim T. Ibrahim, Pharm.D., MPH Drug Utilization Data Analyst Division of Epidemiology II
Team Leader:	Rajdeep Gill, Pharm.D. Drug Utilization Data Analysis Team Leader Division of Epidemiology II
Deputy Director for Drug Utilization:	LCDR Grace Chai, PharmD Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology
Subject:	Pediatric Utilization Patterns of Leukotriene-Modifying Agents
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2018-1992

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

3.1. Executive Summary

In preparation for a Pediatric Advisory Committee (PAC) meeting in September 2019, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested an analysis of montelukast utilization patterns in pediatric patients. The Office of Pediatric Therapeutics (OPT) received a letter by the Parents United for Pharmaceutical Safety and the Facebook Montelukast Side Effects Support and Discussion Group regarding the link between the adverse events of hyperkinesia, excoriation, obsessive-compulsive disorder (OCD), and adverse events related to drug withdrawal associated with montelukast. To help with this assessment, this drug utilization review provides the extent of pediatric utilization of montelukast compared to zafirlukast and zileuton to provide context for the PAC meeting discussion. Based on prescription dispensing data from U.S. outpatient retail pharmacies, an estimated total of 2.3 million pediatric patients 0-16 years old (a quarter of the total 9.3 million patients of all ages) were dispensed montelukast in 2018; less than 1000 pediatric patients were dispensed zafirlukast and negligible number of pediatric patients dispensed zileuton. The highest proportion of pediatric montelukast use was among patients ages 6-11 years, followed by patients 12-16 years, 2-5 years and 0-1 year. The number of pediatric patients who received prescriptions dispensed for montelukast remained relatively steady from 2014 through 2018.

As reported by U.S. office-based physician surveys in 2018, the top diagnosis associated with montelukast use in patients ages 2-16 years old was asthma (ICD-10 code J45). Cough (ICD-10 code R05) was the top diagnosis associated with montelukast use in patients 0-1 year old. For all pediatric patients (0-16 years), vasomotor and allergic rhinitis (ICD-10 code J30) was the second most common diagnosis associated with montelukast.

3.2. Introduction

In preparation for a Pediatric Advisory Committee (PAC) meeting, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested an analysis of montelukast utilization patterns in pediatric patients. This request is to assist in providing context for the PAC meeting discussion on neuropsychiatric events of interest associated with montelukast use, namely hyperkinesia, excoriation, obsessive-compulsive disorder (OCD), and adverse events related to drug withdrawal. In support of this request, the Division of Epidemiology II (DEPI II) was asked to examine the utilization of montelukast (as well as zafirlukast and zileuton for comparison) in pediatric patients 0-16 years old from 2014 through 2018.

3.2.1. Background

On November 3, 2017, the Parents United for Pharmaceutical Safety and the Facebook Montelukast Side Effects Support and Discussion Group sent a letter to the Office of Pediatric Therapeutics (OPT) raising safety concerns about hyperkinesia, excoriation, obsessive-compulsive disorder (OCD), and adverse events related to drug withdrawal associated with montelukast use. In assessing these safety concerns, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested the

Division of Pharmacovigilance I (DPV-I) and DEPI-II from the Office of Surveillance and Epidemiology (OSE) to analyze case reports in the FDA Adverse Event Reporting System (FAERS) database and published medical literature for an association between montelukast and neuropsychiatric events of interest, including hyperkinesia, excoriation, OCD, and adverse events related to drug withdrawal. DPARP also requested a review of the epidemiologic data contained in the letter sent to OPT as well as observational literature for new information related to montelukast and neuropsychiatric events.

3.2.2. Products Information

Leukotriene-modifying agents (LTMAs) are used in the management of asthma, allergic rhinitis and acute prevention of exercise induced bronchoconstriction in patients 12 months of age or older. LTMAs are mainly used for chronic control. Montelukast suppresses both early and late bronchoconstrictor responses of inhaled irritants.

Table 3. U.S Product Information for Leukotriene-Modifying Agents

Proprietary Name	Active Ingredient	NDA*	Original Approval	Mechanism	Indication for Use
Accolate	Zafirlukast	020547	9/26/96	Leukotriene receptor antagonist (LTD_4 and LTE_4)	Prophylaxis and chronic treatment of asthma in adults and children ≥ 5 years of age
Singulair	Montelukast	020829 (oral tablet) 020830 (chewable tablet) 021409 (oral granule)	2/20/98 2/20/98 7/26/02	Leukotriene receptor antagonist (LTD_4)	Prophylaxis and chronic treatment of asthma in patients ≥ 12 months of age Acute prevention of exercise-induced bronchoconstriction (EIB) in patients ≥ 6 years of Age Relief of symptoms of allergic rhinitis: seasonal allergic rhinitis in patients ≥ 2 years of age, and perennial allergic rhinitis in patients ≥ 6 months of age
Zyflo CR	Zileuton Zileuton CR	020471 022052	12/9/96 5/30/07	Inhibitor of 5-lipoxygenase, which inhibits leukotriene (LTB_4, LTC_4, LTD_4, and LTE_4) formation	Prophylaxis and chronic treatment of asthma in adults and children ≥ 12 years of age

* There is one FDA approved ANDA for zafirlukast and zileuton and multiple FDA approved ANDAs formontelukast.

3.2.3. Regulatory History

Past reviews by OSE related to the safety issues raised by OPT with regards to montelukast and neuropsychiatric events:

1) In 2007, as part of a tracked safety issue (TSI) #415 and a correspondence from a petition received by New York State Senator Elizabeth Little. TSI #415 led to the sponsor adding more neuropsychiatric events to the post-marketing adverse events section of the montelukast prescribing information under the precautions section (currently WARNINGS AND PRECAUTIONS section).[90]
2) In 2008, as part of TSI #837 requesting the removal of the indication for use in children after a citizen's petition by Parents United for Pharmaceutical Safety and Accountability. They requested labeling changes to also include seizures, neurological damage, neuropsychiatric events, and Churg-Strauss Syndrome. The petition was denied but Henoch-Schönlein purpura was added to the ADVERSE REACTIONS section.[4]
3) Office of Regulatory Policy consulted OSE in 2009 by reason of a Citizens Petition that requested the removal of montelukast indication for children (RCM#2009-1006), as well as changes to product labeling and requesting requirements for physicians to report adverse events to consumers. OSE recommended no labeling changes at that time.[91]
4) In 2010, OSE reviewed a submission by the sponsor to add disorientation to the WARNINGS AND PRECAUTIONS section of the product labeling which was approved (RCM#2010-1209).[5]
5) In 2013, OSE concluded an epidemiologic review on the association between LTMA use and suicide (RCM# 2012-1478). The review found that the risk of suicide cannot be accessed based on epidemiologic studies, thus regulatory action was not needed.[92,93]
6) In 2013, OSE performed a review of neuropsychiatric events associated with montelukast as an update from a prior consult (RCM#2008-474) in 2013 (part of an NDA submission (NDA#204804)). OSE concluded that montelukast Drug Facts label submitted with NDA 204804 was adequate but lacked information about a potential association between the drug and Churg-Strauss Syndrome.[94]
7) OSE performed a Postmarketing Pharmacovigilance and Drug Utilization Review in 2014 (RCM#2014-585) that did not identify any new safety concerns in children 0 to <17 years treated with Montelukast.[95]

3.3. Methods and Materials

This drug utilization review was conducted using proprietary databases available to the FDA (See Section 3.8 for full database descriptions). Zileuton and zafirlukast were included in some of the data for comparison.

3.3.1. Determining Settings of Care

The primary setting of care for leukotriene-modifying agents (LTMAs) was determined based on sales volume (bottles or packages) from manufacturers in 2018 using the IQVIA National Sales Perspectives™ (NSP) database.

3.3.2. Outpatient Retail Utilization Data

National annual estimates of patients, stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17+ years), who received prescriptions dispensed for LTMAs from U.S. outpatient retail pharmacies from 2014 through 2018 were determined using the IQVIA Total Patient Tracker™ (TPT) database.

The top 10 prescriber specialties based on volume of montelukast prescriptions dispensed in the U.S. outpatient retail pharmacy setting in 2018 were determined using the IQVIA National Prescription Audit™ (NPA) database.

3.3.3. Office-based Physician Survey Data

Diagnosis associated with the use of montelukast stratified by patient age (0-1, 2-5, 6-11, 12-16, and 17+ years) as reported by U.S. office-based physician surveys in 2018 were determined using the Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel database. Diagnoses data are reported by the of drug use mentions[e] captured based on International Classification of Diseases, Tenth Revisions, Clinical Modification (ICD-10-CM) codes with 95% confidence intervals.

3.4. Results

3.4.1. Settings of Care

In 2018, 87% of total bottles or packages of LTMAs were sold from the manufacturers to the outpatient retail pharmacies.[f] Montelukast alone accounted for 99% off all LTMA bottles or packages sold in 2018. Therefore, the utilization data from outpatient retail pharmacies where montelukast was primarily utilized is examined in this review.

3.4.2. U.S. Outpatient Retail Pharmacy Data

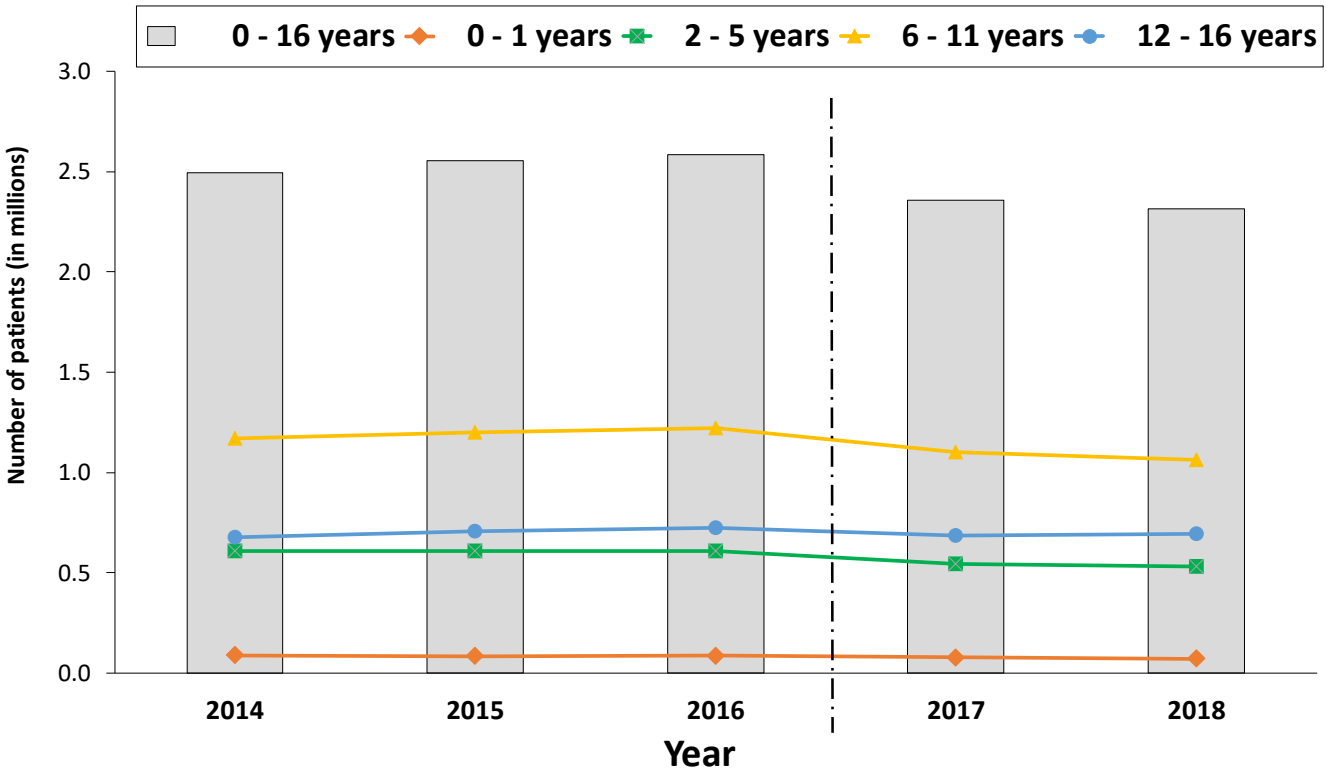
Table 4 in Section 3.7 provides the national estimates of patients, stratified by patient age, who received LTMA prescriptions dispensed from U.S. outpatient retail pharmacies from 2014 through 2018, annually. In 2018, an estimated 2.3 million pediatric patients (0-16 years) received montelukast prescriptions; less than 1000 pediatric patients received zafirlukast prescriptions and less than 100 pediatric patients received zileuton prescriptions. Pediatric patients (0-16 years) accounted for 25% of total 9.3 million patients of all ages who received montelukast prescriptions in 2018. Pediatric utilization of montelukast remained relatively steady from 2014 through 2018.

As illustrated in Figure 1 below pediatric patients age 6-11 years accounted for the highest proportion of montelukast pediatric use at 46%, followed by ages 12-16 years at 30%, 2-5 years at 23% and 0-1 year at 3% in 2018.

[e] The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

[f] IQVIA™ National Sales Perspectives. Year 2018. Extracted March 2019. File NSP 2018-1992. LTMA by Supercha_Mar-27-2019.xlsx

Figure 1. National estimates of pediatric patients* (0-16 years old) who received prescriptions dispensed for montelukast, stratified by patient age, from U.S. outpatient retail pharmacies**, 2014-2018



Data Source: IQVIA Total Patient Tracker™. 2014-2018. File: TPT 2018-1992 MontelukastwComp by age6_27_19 no vet.xlsx. Data extracted June, 2019.
*Note: Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients age 0-16 years include patients less than 17 years of age (16 years and 11 months).
**Of note, there was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between the 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

3.4.3. Prescriber Specialties

Table 5 in Section 3.7 provides the top 10 specialties prescribing montelukast based on prescriptions dispensed from U.S. outpatient retail pharmacies in 2018. Of the estimated 35 million montelukast prescriptions dispensed to all ages, family practice, general practice and internal medicine specialties combined wrote approximately 34% followed by nurse practitioner and physician assistant combined specialties at 23% and pediatric specialty at 10% in 2018.

3.4.4. Office-based Physician Survey Data

Table 6 in Section 3.7 provides the top three diagnoses (ICD-10-CM) associated with the use of montelukast for patients 0-16 years old as reported by U.S. office-based physician surveys, stratified by patient ages in 2018.

The top diagnosis associated with montelukast use in patient age groups 2-5, 6-11, and 12-16 years old was asthma (ICD-10 code J45). Cough (ICD-10 code R05) was the top diagnosis associated with montelukast use in patients 0-1 year old. For all pediatric patients (0-16 years), vasomotor and allergic rhinitis (ICD-10 code J30) was the second most common diagnosis associated with montelukast.

3.5. **Discussion**

In 2018, an estimated 2.3 million pediatric patients 0-16 years old (approximately, a quarter of the estimated total 9.3 million patients of all ages) were dispensed montelukast from U.S. outpatient retail pharmacies. The highest proportion of pediatric montelukast use was among patients ages 6-11 years, followed by patients 12-16 years, 2-5 years and 0-1 year. The number of pediatric patients who received prescriptions dispensed for montelukast remained relatively steady from 2014 through 2018.

Findings from this drug utilization review should be interpreted in the context of the known limitations and methodologies of the databases used. This analysis focused on data from the outpatient retail pharmacy setting where montelukast was mainly used, thus the patient estimates reported in this review can only be generalized to the retail setting of care and may not be applicable to other settings in which montelukast may be prescribed or dispensed, such as mail-order/specialty pharmacies or hospitals and various other clinical settings where patients receive health care. The proprietary database vendor has made some changes to the applied projection methodology of prescription volumes dispensed from retail pharmacies in the proprietary database that impact the interpretation of changes over time. These changes do not affect prescription volumes dispensed from the mail-order/specialty or long-term pharmacies.

The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies and should be interpreted with caution as they are based on a small sample size, particularly for the pediatric population. Certain estimates may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation. Summarization of the projected estimates across patient age groups, time periods, and/or products may lead to differences in patient count due to rounding attributable to the projection methodology utilized. Moreover, patient estimates may be double counted across patient age groups, time periods, and/or products due to patients aging or receiving multiple products during the study period. No statistical tests were performed on these estimates to determine statistically significant changes over time. According to the U.S. office-based physician surveys, the most common diagnoses associated with montelukast use in pediatric patients (0-16 years) was asthma, allergic rhinitis, and cough. Other reported drug use mentions were below the acceptable count (<100,000) allowable to provide a reliable national estimate. The term "drug use mentions" is used to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use mention" does not necessarily result in a prescription being generated. Rather, the term indicates that a specific drug was mentioned during an office visit. Given that statistical accuracy increases as the projected number of records increase, data below 100,000 projected “drug use mentions” may not represent national level trends, because results below this threshold represent insufficient raw physician responses prior to applied projection factors. Data below 100,000 (mentions) do not represent

sufficient portion of the population and is not representative of actual physician prescribing habits at a national level. Therefore, the patient exposure estimates reported in this review may not apply to other settings of care or other specialty offices in which these products may be prescribed or dispensed. Thus, the national estimates of "drug use mentions" for the use of montelukast should be interpreted with these limitations in mind.

3.6. Conclusion

The utilization analyses in this review describe the extent of pediatric use of montelukast in the outpatient retail setting where montelukast was primarily utilized. In 2018, an estimated 2.3 million pediatric patients 0-16 years old received prescriptions dispensed for montelukast from outpatient retail pharmacies. According to the U.S. office-based physician surveys, montelukast was mainly mentioned to be used for the diagnoses of asthma, allergic rhinitis, and cough in the pediatric population 0-16 years old in 2018.

3.7. **Additional Tables**

Table 4. National estimates of patients* who received montelukast prescriptions stratified by patient age from U.S. outpatient retail pharmacies, 2014-2018**

	2014		2015		2016		2017		2018	
	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%
Total Patients Dispensed LMTAs	7,483,608	100.0%	8,055,921	100.0%	8,864,102	100.0%	8,795,964	100.0%	9,265,447	100.0%
Montelukast	7,427,305	99.2%	8,008,896	99.4%	8,820,827	99.5%	8,758,793	99.6%	9,230,366	99.6%
0 - 16 years	2,494,056	33.6%	2,554,821	31.9%	2,583,503	29.3%	2,357,721	26.9%	2,315,673	25.1%
0 - 1 year	89,188	3.6%	84,037	3.3%	87,031	3.4%	77,277	3.3%	72,387	3.1%
2 - 5 years	606,693	24.3%	608,817	23.8%	607,810	23.5%	543,564	23.1%	532,548	23.0%
6 - 11 years	1,171,284	47.0%	1,201,454	47.0%	1,219,172	47.2%	1,101,975	46.7%	1,064,491	46.0%
12 - 16 years	675,577	27.1%	705,504	27.6%	724,404	28.0%	684,054	29.0%	693,487	29.9%
17+ years	4,903,902	66.0%	5,531,715	69.1%	6,279,710	71.2%	6,405,190	73.1%	6,907,277	74.8%
UNKNOWN AGE	243,080	3.3%	66,625	0.8%	10,989	0.1%	58,679	0.7%	16,447	0.2%
Zafirlukast	61,636	0.8%	52,077	0.6%	47,888	0.5%	41,225	0.5%	39,012	0.4%
0 - 16 years	2,555	4.1%	1,710	3.3%	1,344	2.8%	1,030	2.5%	899	2.3%
0 - 1 year	2	0.1%	1	<0.1%	--	--	--	--	--	--
2 - 5 years	122	4.8%	64	3.7%	63	4.7%	40	3.9%	36	4.0%
6 - 11 years	1,115	43.6%	735	43.0%	564	41.9%	435	42.2%	386	42.9%
12 - 16 years	1,293	50.6%	901	52.7%	718	53.4%	557	54.1%	489	54.4%
17+ years	57,990	94.1%	50,372	96.7%	46,794	97.7%	40,184	97.5%	38,038	97.5%
UNKNOWN AGE	3,148	5.1%	580	1.1%	84	0.2%	449	1.1%	114	0.3%
Zileuton	6,511	0.1%	5,421	0.1%	4,233	<0.1%	3,468	<0.1%	3,278	<0.1%
0 - 16 years	184	2.8%	111	2.0%	67	1.6%	48	1.4%	43	1.3%
2 - 5 years	3	1.8%	--	--	2	3.3%	--	--	1	2.2%
6 - 11 years	37	19.9%	21	19.4%	12	17.7%	9	19.5%	3	7.5%
12 - 16 years	142	77.2%	88	80.0%	52	77.5%	38	79.3%	38	87.9%
17+ years	6,228	95.7%	5,330	98.3%	4,192	99.0%	3,424	98.7%	3,232	98.6%
UNKNOWN AGE	409	6.3%	75	1.4%	1	0.0%	23	0.7%	4	0.1%

Source: IQVIA Total Patient Tracker™. 2014-2018. Data extracted March 2019. File: TPT 2018-1992 total LTMA age no vet.Updated.xlsx

*Of note, there was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between the 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology. Data are inclusive of all indications. The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies. Summarization of these projected estimates across patient age groups, time periods, and/or products may lead to differences in patient counts due to rounding attributable to the projection methodology utilized as well as double counting of patients across age groups and time as patients aged over time.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

Table 5. Top 10 prescriber specialties based on national estimates of montelukast prescriptions* dispensed from U.S. outpatient retail pharmacies in 2018

	2018	
	TRxs	%
Total Prescriptions Dispensed for Montelukast	**35,400,841**	**100.0%**
Family Practice/General Practice/Internal Medicine	***12,126,035***	***34.3%***
Physician Assistants/Nurse Practitioners	***8,120,006***	***22.9%***
Pediatrics	***3,700,419***	***10.5%***
Osteopathic Medicine	***3,171,214***	***9.0%***
Allergy	***3,097,499***	***8.8%***
All Other Specialties	***1,284,302***	***4.4%***
Pulmonary Diseases	***1,479,090***	***4.2%***
Otolaryngology	***1,084,295***	***3.1%***
Pulmonary Critical Care	***732,305***	***2.1%***
Specialty Unspecified	***337,770***	***1.0%***

Source: IQVIA National Prescription Audit™. 2019. Data extracted March 2019. File: NPA 2018-1992 Montelukast by Spec. Retail_no-Vet.2018.xlsx

Table 6. Diagnoses* associated with the use of montelukast among pediatric patients 0-16 years old as reported by U.S. office-based physician surveys, 2018

	2018		
	Uses N (000)	Share %	95% Confidence Interval (000)
TOTAL USES (Montelukast)	**5,926**	**100.0%**	**5,444 -- 6,409**
Patients (0-16 years old)	**1,780**	**30.0%**	**1,516 -- 2,044**
0-1 year old	**43**	**2.4%**	**2 -- 84**
R05 Cough	19	45.1%	<0.5 -- 47
J30 Vasomotor and allergic rhinitis	14	33.3%	<0.5 -- 38
J45 Asthma	9	20.2%	<0.5-- 27
All Other Diagnoses	1	1.4%	<0.5 -- 5
2-5 years old	**223**	**12.6%**	**130 -- 317**
J45 Asthma	124	55.6%	54 -- 194
J30 Vasomotor and allergic rhinitis	65	28.9%	14 -- 115
R05 Cough	21	9.2%	<0.5 -- 49
All Other Diagnoses	14	6.3%	<0.5 -- 37
6-11 years old	**842**	**47.3%**	**661 -- 1,024**
J45 Asthma	361	42.8%	242 -- 480
J30 Vasomotor and allergic rhinitis	316	37.5%	205 -- 427
Z00 Encntr for general exam w/o complaint, susp or reprtd dx	55	6.5%	8 -- 101
All Other Diagnoses	111	13.1%	45 -- 177
12-16 years old	**671**	**37.7%**	**509 -- 833**
J45 Asthma	388	57.9%	265 -- 512
J30 Vasomotor and allergic rhinitis	125	18.6%	55 -- 195
R05 Cough	37	5.6%	<0.5 -- 75
All Other Diagnoses	120	17.9%	51 -- 189
Patients 17+ years old	**4,077**	**68.8%**	**3,678 -- 4,477**
Unspecified Age	**69**	**1.2%**	**17 -- 121**

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2014-2018. Data extracted February 2019. File: PDDA_2018-1992_singulair_age_ICD10dx3_2-8--2019.xls

*Diagnosis data are not directly linked to dispensed prescriptions but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

3.8. Database Descriptions

IQVIA National Sales Perspectives™ (NSP)

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. The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA Total Patient Tracker™ (TPT)

IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of approximately 58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database, National Prescription Audit™ (NPA), to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Because TPT patient data are derived from NPA prescription data, projected patient estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Of note, the estimated prescription and/or patient counts provided are based on projections of sample prescription claims data and therefore have some degree of inherent sampling error. These estimates are not intended to be representations of exact enumerations and should be interpreted with caution particularly if they are based on a small sample size. In addition, the data cannot be validated due to lack of access to medical records in the data sources.

IQVIA National Prescription Audit™ (NPA)

The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology. Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from mail-order/specialty and retail pharmacies. Summarization of these projected estimates across time periods and/or settings of care may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel

Syneos Health Research & Insights, LLC., TreatmentAnswers™ is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and

treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

4 Division of Pharmacovigilance FAERS Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	September 4, 2019
Reviewer:	Ann Biehl, PharmD, MS, BCPS Division of Pharmacovigilance I (DPV-I)
Medical Officers:	Ivone Kim, MD, FAAP DPV-I Robert Levin, MD DPV-I
Team Leader:	Lisa Harinstein, PharmD, BCCCP DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Division Director:	Cindy Kortepeter, PharmD DPV-I
Product Name(s):	Singulair (Montelukast)
Subject:	Neuropsychiatric events
Application Type/Number:	NDA 20829, NDA 20830, NDA 21409 and multiple ANDAs
Applicant/Sponsor:	Merck
OSE RCM #:	2019-1324
TSI #:	415

4.1. Executive Summary

This review provides 1) a high-level overview of neuropsychiatric adverse events with Singulair (montelukast) contained in the FDA Adverse Event Reporting System (FAERS) database and 2) an updated evaluation of select adverse events (hyperkinesia, excoriation, events related to drug withdrawal) with montelukast in the FAERS database and medical literature. This review will be used to inform a Fall 2019 Pediatric Advisory Committee meeting that will discuss safety concerns raised in a letter sent to the Office of Pediatric Therapeutics (OPT) by Parents United for Pharmaceutical Safety and Accountability and Montelukast (Singulair) Side Effects Support and Discussion Group (herein referred to as Patient Advocacy Groups).

To provide context for the discussion of neuropsychiatric-related safety issues associated with montelukast use at the Fall 2019 Pediatric Advisory Committee meeting, DPV-I performed a high-level overview of neuropsychiatric adverse event reports with montelukast in the FAERS database consisting of an analysis of reporting trends and a hands-on review of domestic neuropsychiatric adverse event reports with a fatal outcome.

DPV-I retrieved a total of 19,685 FAERS reports for montelukast from the date of FDA approval, February 20, 1998, to May 31, 2019. Of these, 10,209 (52%) contained Preferred Terms (PTs) in the Nervous system disorder or Psychiatric disorder System Organ Classes (SOCs). Both total reports and reports with neuropsychiatric adverse events substantially increased in 1999, 2008, 2013, and 2018. The peak in 1999 is most likely attributable to the Weber effect, or a peak in reporting in the first few years a drug is marketed. The spike in event reporting in 2008 may reflect stimulated reporting following the publicity surrounding montelukast and neuropsychiatric events. Other spikes in reporting occurred in 2013, due to an influx of duplicate reports following a Freedom of Information Act request, and in 2018, due to an increase in foreign reports.

DPV-I reviewed all fatal cases containing a PT related to the Nervous system disorder or Psychiatric disorder SOCs. We isolated 82 unique cases of suicide, with 45 cases reported in adults (age over 17 years), 19 cases reported in pediatric patients, and 18 cases lacking age. We noted that the majority of completed suicide cases were reported by someone other than a healthcare professional (e.g., family member, social media) and contained limited information regarding past medical history, past psychiatric history, concomitant medications, and degree of asthma severity. This information is vital when evaluating the possible contribution of montelukast to the event. Most cases that were deemed to be well-documented still contained additional risk factors, including comorbidities and medications, that could contribute to the self-harm event. In light of these additional contributors and the quality of information reported to FAERS, we cannot draw conclusions regarding the causality or frequency of neuropsychiatric events associated with montelukast.

In our updated evaluation of select adverse events (hyperkinesia, excoriation, events related to drug withdrawal) with montelukast in the FAERS database and medical literature, we isolated

two cases of neuropsychiatric events after montelukast withdrawal and no cases of excoriation or hyperkinesia. A previous Office of Surveillance and Epidemiology review with a data lock date of January 16, 2018, identified 15 cases of neuropsychiatric events worsening following montelukast withdrawal.[96] The majority of cases (13/15) were determined to have unassessable causality with regard to the contribution of montelukast to the events due to insufficient information about clinical course, dechallenge and rechallenge trials, temporality, neurodevelopmental and family history, concomitant medications, or diagnostic evaluation. The review noted a lack of consistency among FAERS cases and concluded that there was insufficient evidence to support regulatory action at that time.

The totality of data regarding the potential phenomena of new-onset or worsening neuropsychiatric events following montelukast withdrawal remains sparse even with the addition of the two cases described in this review. DPV-I will continue pharmacovigilance for withdrawal neuropsychiatric events following montelukast cessation.

4.2. Introduction

This review provides 1) a high-level overview of neuropsychiatric adverse events with Singulair (montelukast) contained in the FDA Adverse Event Reporting System (FAERS) database and 2) an updated evaluation of select adverse events (hyperkinesia, excoriation, events related to drug withdrawal) with montelukast in the FAERS database and medical literature. This review will be used to inform a Fall 2019 Pediatric Advisory Committee meeting that will discuss safety concerns raised in a letter sent to the Office of Pediatric Therapeutics (OPT) by Parents United for Pharmaceutical Safety and Accountability and Montelukast (Singulair) Side Effects Support and Discussion Group (herein referred to as Patient Advocacy Groups).

4.2.1. Background

Montelukast belongs to the leukotriene-modifying agents (LTMA) class and is available in three formulations. See Table 7 below for a summary of montelukast formulations by NDA and date of initial FDA approval.

Table 7. Summary of Montelukast Formulations by NDA and Initial U.S. Approval Dates

NDA	Formulation	Approval date
020829	Tablet	2/20/1998
020830	Chewable Tablet	2/20/1998
021409	Granule	7/26/2002

Initially approved on February 20, 1998, for the prophylaxis and chronic treatment of asthma in adults and pediatric patients ages 6 and older, montelukast has a complex regulatory history, specifically regarding neuropsychiatric events. Currently, montelukast products are indicated for use in children as young as six months of age for perennial allergic rhinitis. Additional indications include prophylaxis and treatment of asthma, prevention of exercise-induced bronchospasm, and relief of symptoms of allergic rhinitis.[97]

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Office of Surveillance and Epidemiology (OSE) have reviewed the association between montelukast and neuropsychiatric events previously as part of tracked safety issue (TSI) #415 after Merck submitted supplements in 2007[g] to add several different neuropsychiatric events to the postmarketing adverse event section of the montelukast prescribing information. Additionally, on October 22, 2007, correspondence was received by FDA from New York State Senator Elizabeth Little, requesting FDA to review the safety of montelukast after a 15-year-old within her district committed suicide 17 days after starting montelukast. Several Drug Safety Communications (DSCs) were also posted on the FDA website to inform healthcare professionals and patients of the new safety information.[1,3]

On September 28, 2008, the safety of montelukast was further reviewed after a Citizen Petition was submitted by Parents United for Pharmaceutical Safety and Accountability (FDA-2009- P-0039). The Citizen Petition requested that FDA remove the indication for montelukast use in children and requested labeling changes for the following adverse events: seizures, neurological damage, neuropsychiatric events, and Churg-Strauss Syndrome. DPARP and OSE opened TSI #837 for the Petition and reviewed these safety issues. The reviewers found the montelukast labeling to be adequate for the concerns raised by the Petition.[4] FDA denied the Petitioner's request to remove the indication for use in children, but added Henoch-Schönlein purpura, a form of systemic vasculitis, to the ADVERSE REACTIONS Post-Marketing Experience section of the label.

On April 23, 2009, the FDA issued a letter to the Sponsor requesting that language regarding neuropsychiatric events be elevated to the PRECAUTIONS section of the product label (currently WARNINGS AND PRECAUTIONS section, see Section 1.3 of this review). This request was addressed in a supplement submitted to the FDA by the Sponsor on May 1, 2009.

On September 23, 2014, the Pediatric Advisory Committee reviewed the current montelukast labeling regarding the risk of neuropsychiatric events. Ultimately, the committee felt that the patient information was clear, but the physician labeling might be strengthened.[7]

On November 3, 2017, Patient Advocacy Groups submitted a letter to OPT asserting that the incidence of neuropsychiatric side effects with montelukast is much more common than currently reported, particularly in children. As evidence, the letter contained an analysis of the FAERS Public Dashboard (30,027 total adverse event cases with Singulair, montelukast, and montelukast sodium from 1998 to 2017 as of August 31, 2017)[h], citations of numerous case reports and studies, and an online survey by the Patient Advocacy Groups. The letter requested the FDA to do the following:

[g] The supplement to include neuropsychiatric events, including suicidality, in post-marketing labeling was submitted October 2, 2007.

[h] The total of 30,027 cases is incorrect because the product term "montelukast sodium" retrieves reports for Singulair, montelukast, and montelukast sodium in the FAERS Public Dashboard. Therefore, the true total in the FAERS public dashboard through August 31, 2017, was 15,738 reports.

1. determine the mechanisms for montelukast's neuropsychiatric side effects.
2. determine risk factors for an adverse reaction.
3. determine the appropriate way to discontinue montelukast ("cold turkey" vs. tapering).
4. determine withdrawal symptoms and long-term implications of an adverse reaction.
5. reclassify the neuropsychiatric side effects of montelukast (Singulair) to be 'common' in children.
6. update the label with a warning for the possible delayed-onset of side effects and include 'excoriation', 'hyperkinesia,' and 'obsessive-compulsive disorder (OCD)' as reported side effects.
7. issue a Medication Guide for montelukast due to the life altering and life-threatening potential of its neuropsychiatric effects.
8. consider a black box warning.

On January 2, 2018, DPARP sent an information request (IR) to the Sponsor of Singulair (montelukast), Merck, requesting the following information:

1. an assessment of whether excoriation, hyperkinesia, and OCD are associated with use of Singulair.
2. an assessment of whether there are any risk factors for neuropsychiatric adverse reactions with Singulair.
3. an assessment of continued or worsening symptoms including but not limited to neuropsychiatric symptoms, following discontinuation of Singulair and whether the method of discontinuation of Singulair (e.g., tapering or sudden withdrawal) had an impact on symptoms.

On April 26, 2018, DPARP received the IR response from the Sponsor. The Sponsor analyzed clinical and postmarketing data from market introduction (July 31, 1997) to January 5, 2018, for an association between montelukast and excoriation, hyperkinesia, OCD, and adverse events not limited to neuropsychiatric events that persisted for more than 14 days following the last dose of montelukast. Based on the data, the Sponsor intended to update the montelukast Prescribing Information to include information related to obsessive-compulsive symptoms. See Section 4.4.2 for a brief summary of the IR response.

The specific requests contained in the letter by Patient Advocacy Groups to update the montelukast label with possible delayed-onset of side effects, excoriation, hyperkinesia, and OCD were evaluated in a Division of Pharmacovigilance I (DPV-I) and Division of Epidemiology (DEPI) review dated September 12, 2018. See Appendix, Section 6.3 for the full review. The review included an analysis of data from multiple sources including postmarketing case reports in the FAERS database, postmarketing case reports in the medical literature, and epidemiologic literature. The reviewers concluded that there was sufficient evidence to update the montelukast product label with 1) obsessive compulsive symptoms in the ADVERSE REACTIONS *Postmarketing Experience* section and 2) add the phrase "including, but not limited to" as a precursor to labeling sections regarding neuropsychiatric events.[96] The reviewers concluded there was insufficient evidence to add the terms excoriation, hyperkinesia, and

neuropsychiatric events following montelukast withdrawal to the montelukast label. These labeling changes were incorporated into the current label, dated December 21, 2018.

On February 13, 2019, the Sponsor of montelukast submitted a Changes Being Effected (CBE) supplement to add the term "dysphemia" (stuttering) to the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS *Postmarketing Experience,* and patient information sections of the montelukast product label. In a DPV-I review dated June 7, 2019, DPV-I concluded the totality of data contained in the FAERS case series in conjunction with the data provided by the Sponsor supported the addition of the term dysphemia (stuttering) to the ADVERSE REACTIONS *Post-Marketing Experience* section and the patient information leaflet. DPV-I also agreed with listing the term dysphemia in WARNINGS AND PRECAUTIONS *Neuropsychiatric Effects* to be consistent with prior labeling updates.[98]

A summary of the previous reviews completed by OSE related to the safety issues outlined in the letter to OPT is available in Section 4.5.

4.2.2. Product Labeling

Relevant sections of the current montelukast labeling are reproduced below.[99]

----------WARNINGS AND PRECAUTIONS----------

5.4 Neuropsychiatric Events
Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include, but are not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug- induced effect.
Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur [see Adverse Reactions (6.2)].

---------- ADVERSE REACTIONS ----------

6.2 Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of SINGULAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Psychiatric disorders: including, but not limited to, agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, obsessive-compulsive symptoms,

restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor [see Warnings and Precautions (5.4)].

----------PATIENT INFORMATION LEAFLET----------

SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:
  - agitation including aggressive behavior or hostility
  - attention problems
  - bad or vivid dreams
  - depression
  - disorientation (confusion)
  - feeling anxious
  - hallucinations (seeing or hearing things that are not really there)
  - irritability
  - memory problems
  - obsessive-compulsive symptoms
  - restlessness
  - sleep walking
  - suicidal thoughts and actions (including suicide)
  - tremor
  - trouble sleeping
  - uncontrolled muscle movements

4.3. High-Level Overview of Neuropsychiatric Adverse Events Reported to FAERS

To provide context for the discussion of neuropsychiatric-related safety issues associated with montelukast use at the Fall 2019 Pediatric Advisory Committee meeting, DPV-I performed a high-level overview of neuropsychiatric adverse event reports with montelukast in the FAERS database consisting of an analysis of reporting trends and a hands-on review of domestic neuropsychiatric adverse event reports with a fatal outcome.

4.3.1. Methods

FAERS Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 8.

Table 8. FAERS Search Strategy*

	Search 1	Search 2
Date of Search	June 7, 2019	June 24, 2019
Time Period of Search	February 20, 1998† - May 31, 2019	February 20, 1998† - May 31, 2019
Search Type	FBIS Product Manufacturer Reporting Summary	FBIS Quick Query
Product Terms	Product Active Ingredient:‡ Montelukast sodium; Montelukast\Montelukast sodium	Product Active Ingredient:‡ Montelukast sodium; Montelukast\Montelukast sodium

MedDRA Search Terms (Version 22.0)	All events	System Organ Class (SOC): Nervous system disorders, Psychiatric disorders
Other Criteria		Outcome: Death Country: Domestic
* See Section 4.5.2 for a description of the FAERS database. † Date of U.S. approval ‡ FAERS search by product active ingredient retrieves reports for Singulair in the FAERS product dictionary.		

4.3.2. Results

Analysis of Reporting Trends

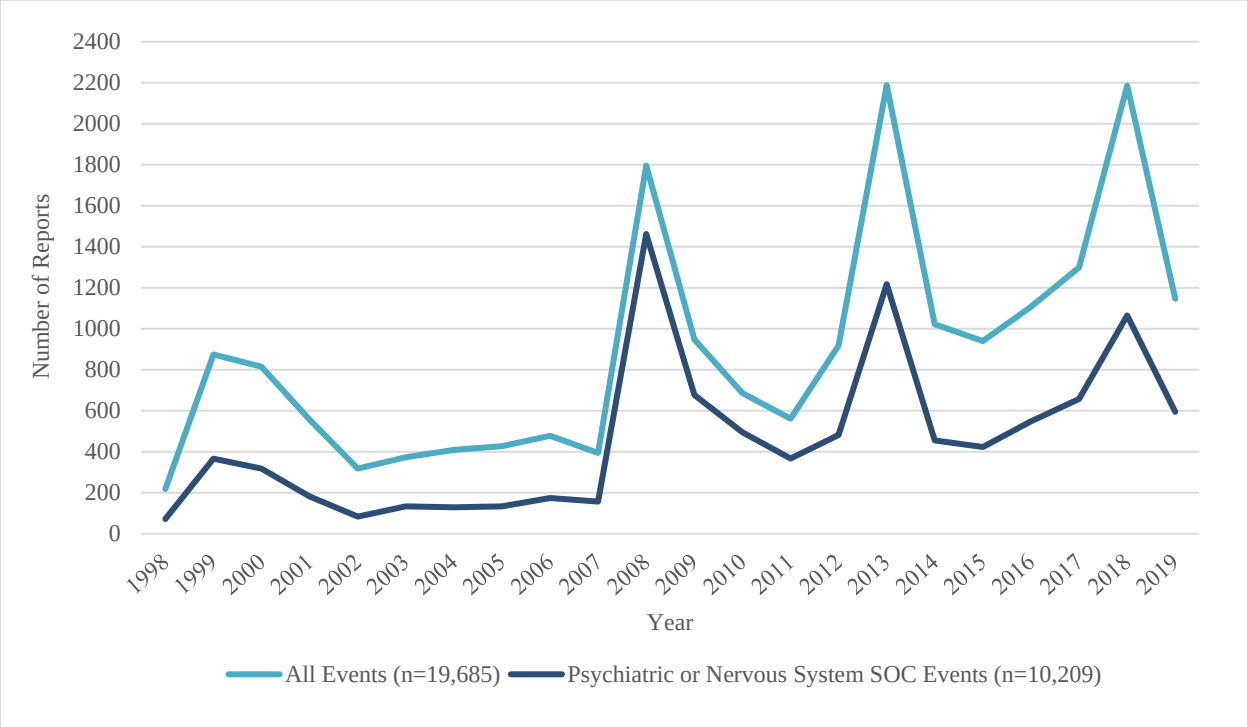
FAERS search 1 retrieved 19,685 crude reports with montelukast, of which 10,209 were coded with a MedDRA Preferred Term (PT) in the Nervous system disorders SOC or Psychiatric disorders SOC (will also be referred to as a neuropsychiatric adverse event). Table 9 presents the total number of adult and pediatric FAERS reports as well as the total number of neuropsychiatric adverse event reports with montelukast received by FDA from February 20, 1998, to May 31, 2019.

Table 9. Total Reports and Neuropsychiatric Adverse Event Reports with Montelukast, Stratified by Age, Received by FDA from February 20, 1998, to May 31, 2019*

	Total reports (N=19,685)			**Nervous system disorders or Psychiatric disorders SOC Reports (n=10,209)**		
	Total (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**	**Total (U.S.)**	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 yrs)	9,351 (4,934)	7,633 (3,261)	575 (331)	4,263 (2,687)	3,583 (1,868)	270 (210)
Pediatrics (0-16.99 yrs)	5,504 (3,496)	4,464 (2,500)	74 (59)	4,006 (2,537)	3,369 (2,063)	41 (38)
Null Age‡	4,830 (3,321)	2,783 (1,297)	161 (94)	1,940 (1,316)	1,295 (676)	55 (48)
* May include duplicates and transplacental exposures, and have not been assessed for causality † 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. ‡ Reports lacking age in the coded field were not included in the breakdown by age.						

Figure 2 below depicts the total number of montelukast reports contained in the FAERS database from February 20, 1998, through May 31, 2019, by FDA received year. The reports are further broken down into those coded with a MedDRA PT in the Nervous system disorders SOC or Psychiatric disorders SOC.

Figure 2. 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.

Reviewer comment: Of the 19,685 total reports depicted in Figure 1, 52 percent (n=10,209) reported events in the Nervous system disorders SOC or the Psychiatric disorders SOC. Both total reports and reports with neuropsychiatric adverse events substantially increased (≥ 1.5-fold increase from previous year) in 1999, 2008, 2013, and 2018.

The peak in 1999 may be ascribed to the Weber effect which suggests that after approval of a drug, adverse event reporting increases over the first 2 years of time on the market, peaks in year 2, followed by a decline in reporting.[100]

Stimulated reporting refers to the concept that public disclosure of a safety issue by issuance of an FDA alert, for example, will result in a substantial increase in adverse event reports regarding the drug and/or the specific adverse event mentioned in such an alert.[101] FDA first alerted healthcare professionals and patients about a possible association between the use of LTMAs and neuropsychiatric events in 2008, and stimulated reporting may explain the sharp increase in reports.

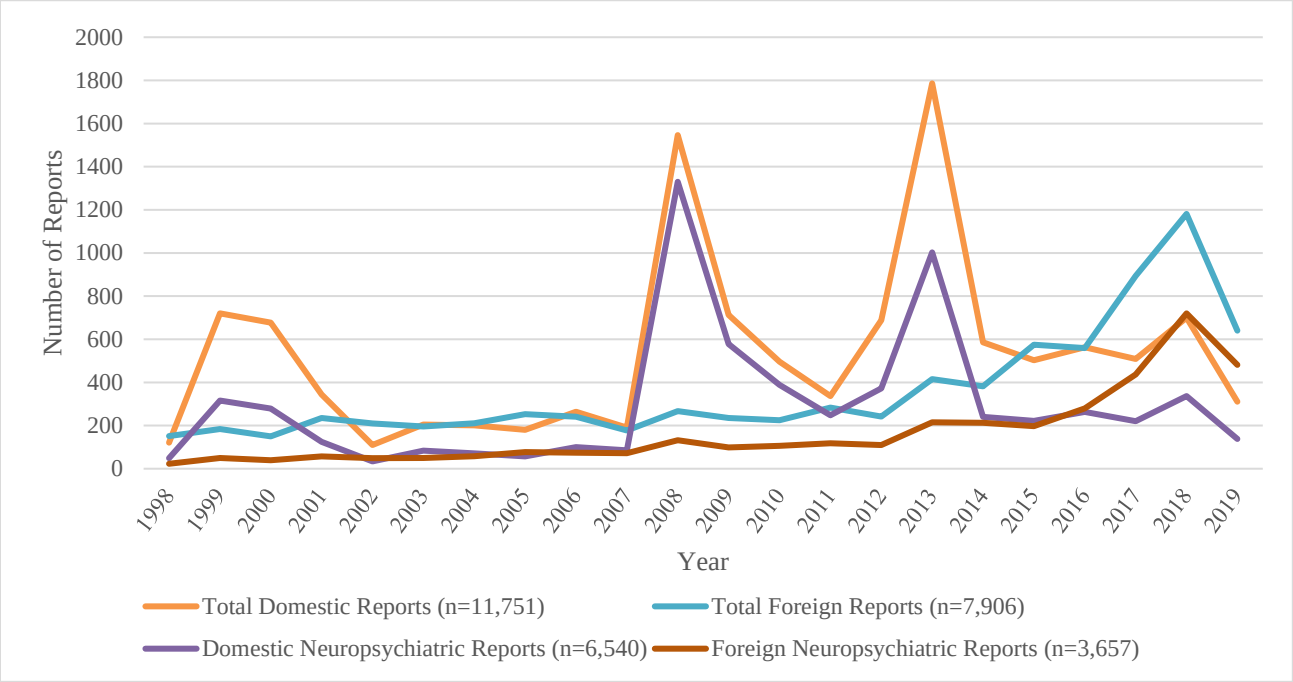
In 2013, there was an influx of reports that were received from a line listing from the AERS database[i] (approximately 857 duplicate reports resulting from a Freedom of Information Act request). In late 2017, the letter by Patient Advocacy Groups was received by OPT. The peak in

[i] The FAERS database deployed in September 2012.

2018 is most likely driven by an influx in total foreign reports as well as foreign neuropsychiatric reports (see Figure 3 *below).Figure 3 below).*

Figure 3 compares the annual number of domestic and foreign total reports as well as domestic and foreign reports containing an event in the Nervous system disorder SOC or Psychiatric disorder SOC with montelukast.

Figure 3. Domestic versus Foreign Reporting Trends for Montelukast by FDA Received Year, stratified by Total Reports and Neuropsychiatric Reports*

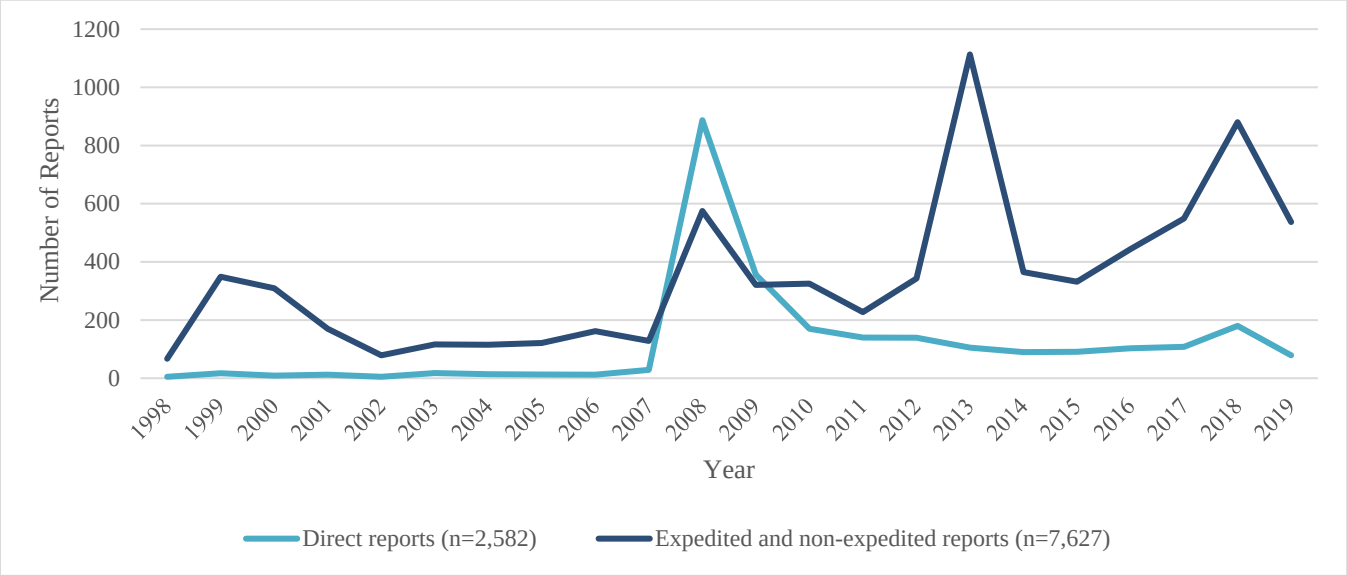


* May include duplicates and not assessed for causality. This graph does not include reports lacking reporting country in the coded field. Data lock date May 31, 2019.

Reviewer comment: Figure 3 illustrates the sharp uptick in events reported domestically during the initial publicity surrounding neuropsychiatric events associated with montelukast in 2008. In contrast, we see that foreign-reported events remain relatively stable until 2016, when we begin to see increases in reporting for both total events as well as neuropsychiatric events. Foreign-reported events peak in 2018; however, reporting for 2019 is not yet complete. With regards to the spike in foreign neuropsychiatric reports, additional analysis shows that approximately 78% of the foreign reports originated from Great Britain or Canada.

Figure 4 compares the annual number of direct reports with reports received from the manufacturer (i.e., expedited and non-expedited reports) in the FAERS database containing an event in the Nervous system disorder SOC or Psychiatric disorder SOC with montelukast.

Figure 4. Annual Number of Neuropsychiatric Adverse Event Reports Received in the FAERS Database from 1998-2019 by Report Type*

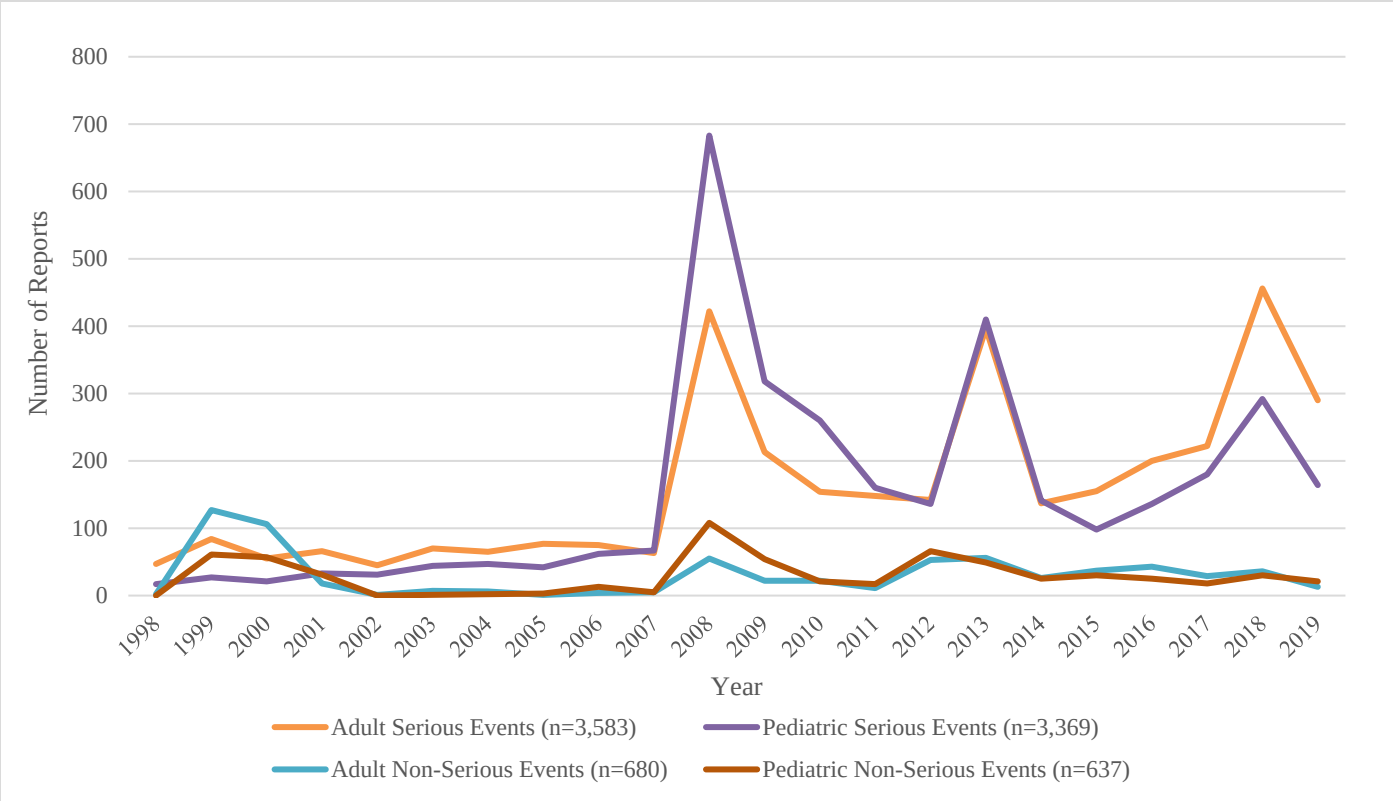


*May include duplicates and not assessed for causality. Data lock date May 31, 2019.

Reviewer comment: The sharp increase in the number of direct neuropsychiatric adverse event reports with montelukast in 2008 and 2009 further suggests that stimulated reporting may explain the rise in overall reporting of adverse events and neuropsychiatric adverse events with montelukast in those years.[101]

Figure 5 depicts the number neuropsychiatric events reported for adults versus pediatric patients by year, stratified by outcome (serious versus non-serious).

Figure 5. Adult versus Pediatric Neuropsychiatric Events Reported by Year, Stratified by Seriousness



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

Reviewer comment: The peaks in reporting for both pediatric and adult serious adverse event reports coincide with the overall trends observed in Figure 1 for total reports and total neuropsychiatric adverse event reports with montelukast (sharp increases in 2008, 2013, and 2018). Whereas there is fluctuation in serious adverse event reports, the annual number of non-serious pediatric and adult adverse events reports stay relatively stable from 1998 to 2019 and make up a small proportion of total reports. According to the most recent review, montelukast use in pediatric patients in the United States for the years of 2014 to 2018 has remained relatively stable and the increase in reports observed in 2018 was driven by an influx of reports from foreign countries.[102]

To investigate the differences, if any, in neuropsychiatric events for the pediatric population compared to adults, we also compared the top 10 reported neuropsychiatric PTs for each population.

Table 10 contains a listing of the top Neuropsychiatric PTs with montelukast for adults versus pediatric patients.

Table 10. Comparison of Top 10 Neuropsychiatric Preferred Terms (PTs) reported with Montelukast for Pediatric (ages 0-16.99 years) and Adult Populations

Ranking	Adult	Pediatric
1	Anxiety	Aggression
2	Headache	Abnormal behaviour
3	Suicidal ideation	Anxiety
4	Insomnia	Suicidal ideation
5	Dizziness	Depression
6	Paraesthesia	Nightmare
8	Hypoaesthesia	Anger
9	Completed suicide	Crying
10	Nightmare	Insomnia

Reviewer comment: Comparison of the top reported neuropsychiatric PTs for adult and pediatric patients shows the terms Anxiety, Suicidal ideation, Nightmare, and Insomnia are reported for both populations. The majority of terms reported for both populations are currently labeled. Abnormal behavior and Crying, which are within the top 10 PTs for pediatric patients, are unlabeled terms; however, these terms are symptoms of other labeled neuropsychiatric terms.

Hands-On Review of Fatal Neuropsychiatric Adverse Event Reports

With interest in cases of completed suicide, we performed a hands-on review of 296 domestic neuropsychiatric adverse event reports with a fatal outcome retrieved in FAERS search 2. Of the 296 reports, 214 were excluded from further analysis 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 suicide (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 were not reported),
- 4 were miscoded and did not report fatalities,
- 2 described transplacental exposure, and
- 2 described illicit drug overdoses.

Table 11 summarizes the remaining 82 unique FAERS cases of completed suicide reported with montelukast for this case series. Section 4.5.3 contains a line listing of the 82 cases of completed suicide reported with montelukast use.

Table 11. Descriptive Characteristics of Domestic Cases of Completed Suicide Reported 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
Report type	Expedited	47	18	13	16
	Direct	34	26	6	2
	Non-expedited	1*	1*	--	--
Report source	HCP	22	8	9	5
	Family member	36	22	6	8
	Consumer	8	5	2	1
	Social media	6	4	1	1
	News article	3	--	--	3
	Not reported	7	6	1	--
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	--	--	--
Montelukast indication for use	Asthma	37	21	12	5
	Seasonal allergy	8	6	2	--
	Asthma and allergies	5	3	1	--
	COPD	1	1	--	--
	Bronchitis	1	1	--	--
	Angioedema	1	1	--	--
	Not reported	29	12	4	13
Additional comorbidities reported†	Yes	27	19	4	2
	Reported as none	6	4	2	--
	Not reported	49	22	13	16
Previous psychiatric history§	Yes	11	7	4	--
	No	13	5	7	1
	Not reported	58	33	8	17
Concomitant medications reported	Yes	28	17	9	2
	Reported as none	1	--	1	
	Not reported	53	28	9	16
Concomitant medications associated with self-harm or behavioral disturbances‖		(n=20)	(n=13)	(n=7)	(n=0)
	LABA/ICS	9	6	3	--
	Antidepressants	4	2	2	--
	ICS alone	4	2	2	--
	Sedatives	2	2	--	--
	OCS	2	2	--	--

		Total (n=82)	Adult (≥17 years) (n=45)	Pediatric (0-16.99 years) (n=19)	Age not reported (n=18)
	Stimulants	2	--	2	--
	Atypical antipsychotics	1	1	--	--
	Neuramidase inhibitor	2	2	--	--
	Hypnotics	1	1	--	--
	Anticonvulsants	1	1	--	--
	Beta-blocker	1	1	--	--
Emergence of additional NP events during montelukast therapy	Yes	18	8	7	3
	No	1	1	--	--
	Not reported	63	36	12	15
Approximate duration of use prior to event	Less than 30 days	6	3	3	--
	1 – 5.99 months	5	3	1	1
	6 -11.99 months	4	2	1	1
	Over 1 year	25	16	7	2
	Not reported	42	21	7	14
Reported patient counseling by HCP	No	6	3	2	1
	Not reported	76	42	17	17
Evidence of stimulated reporting¶	Yes	27	14	6	7
	Not reported	55	31	13	11

* FAERS Case #6601896 was submitted by AstraZeneca as a non-expedited report in 2004.
† A case may report one or more additional comorbidities beyond the indication for montelukast therapy. Specific comorbidities reported include depression (n=10), GERD (n=3), back pain (n=2), COPD (n=2), diabetes mellitus (n=2), hypercholesterolemia (n=2), hypertension (n=2), smoking (n=2), alcohol use (n=1), arthritis (n=1), bipolar disorder (n=1), coronary artery disease (n=1), Crohn's disease (n=1), cystic acne (n=1), chronic gastrointestinal illness NOS (n=1), end stage renal disease (n=1), history of anorexia (n=1), hemolytic anemia (n=1), cardiac surgery NOS (n=1), illicit drug use (n=1), lung cancer (n=1), migraine (n=1), obesity (n=1), osteoporosis with fracture (n=1), pain NOS (n=1), periodic limb movement disorder (n=1), schizoaffective disorder with auditory hallucinations (n=1), sleep apnea (n=1), and thyroid disorder (n=1).
§ A case may report one or more psychiatric comorbidities. Cases reported the following psychiatric conditions: depression (n=10), history of anorexia (n=1), bipolar disorder (n=1), schizoaffective disorder with auditory hallucinations (n=1).
‖ A case may report one or more concomitant medications associated with self-harm/behavioral disturbances; medications were selected based on their current labeling. Specific medications reported include fluticasone/salmeterol (n = 8), fluticasone (n=3), amphetamine/dextroamphetamine (n=2), oseltamivir (n=2), sertraline (n=2), trazodone (n=2), alprazolam (n=1), aripiprazole (n=1), budesonide (n=1), budesonide/formoterol (n=1), clonazepam (n=1), eszopiclone (n=1), fluoxetine (n=1), lamotrigine (n=1), lorazepam (n=1), methylprednisolone (n=1), metoprolol (n=1), olanzapine (n=1), prednisone (n=1), unspecified antidepressant (n=1).
¶ Evidence of stimulated reporting includes referencing a news report, previous knowledge of the association of suicide/suicidal ideation with montelukast, or submission of the report in conjunction with or by the Patient Advocacy Groups.
HCP = healthcare professional, COPD = chronic obstructive pulmonary disease, NP = neuropsychiatric, LABA = long-acting beta agonist, ICS = inhaled corticosteroid, OCS = oral corticosteroid, GERD = gastroesophageal reflux disease, NOS = not otherwise specified

Notable patient characteristics and key themes identified during the hands-on review of the 82 cases are highlighted below.

- **Patient Characteristics**
  - **Patient Demographics**

    Of the 64 completed suicide cases reporting the patient age, 35 (55 percent) occurred in patients 11 to 24 years of age. Of the 76 completed suicide cases reporting patient sex, the majority were reported in males (71 percent, 54/76).

    Reviewer comment: Although incidence rates cannot be calculated from FAERS data, the age and sex characteristics reported in our data align with a recent publication in the Journal of the American Medical Association noting an overall trend of increasing suicide rates among adolescents, with rates in 2017 for those aged 15-19 and 20-24 years at their highest point since 2000. The article notes increases especially in males and in ages 15-19 years.[103] A retrospective cohort study examining suicide risk in patients with asthma on LTMAs reports a positive association of neuropsychiatric events with LTMAs in the age group of 19-24 years; however, the study "reassessed the covariates included in [the] adjusted model" and added "previous exposure to both other asthma medications and drugs associated with suicide" until no further association was seen.[84] A previous OSE review notes there is likely a positive association in this age group; FAERS data cannot support or refute this hypothesis.[96]

  - **Previous Psychiatric History**

    Of the 82 cases, 11 confirmed the patient had a previous psychiatric history, 13 denied the patient had a previous psychiatric history, and 58 did not report this information. Of the 11 cases confirming the patient had a previous psychiatric history, 2 contained sufficient information to determine that the psychiatric condition preceded montelukast initiation. The remaining nine cases did not provide sufficient information regarding treatment dates with montelukast and/or duration of mental illness to determine if the psychiatric condition preceded montelukast initiation. Select cases reporting pre-existing psychiatric diagnoses are highlighted below.

    FAERS Case #6636756, a direct report submitted in 2008 by a son, reports his father suffered from depression for many years and was treated with fluoxetine (for 15 years), followed by aripiprazole and lamotrigine. He was initiated on montelukast, in conjunction with azithromycin, for treatment of acute bronchitis. After initiating montelukast, his son observed him to be agitated and he suffered from insomnia. He stopped the montelukast 2 days after initiation and his insomnia resolved; however, 4 days after montelukast initiation, he committed suicide.

    FAERS Case #7262258, a direct report submitted in 2010 by a spouse, reports his wife, who had a history of anorexia for years and alcohol use, initiated montelukast and fluticasone/salmeterol inhalation for treatment of her asthma and committed suicide approximately 9 months to 1 year later.

- **Concomitant Medications**
  Of the 82 cases, 28 reported that the patient received 1 or more concomitant medications, 1 reported the patient received no other medications, and 53 did not report whether or not the patient received concomitant medications. Of the 28 cases confirming the patient received concomitant medications, 20 (71 percent) specified use of at least one medication associated with behavioral disturbances or an increased risk of self-harm.[j] The majority of patients (n=11) were receiving concomitant treatment with inhaled corticosteroids (ICSs), ICS/long-acting beta agonists (LABAs), or oral corticosteroids (OCSs), which are labeled for psychiatric events.[104,105] Other concomitant medications associated with increased risk of self-harm or behavioral disturbances included antidepressants[k], atypical antipsychotics, stimulants for treatment of Attention-Deficit/ Hyperactivity Disorder (ADHD), oseltamivir, sedatives, hypnotics, and beta-blockers. Most cases did not provide sufficient information (e.g., dates of medication administration, dosages/dosage changes, tolerability) to assess the possible contribution of the concomitant medications to the patient's completed suicide.

- **Asthma Severity**
  Asthma as an underlying disease has been associated with an increased risk of self-harm,[106] and more severe asthma has also been associated with an increased risk of depression.[107,108] Of the cases reporting the indication for montelukast use, 79 percent (42/53) reported using montelukast for treatment of asthma or asthma with allergies; only 2 of 43 cases specified the level of asthma severity (one severe, one mild to moderate but well-controlled). Of the asthma cases reporting concomitant medications (n=21), 43 percent (9/21) report the use of oral steroids or long-acting bronchodilators, which are indicated for use in more severe, persistent asthma.[109] Due to the limited information contained in the cases regarding ICS doses, number of exacerbations, and hospitalizations for asthma-related conditions, we cannot further assess the contribution of asthma severity to the reports of completed suicide associated with montelukast use.

- **Concomitant Comorbidities**
  Of the 82 cases, 27 reported the presence of additional comorbid conditions beyond the indication for montelukast use. Eight cases reported solely mental health-related comorbidities. The remaining 19 cases reported mental and physical comorbidities (n=3) or physical comorbidities in the absence of mental health conditions (n=16). Chronic physical illness may be associated with increased risk of suicide, although the risk may vary by specific illness.[110,111] We could not assess the contribution of the reported chronic illnesses (listed in Table 4) due to limited

[j] DPV-I reviewed current labeling for the reported concomitant medications and included those labeled for behavioral disturbances or self-harm.
[k] Two adult patients received multiple psychotropic medications.

information regarding specific diseases, disease duration, and level of disease control contained in the cases.

- **Limited Information**

The majority of cases (48/82, 59 percent) did not contain sufficient information for appropriate evaluation of the relationship between montelukast and the adverse events.[l,112] These cases were missing documentation of the presence or absence of characteristics suggestive of a good or well-documented case report such as time to onset of the event, use of concomitant medications, presence of past or current comorbidities including psychiatric illness, and presence of other risk factors for the events. For example, 60 percent (49/82) of cases did not report the presence or absence of additional comorbid conditions, 63 percent (52/82) of cases did not report the presence or absence of concomitant medications, and 71 percent (58/82) did not specify the presence or absence of previous psychiatric history. Two cases that contain limited information are briefly summarized below:

FAERS Case #6621413, a direct report submitted by a consumer in 2008, describes a 27-year-old male receiving montelukast who "hanged himself." No additional information is provided such as the patient's past medical or psychiatric history, concomitant medications, or duration of use of montelukast prior to the event.

FAERS Case #7000825, a direct report submitted by a consumer in 2009, describes a 51-year-old male receiving montelukast for asthma with a single word "suicide" listed in the narrative. The reporter does not provide past medical or psychiatric history, concomitant medications, or duration of use of montelukast prior to the event.

Of the remaining 34 cases containing two or more characteristics suggestive of a good case report, many contained additional risk factors including comorbidities and medications that may have contributed to the self-harm event. Specifically, 18 cases contained one or more medications associated with increased risk for self-harm or behavioral disturbances (see Table 4 and Patient Characteristics section above). Potentially contributory comorbidities were identified in 27 cases (see Table 4 above).[111] Six cases were isolated without potentially contributory medications or additional comorbidities beyond the indication for montelukast use, and of these, four were reported in pediatric patients. These pediatric cases are briefly summarized below:

FAERS Case #10574089, an expedited report obtained from a mother via a social media blog in 2014, states her 15-year-old son who was previously healthy with no emotional problems started montelukast for treatment of seasonal allergies. After an unstated period of time, the patient committed suicide.

[l] DPV-I assessed cases for information quality by scoring cases based on the presence or absence of the main characteristics of a good case report outlined in the guidance for industry. Cases missing two or more of the main characteristics of a good case report (time to onset, concomitant products or lack thereof, concomitant comorbidities or lack thereof, and reporting the presence of other risk factors) were designated as containing limited information for assessment.

FAERS Case #6414536, a direct report submitted by a mother in 2007, states her 15-year-old son initiated montelukast for treatment of allergies after assurance from their physician that the side effect profile was "less than an antihistamine." The mother stated the patient was healthy and was taking no other medications. The mother noticed some physical side effects occurring after treatment initiation (not specified in the report), and then in the second week of therapy noticed behavior changes in her son including extreme anxiety, mood swings, fatigue, feeling overwhelmed, restless, hopeless, and negative. The child committed suicide 17 days after treatment initiation on montelukast. The mother also states, "IT HAS COME TO OUR ATTENTION THAT SINGULAIR IS AFFECTING ALOT OF PEOPLE IN AN ADVERSE WAY" and advocates for a boxed warning and follow-up for teens in her report.

FAERS Case #9277389, a direct report submitted by a pharmacist in 2013, states a 9-year-old male patient with no history of depression or mood disorders taking montelukast "for years" for an unknown indication, died from an apparently self-inflicted gunshot wound. The reporter specifies that montelukast was the patient's only medication and expresses concern regarding any "possible link between suicide and Singulair."

FAERS Case #7015118, an expedited report submitted by a physician in 2009, states a 7-year-old female patient with no history of depression taking montelukast for treatment of asthma intermittently and then daily for eight months, died from an apparent suicide by hanging. The child was found on the floor with a belt around her neck, and it was noted in the report the child had been watching a violent show on television at the time of the event.

Reviewer comment: Even cases containing at least two characteristics of a good case report and lacking potentially contributory medications or additional comorbidities beyond the indication for montelukast contain limited information for a robust causality assessment. For example, FAERS Case #10574089 does not describe how long the patient received montelukast before the completed suicide. FAERS Case #9277389 does not give an indication for montelukast use or provide detail to explain why the reporter submitted this event as a potential suicide versus an accidental death in a child having access to a firearm. All four cases lack information regarding social and family history and most bear evidence of stimulated reporting.

- **Stimulated Reporting**

To further assess the role of stimulated reporting, we analyzed the 82 case narratives for the presence of objective evidence suggestive of stimulated reporting (e.g., referencing a news report, prior knowledge of the possible association of suicide with montelukast, or reporting to a social media group). Evidence of stimulated reporting was found in 33 percent of cases (27/82). Two cases containing information suggestive of stimulated reporting are summarized below.

FAERS Case #6606979, a direct report submitted in 2008 by a parent who is also a pediatrician, describes his 17-year-old daughter with mild to moderate persistent asthma who committed

suicide after approximately 11 years of montelukast therapy. She was taking concomitant budesonide inhalation, did well at school, did not have a history of alcohol or drug use, and exhibited no signs of depression prior to her death. **The parent states an interest in the news coverage regarding the possible link between montelukast and depression and suicidal thoughts as he is a pediatrician and prescribes this medication to patients.**

FAERS Case # 6607741, a direct report submitted in 2008 by a spouse, describes the suicide of his 63-year-old wife who took montelukast for an unspecified time period; the earliest prescription bottle he could find was dated 2.5 months prior to her death. The husband specifies his wife suffered from allergies, back pain, and arthritis. She had no history of liver or kidney dysfunction and did not smoke, drink, or abuse drugs. **The husband stated that he didn't know what triggered her suicide but noticed a news report that says only four suicides had been reported and he wanted to report another.**

- **Role of Patient/Caregiver Education**

Of the 82 cases, 6 reported the absence of knowledge or lack of provider education regarding possible neuropsychiatric effects of montelukast. The remaining 76 cases did not report whether or not they had knowledge of the neuropsychiatric adverse event or were educated regarding the potential association between montelukast and neuropsychiatric events. In reviewing the event dates of these six cases in the context of the dates of the labeling changes regarding neuropsychiatric effects with montelukast, four occurred prior to the addition of suicidality to the labeling for montelukast (prior to 2008) and two occurred following the labeling addition of neuropsychiatric events to WARNINGS AND PRECAUTIONS. These two cases are summarized below.

FAERS Case #14562296, a direct report submitted by a parent in 2018 (event date 2017), describes their daughter (age not reported) with a history of asthma and chronic atopic dermatitis who was initiated on montelukast. **The parent states "she had depression and anxiety but I didn't know it could have been the medication."** The patient stopped montelukast "after allergy season" but restarted almost a year later (after initially starting montelukast). Three months after restarting montelukast, she suffered from severe depression and anxiety leading to her suicide.

FAERS Case #14699502, a direct report submitted by a parent in 2018 (event date 2017), describes their 18-year-old son, who initiated montelukast for treatment of asthma and multiple allergies. **The parent states "…my son died by suicide. I never knew there was a problem, nobody did until it was too late. Seven and a half months after his death I was informed that Singulair/Montelukast has adverse side effects such as depression and suicide."** The parent reports the child took montelukast intermittently for approximately 2 years, switching to daily use for almost a year preceding his death. The parent reported a decline in his mental health over 3 years prior to his death, although he was successful in school and sports.

4.3.3. Discussion

DPV-I's high-level overview of adverse events with montelukast use for all ages notes the majority of events (52 percent) include a PT related to the Psychiatric or Nervous System Disorders SOCs. Event reporting dates reflect a spike in reports in 2008, both for overall adverse events and for neuropsychiatric events. This spike may reflect stimulated reporting following the publicity surrounding montelukast and neuropsychiatric events. Other spikes in reporting occurred in 2013, due to an influx of duplicate reports following a FOIA request, and in 2018, due to an increase in foreign reports.

Our hands-on review of all domestic fatal neuropsychiatric events with montelukast reported to FAERS identified 82 unique cases of completed suicide. Of the 82 cases, the majority were reported between 2008 and 2009 (n=51) and may reflect stimulated reporting.[m] Approximately one-third of cases specifically mentioned factors related to stimulated reporting including news or social media coverage. Stimulated reporting can have implications for identifying (e.g., alter disproportionality scores) and evaluating signals from postmarketing adverse event reporting systems (e.g., recall bias).

We noted that the majority of completed suicide cases were reported by someone other than a healthcare professional (e.g., family member, social media) and contained limited information regarding past medical history, past psychiatric history, concomitant medications, and degree of asthma control. This information is vital when evaluating the possible contribution of montelukast to the event. Most cases that were deemed to be well-documented still contained additional risk factors, including comorbidities and medications, that could contribute to the self-harm event. Additionally, our case series should be interpreted with caution as data shows increasing overall rates of suicide among adolescents and adults and a differential risk among patients with varying comorbid disease states. [103,110,111]

Interestingly, despite the majority of cases being reported by family members and consumers, we noted that no cases confirmed receiving patient counseling regarding possible neuropsychiatric effects of montelukast. Most cases did not report any information regarding the presence or absence of patient counseling, but six confirmed that they did not receive healthcare provider counseling.

DPV-I selected fatal neuropsychiatric events as the endpoint to examine in detail due to the severity of the outcome. However, in selecting this endpoint, we acknowledge that this is an endpoint where dechallenge cannot be assessed, removing a key contributor to causality assessment. Spontaneous adverse event reports are often limited in the amount of information provided, which can also hinder causality assessment, as was observed in this analysis.

[m] Of the reports with received years of 2008-2009, 20/51 (39%) contained evidence of stimulated reporting.

In light of these challenges and the quality of information reported to FAERS, we cannot draw conclusions regarding the causality, additional risk factors predisposing patients to neuropsychiatric events, or frequency of neuropsychiatric events associated with montelukast. In this setting FAERS data is hypothesis-generating, and can contribute to the total body of knowledge regarding these labeled events; however, it cannot provide firm conclusions.

4.4. Updated Evaluation of Hyperkinesia, Excoriation, and Events Related to Drug Withdrawal with Montelukast

4.4.1. Background

On November 3, 2017, the Patient Advocacy Groups submitted a letter to OPT. Among many requests, the letter asked FDA to update the montelukast label with a warning for the possible delayed onset of side effects and to include excoriation, hyperkinesia, and OCD as reported side effects.

These requests were evaluated in a joint DPV-I and DEPI review dated September 12, 2018. See Appendix, Section 6.3 for the full review. An analysis of the FAERS database identified 23 cases of obsessive-compulsive-like-disorder, 15 cases of neuropsychiatric symptoms reported after montelukast withdrawal, 3 cases of hyperkinesia, and 0 cases of excoriation reported in association with montelukast. The review concluded that there was sufficient evidence to update the labeling for montelukast products to reflect obsessive compulsive symptoms in 6.2 ADVERSE REACTIONS *Postmarketing Experience* portion of the labeling and recommended broadening the labeling language regarding neuropsychiatric events by addition of the phrase "including, but not limited to" as a precursor to labeling sections regarding neuropsychiatric events.[96] These labeling changes were incorporated into the current label, dated December 21, 2018. The review also concluded that there was insufficient information to add the remaining terms (delayed onset of side effects, excoriation, hyperkinesia) to the labeling at that time.

This section of the current review will update FAERS and medical literature searches from the data lock date of the previous review to identify postmarketing case reports for the currently unlabeled terms of excoriation, hyperkinesia, and withdrawal symptoms upon montelukast cessation.

4.4.2. Brief Summary of Sponsor's IR Response

On April 26, 2018, the Sponsor of Singulair (montelukast) completed an analysis of clinical trial and postmarketing data for an association between montelukast and the adverse events of excoriation, hyperkinesia, OCD,[n] and persistent adverse events. The Sponsor reviewed a large pooled clinical dataset (42 interventional clinical trials) to provide an assessment of whether

[n] OCD was added to current labeling as a result of the OSE review dated September 12, 2018, and will not be discussed further in the summary of the Sponsor's IR.

excoriation, hyperkinesia, and OCD are associated with the use of montelukast. Hyperkinesis was observed in a single pediatric individual treated with montelukast in the controlled clinical studies and was assessed as definitely not related by the investigator. Fifteen events of excoriation were reported in 15 subjects. All 15 events were reported as nonserious and the events were assessed as not related by the investigator. The study drug was continued, and all events had resolved prior to the end of the trial.

The Sponsor searched their safety database for spontaneous and non-interventional study reports with the PTs of excoriation and hyperkinesia received from healthcare providers, regulatory agencies, and consumers from market introduction (July 31, 1997) to January 5, 2018. The Sponsor found low numbers of excoriation and hyperkinesia cases in the postmarketing database.

In their analysis of persistent adverse events, the Sponsor searched for cases of continued or worsening symptoms including, but not limited to neuropsychiatric symptoms, that did not resolve after 2 or more weeks following montelukast discontinuation in the clinical trial data. The Sponsor identified an overall low number of cases. The 10 most frequently reported adverse events identified among the cases were then evaluated in the Sponsor's postmarketing database. Of the 10 most frequently reported adverse events that did not resolve after 2 or more weeks following montelukast discontinuation, 7 were from either the Nervous system disorders SOC or the Psychiatric disorders SOC; the 7 adverse events were abnormal behavior, aggression, anxiety, depression, headache, insomnia, and paraesthesia. Abnormal behavior was noted by the Sponsor to be the only term not contained in the montelukast U.S. prescribing information (USPI). However, many terms were already contained in the USPI that were suggestive of abnormal behavior such as disorientation, disturbance in attention, and hallucinations. The Sponsor concluded that the low number of cases in the clinical trials with the limited information from the postmarketing database make it difficult to assess montelukast's role in the events. The most frequently reported adverse events were labeled in the montelukast USPI, therefore, no new safety concerns regarding persistent adverse events after withdrawal of montelukast were identified.

Based on the review of the data, the Sponsor concluded that there was insufficient evidence to support the addition of these three adverse events to the labeling.

4.4.3. Methods

FAERS Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 12.

Table 12. FAERS Search Strategy*

Date of Search	July 11, 2019
Time Period of Search	January 17, 2018† - May 31, 2019

Search Type	FBIS Quick Query	
Product Terms	Product Active Ingredient: Montelukast sodium; Montelukast\Montelukast sodium	
	Search 3	Search 4
MedDRA Search Terms (Version 22.0)	PT: Hyperkinesia, Skin abrasion‡	High Level Term (HLT): Withdrawal and rebound effects§
* See Section 4.5.2 for a description of the FAERS database. † Data lock date of previous review was January 16, 2018. ‡ The previous search was performed using MedDRA version 20.0, where Excoriation was a PT. In MedDRA version 22.0, Excoriation is a Lower Level Term related to the PT Skin abrasion. § For completeness, DPV-I also searched FAERS with the same parameters using the Standardized MedDRA Query (SMQ) *Drug Withdrawal* (Broad). This search returned the same reports as the HLT search above.		

Literature Search for Case Reports

DPV-I searched the medical literature with the strategy described in Table 13 to identify case reports of the three adverse events of interest with montelukast.

Table 13. Medical Literature Search Strategy

	Search 1	Search 2
Date of Search	July 12, 2019	
Database	PubMed@FDA	EMBASE
Search Terms	(Montelukast) AND (hyperkinesia) (Montelukast) AND (hyperkinesis) (Montelukast) AND (excoriation) (Montelukast) AND (withdrawal)	(Montelukast) AND (hyperkinesia) (Montelukast) AND (hyperkinesis) (Montelukast) AND (excoriation) (Montelukast) AND (withdrawal)
Years Included	2018, 2019	
Limits	Human; Case study; Case series; English	

Case Selection Criteria

Excoriation

- A report that contains a diagnosis of excoriation disorder by a healthcare provider or describes recurrent or excessive picking, scratching, or rubbing of normal skin.[o]

Hyperkinesia

- A report that contains a diagnosis of hyperkinesia by a healthcare provider or describes involuntary or excessive spontaneous movements.

[o] Adapted from the Diagnostic and Statistical Manual of Mental Disorders V criteria for excoriation disorder.

Neuropsychiatric adverse events after drug withdrawal

- A report of new-onset neuropsychiatric adverse events or continued or recurrence of existing neuropsychiatric adverse events after withdrawal[p] or discontinuation of a drug.

Causality Assessment

Cases of excoriation, hyperkinesia, and neuropsychiatric adverse events after drug withdrawal were assessed for a causal relationship with montelukast using the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) classification system as shown in Table 14.

Table 14. World Health Organization – Uppsala Monitoring Centre (WHO-UMC) classification system

Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely*	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable*	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
*Excluded from further analysis in the case series	

4.4.4. Results

FAERS

FAERS searches 3 and 4 retrieved 19 total reports with montelukast (excoriation n=2, hyperkinesia n=9, withdrawal neuropsychiatric adverse events n=8). After accounting for duplicate reports, applying the case selection criteria in Section 3.2.1, and performing causality assessment in Section 3.2.2, two cases of neuropsychiatric adverse events after montelukast withdrawal were included in the case series. Figure 6 below details the FAERS case selection.

[p] Withdrawal is defined as tapering the dose or missing doses of montelukast.

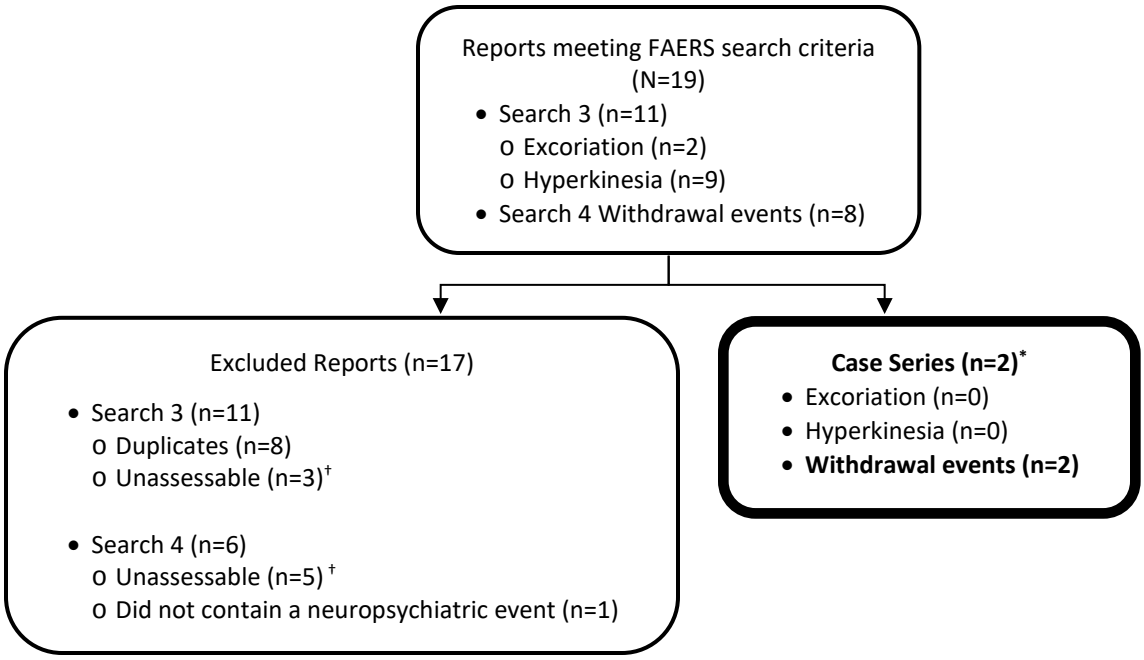


Figure 6. FAERS Case Selection

*We did not identify any cases of hyperkinesia or excoriation; therefore, these events will not be discussed further in the results.

†Reports were deemed unassessable if they contained insufficient documentation of the presence or absence of two or more characteristics suggestive of a good or well-documented case report such as time to onset of the event, use of concomitant medications, presence of past or current comorbidities including psychiatric illness, and presence of other risk factors for the events.

The two cases meeting case selection criteria for neuropsychiatric events after montelukast withdrawal are summarized below. A line listing of these cases is located in Section 4.5.4

FAERS Case #14996115, Direct, GBR, HO, OT, 2018

FAERS Case #14996115, submitted by a parent, describes a 17-year-old female who developed insomnia and suicidal urges while taking montelukast for 18 months for treatment of asthma exacerbated by pollen. After approximately one year of treatment with montelukast, the daughter noted "feeling different" while away on an international school trip. Specifically, the daughter developed insomnia and suicidal urges of wanting to jump from a high place. The parent reported the daughter had suffered from pre-existing exam-related anxiety, for which she had sought mental health care but had been discharged from this care prior to leaving on her school trip. The daughter was sent home from the trip early and sought treatment with a psychologist. Three months after these events and treatment enrollment, the daughter discontinued montelukast. The parent and allergist saw no indication to continue the therapy as it was no longer pollen season and the patient was receiving immunotherapy. One day after montelukast discontinuation, the daughter's anxiety worsened significantly, she did not want to socialize with others, and her suicidal urges worsened. She was admitted to an inpatient psychiatric facility and started fluoxetine 20 mg daily. After 2 months on fluoxetine, the parent

reported improvement in symptoms. At the time of reporting, 3 months later (5 total months from the initial events), the parent reports improvement in suicidal urges where the daughter only occasionally feels these urges (as compared with 3-4 times/day) and improvements in anxiety and sleep. The parent reports they were not informed by the health care provider that montelukast could cause neuropsychiatric side effects when it was prescribed to her through the pediatric allergy clinic. Concomitant medications included iron, fluticasone/salmeterol inhaler, and vitamin D.

Reviewer comment: This case describes worsening of suicidal urges, anxiety, and insomnia in a teenage girl with baseline anxiety. The initial presentation of symptoms resulted in the child seeking medical care, and the escalation of symptoms following montelukast withdrawal resulted in psychiatric hospitalization. The acute worsening of symptoms one day after montelukast withdrawal is notable. The previous OSE review on this topic reported a mean onset of symptoms 3.8 days (median 5 days) after montelukast discontinuation with a range of 0-8 days after discontinuation.[96] WHO-UMC causality assessment for this case is determined as possible, as it is difficult to discern what could be underlying psychiatric conditions versus worsening due to montelukast withdrawal.

Many psychiatric conditions emerge during adolescence. [113] Complex hormonal, chemical, anatomical, and psychosocial changes characteristic of this period may contribute to the pathophysiology of these conditions.[113-117] The prolonged time to symptom onset after drug exposure, pre-existing neuropsychiatric symptoms, patient age, and lack of information to explore other potential contributory factors limit case interpretation and obfuscate the relationship between montelukast and adverse events.

FAERS Case #15341934, Direct, USA, OT, 2018

FAERS Case #15341934, reported by a parent, describes a 10-year-old female who developed OCD-like behaviors and anger within two months after stopping montelukast which she had received for almost 2 years to treat intermittent asthma and seasonal allergies. Other home medications included cetirizine. She developed side effects including headaches and tics shortly after starting montelukast, but it was not attributed to montelukast. Two months before stopping montelukast, she experienced sudden-onset anxiety and depression with severe mood swings. No major life changes were noted to explain these changes in behavior. She had "full blood work", including testing for diabetes, with no notable findings. Her depression and anxiety continued to worsen. The mother read that these behavioral changes could be rare side effects of montelukast, so montelukast was discontinued. She then developed OCD-like behaviors accompanied by anger. At the time of reporting (approximately 3 months after montelukast discontinuation), she was under the care of a psychologist for treatment of anxiety/OCD and continued to improve with increased time off montelukast.

Reviewer comment: This case describes a child who experienced new-onset depression and anxiety during treatment of montelukast that evolved into OCD-like symptoms with anger/outbursts within the 2 months after montelukast discontinuation. These symptoms

resulted in the child seeking medical care with a psychologist. Although this case may bear evidence of stimulated reporting (e.g., the source of information where the parent learned of possible neuropsychiatric events with montelukast was not stated), the initial withdrawal symptoms described as well as the improvement with increased time off montelukast are notable. OCD-like behaviors are currently a labeled event; however, the timing of these behaviors having developed while off the medication are not described in current labeling. The WHO-UMC causality assessment for this case is assessed as possible.

Medical Literature

We did not identify any case reports meeting our case selection criteria for these neuropsychiatric events of interest.

4.4.5. Discussion

DPV-I's search of FAERS identified two additional cases occurring after the data lock date for the previous OSE review that describe neuropsychiatric events worsening after montelukast withdrawal. No cases of hyperkinesia or excoriation were identified in FAERS or the medical literature.

The cases of neuropsychiatric events worsening following montelukast withdrawal provide details regarding concomitant medications, baseline psychiatric status, timing of events, and improvement after initiation of additional medical interventions (medication, psychotherapy). Both cases were assessed as possible causality. Although we cannot exclude the role of montelukast in the development of these events, significant information regarding prior medications, past medical history, family history, psychosocial development and stressors, clinical workup, and timing and quality of symptomatic improvement remain missing and prevent a robust causal association.

The previous OSE review identified 15 cases of neuropsychiatric events worsening following montelukast withdrawal. Six of the 15 cases described new-onset psychiatric events after montelukast discontinuation. The remaining nine cases described symptoms that developed during montelukast use and persisted after discontinuation. Two cases described symptom resolution following montelukast reinitiation (positive dechallenge); one of the two cases also reported that montelukast was discontinued again and the patient again developed neuropsychiatric symptoms (positive rechallenge). These events developed in patients who had been taking montelukast for short periods of time (e.g., less than four months) as well as in patients exposed to montelukast for several years. The most common neuropsychiatric symptoms reported are included in the current labeling (anxiety, abnormal behavior, aggression, fear, and suicidal ideation). The majority of cases (13/15) were determined to have unassessable causality with regard to the contribution of montelukast to the events due to insufficient information regarding clinical course, dechallenge and rechallenge trials, temporality, neurodevelopmental and family history, concomitant medications, or diagnostic evaluation. The review noted a lack of consistency among FAERS cases and concluded that

there was insufficient evidence to support regulatory action at that time. The Sponsor's analysis of adverse events persisting after montelukast withdrawal also concluded that there was insufficient evidence to support adding this adverse event to the labeling.

We acknowledge that a major limitation to the assessment of withdrawal events is the variability in clinical detection of these events. For example, during the hands-on review of the fatal neuropsychiatric events in Section 1 of this review, several suicides were noted to have occurred after discontinuation of montelukast. Whether these events represent worsening neuropsychiatric conditions in light of montelukast withdrawal or progression of mental illness is unknown. In addition, our search strategy identified cases in which the reporter associated the event as a withdrawal or rebound event, missing cases where the reporter believed these events may be a sign of mental illness progression.

Regardless, the totality of data regarding the potential phenomena of new-onset or worsening neuropsychiatric events following montelukast withdrawal remains sparse even with the addition of the two cases described in this review. Regulatory action is not warranted at this time.

4.4.6. Conclusion

The totality of data regarding the potential phenomena of new-onset or worsening neuropsychiatric events following montelukast withdrawal remains sparse. DPV-I will continue pharmacovigilance for withdrawal neuropsychiatric events following montelukast cessation.

4.5. Supplements

4.5.1. Regulatory History

Below are the previous reviews by OSE related to the safety issues outlined in the letter to OPT:

- 12/19/08 (RCM # 2008-474) OSE Adverse Event Reporting System (AERS) Postmarketing Safety Review of Mood, Cognitive, Perception, Sleep and Movement Adverse Events:[90] This review examined the association between mood (including suicide and suicidal ideation), cognitive, perception, and sleep adverse events with montelukast use. This review was initiated by an inquiry to FDA from New York State Senator Little regarding a 15-year-old who committed suicide while taking montelukast to treat allergic rhinitis in August 2007. The review recommended neuropsychiatric events to be added to the PRECAUTIONS section (currently WARNINGS AND PRECAUTIONS section) of the label.
- 06/30/10 (RCM# 2010-1209) OSE Review of Labeling Submission for 'Disorientation':[92] This review examined the association between disorientation and montelukast use and recommended to add disorientation to the label based on data provided in a CBE supplement.
- 05/14/11 (RCM #2009-1006) OSE Response to Citizen Petition:[91] A consult was received from the Office of Regulatory Policy. The Petitioner requested the removal of the montelukast indication for use in children, changes to the product labeling, to implement requirements that adverse events are reported by physicians, and that all labeling changes are communicated to consumers. This OSE review evaluated neuropsychiatric events (vocal and motor tics, seizures and brain damage, status epilepticus, death) and vasculitis (vasculitides, deaths, Churg-Strauss syndrome) with montelukast use. The reviewers recommended no labeling changes to the product labeling at that time.
- 02/27/13 (RCM# 2012-1478) DEPI Review of Association Between LTMA Use and Suicide:[93] This epidemiology review evaluated a newly published nested case-control study which examined the association between suicide/suicide attempt and LTMA use. The reviewer concluded that the risk of suicide cannot be quantified based on the epidemiologic studies and regulatory action by FDA was not warranted.
- 02/21/14 (RCM#2013-2360) OSE Review of Neuropsychiatric events and Churg-Strauss Syndrome:[94] This review did not identify any new safety issues that have not been previously recognized and reviewed by the FDA. The neuropsychiatric events appear to be adequately labeled in the proposed over-the-counter (OTC) montelukast Drug Facts label submitted with NDA 204804; however, the proposed OTC montelukast Drug Facts label lacked information about the potential association between montelukast use and Churg-Strauss Syndrome.
- 09/02/14 (RCM# 2014-585) OSE Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review for Singulair:[95] This review did not identify any new safety concerns in children 0 to <17 years old treated with montelukast.

- 09/12/2018 (RCM# 2017-2297) OSE Pharmacovigilance and Epidemiology Review of Neuropsychiatric Effects with the Leukotriene Modifying Agents:[96] This joint review by DPV-I and DEPI was completed in response to the safety concerns raised in a letter from a concerned parents group to OPT and contained an analysis of the FAERS database with regards to four neuropsychiatric events: hyperkinesia, excoriation, obsessive-compulsive disorder, and adverse events related to drug withdrawal. DEPI completed an analysis of the observational literature and the epidemiologic data contained in the letter. FAERS data supported the addition of the term obsessive-compulsive disorder to the montelukast labeling as well as the phrase "including but not limited to" as a precursor to labeling sections describing neuropsychiatric adverse events. The Sponsor updated the montelukast label with these changes on December 21, 2018. The literature analysis completed by DEPI concluded that the observational studies did not provide conclusive evidence regarding neuropsychiatric events and montelukast exposure in pediatric patients. DEPI recommended a Sentinel study to examine clinically relevant determinants that may increase the risk of neuropsychiatric events in montelukast users.
- 06/07/2019 (RCM# 2019-763) OSE Labeling Consult for Dysphemia:[98] This review was completed in response to a CBE labeling supplement submitted by the Sponsor regarding dysphemia (stuttering) associated with montelukast use. DPV-I concluded the totality of data contained in the FAERS case series in conjunction with the data provided by the Sponsor supported the addition of the term dysphemia (stuttering) to the ADVERSE REACTIONS *Post-Marketing Experience* section and the patient information leaflet. DPV-I also agreed with listing the term dysphemia in WARNINGS AND PRECAUTIONS *Neuropsychiatric Effects* to be consistent with prior labeling updates.

4.5.2. 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.

4.5.3. FAERS Line Listing of Domestic Suicides Reported with Montelukast Use Case Series (n=82)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	11/10/2014	10574089	1	US-009507513-1411USA003599	Expedited (15-Day)	15	MALE	USA	DE,OT
2	5/12/2015	11105261	1	US-009507513-1505USA003312	Expedited (15-Day)		MALE	USA	DE,OT
3	5/19/2015	11120901	1	US-MERCK-1505USA006764	Expedited (15-Day)	48	MALE	USA	DE,OT
4	6/17/2016	12478227	1	US-009507513-1606USA007257	Expedited (15-Day)		MALE	USA	DE,OT
5	1/6/2017	13092303	1	AU-009507513-1701USA002263	Expedited (15-Day)		NR	USA	DE,OT
6	2/17/2017	13247490	1	US-009507513-1702USA006199	Expedited (15-Day)		MALE	USA	DE,OT
7	7/18/2017	13762931	1	US-009507513-1707USA005289	Expedited (15-Day)		MALE	USA	DE,OT
8	8/22/2017	13896809	1		Direct		MALE	USA	DE
9	8/24/2017	13900712	2	US-009507513-1708USA010008	Expedited (15-Day)		FEMALE	USA	DE,OT
10	1/5/2018	14355428	1	US-009507513-1801USA001780	Expedited (15-Day)	18	FEMALE	USA	DE
11	2/16/2018	14538031	3	US-009507513-1802USA008352	Expedited (15-Day)	18	FEMALE	USA	DE,OT
12	2/21/2018	14562296	1		Direct		FEMALE	USA	DE
13	3/29/2018	14699502	1		Direct	18	MALE	USA	DE
14	5/5/2018	14934244	1		Direct	22	MALE	USA	DE
15	6/23/2018	15056570	1	US-009507513-1806USA008441	Expedited (15-Day)	18	FEMALE	USA	DE,OT
16	8/10/2018	15262816	1	US-009507513-1808USA003669	Expedited (15-Day)		MALE	USA	DE,OT
17	9/12/2007	6414536	1		Direct	15	MALE	USA	DE
18	3/11/2008	6578069	2	US-MERCK-0803USA01124	Expedited (15-Day)		NR	USA	DE
19	3/12/2008	6579040	3	US-MERCK-0803USA00882	Expedited (15-Day)		MALE	USA	DE
20	7/29/2004	6601896	1	2003AP04255	Non-Expedited	24	NR	USA	DE
21	4/2/2008	6604294	4	US-MERCK-0803USA04626	Expedited (15-Day)	11	MALE	USA	DE,OT
22	4/2/2008	6604297	6	US-MERCK-0803USA04781	Expedited (15-Day)	9	MALE	USA	DE,DS,LT
23	4/3/2008	6605357	1	US-MERCK-0804USA00099	Expedited (15-Day)	63	MALE	USA	DE,DS,LT

24	4/4/2008	6606352	4	US-MERCK-0804USA00713	Expedited (15-Day)	11	MALE	USA	DE,HO,OT
25	3/31/2008	6606979	1		Direct	17	FEMALE	USA	DE
26	3/28/2008	6607009	1		Direct	79	FEMALE	USA	DE
27	3/31/2008	6607318	1		Direct	17	MALE	USA	DE
28	3/31/2008	6607397	1		Direct	25	FEMALE	USA	DE
29	3/31/2008	6607558	1		Direct	25	MALE	USA	DE
30	3/31/2008	6607741	1		Direct	63	FEMALE	USA	DE
31	3/31/2008	6608039	1		Direct	15	MALE	USA	DE
32	3/31/2008	6610084	1		Direct	17	FEMALE	USA	DE
33	3/31/2008	6610085	1		Direct	53	FEMALE	USA	DE
34	4/1/2008	6610459	1		Direct	19	MALE	USA	DE
35	4/1/2008	6613333	1		Direct	21	MALE	USA	DE
36	4/4/2008	6613373	1		Direct	41	FEMALE	USA	DE
37	4/4/2008	6614162	1		Direct	41	MALE	USA	DE
38	4/14/2008	6614185	1	US-MERCK-0804USA02440	Expedited (15-Day)	17	MALE	USA	DE,DS,LT
39	4/14/2008	6614186	5	US-MERCK-0804USA01323	Expedited (15-Day)	76	MALE	USA	DE,OT
40	4/14/2008	6621413	1		Direct	27	MALE	USA	DE
41	4/18/2008	6626565	1		Direct	15	MALE	USA	DE
42	5/2/2008	6631499	3	US-MERCK-0804USA06411	Expedited (15-Day)	22	MALE	USA	DE,LT,OT
43	5/2/2008	6631504	3	US-MERCK-0804USA06250	Expedited (15-Day)	17	MALE	USA	DE,LT
44	4/29/2008	6636683	1		Direct	35	MALE	USA	DE
45	4/29/2008	6636756	1		Direct	65	MALE	USA	DE
46	5/13/2008	6639020	2	US-MERCK-0805USA00340	Expedited (15-Day)	46	FEMALE	USA	DE,OT
47	5/23/2008	6659786	1		Direct	11.28	FEMALE	USA	DE
48	6/3/2008	6669333	1		Direct	16	MALE	USA	DE
49	6/17/2008	6669700	2	US-MERCK-0806USA02726	Expedited (15-Day)	14	FEMALE	USA	DE,LT
50	8/1/2008	6717135	3	US-MERCK-0807USA04321	Expedited (15-Day)	15	FEMALE	USA	DE,DS,HO,LT,OT
51	8/7/2008	6721354	2	US-MERCK-0808USA00349	Expedited (15-Day)	17	MALE	USA	DE
52	8/7/2008	6721375	1	US-MERCK-0808USA00352	Expedited (15-Day)		FEMALE	USA	DE
53	9/3/2008	6752575	1		Direct	41	MALE	USA	DE,DS,HO,RI,OT
54	9/11/2008	6753899	3	US-MERCK-0809USA01237	Expedited (15-Day)	56	FEMALE	USA	DE
55	10/31/2008	6801437	2	US-MERCK-0810USA05003	Expedited (15-Day)		NR	USA	DE
56	1/15/2009	6890741	1		Direct	77	MALE	USA	DE
57	1/16/2009	6891211	1		Direct	77	MALE	USA	DE
58	1/26/2009	6900030	1		Direct	21	MALE	USA	DE
59	4/6/2009	6974144	1		Direct	50	FEMALE	USA	DE
60	5/13/2009	7000825	1		Direct	50.31	MALE	USA	DE
61	5/29/2009	7006891	1	US-MERCK-0905USA03621	Expedited (15-Day)		NR	USA	DE

62	6/3/2009	7010036	3	US-MERCK-0905USA03623	Expedited (15-Day)	14	MALE	USA	DE
63	6/9/2009	7015118	3	US-MERCK-0906USA00972	Expedited (15-Day)	7	FEMALE	USA	DE,DS,LT
64	6/11/2009	7017567	1	US-MERCK-0906USA01254	Expedited (15-Day)	62	MALE	USA	DE,LT
65	6/17/2009	7025974	2	US-MERCK-0906USA02512	Expedited (15-Day)		MALE	USA	DE
66	6/22/2009	7029695	4	US-MERCK-0906USA02982	Expedited (15-Day)	62	MALE	USA	DE,DS,LT
67	6/23/2009	7031467	1	US-MERCK-0906USA03426	Expedited (15-Day)		NR	USA	DE
68	7/30/2009	7067859	1	US-MERCK-0907USA04598	Expedited (15-Day)	11	MALE	USA	DE
69	9/10/2009	7110089	1	US-MERCK-0909USA00472	Expedited (15-Day)	55	MALE	USA	DE,LT
70	1/27/2010	7262258	1		Direct	50.38	FEMALE	USA	DE
71	3/3/2010	7304308	2	US-MERCK-1002USA04084	Expedited (15-Day)		MALE	USA	DE,DS,LT
72	2/25/2010	7321204	1		Direct	62	MALE	USA	DE
73	3/22/2010	7327169	3	US-MERCK-1003USA02053	Expedited (15-Day)	15	MALE	USA	DE,DS,HO,LT
74	6/3/2010	7409033	2	US-MERCK-1005USA03992	Expedited (15-Day)	15	MALE	USA	DE
75	3/7/2011	7844740	1	US-MERCK-1103USA00462	Expedited (15-Day)	22	MALE	USA	DE
76	8/4/2011	8070128	2	US-MERCK-1107USA04085	Expedited (15-Day)	13	MALE	USA	DE
77	12/27/2011	8312796	2	US-MERCK-1112USA03077	Expedited (15-Day)		MALE	USA	DE,LT
78	2/21/2013	9107341	3	US-009507513-1302USA009793	Expedited (15-Day)		MALE	USA	DE,OT
79	2/22/2013	9108560	3	US-009507513-1302USA008908	Expedited (15-Day)	11.792	FEMALE	USA	DE
80	1/16/2013	9124347	1	US-009507513-1301XAA004218	Expedited (15-Day)	51	MALE	USA	DE
81	3/27/2013	9198384	1		Direct	48	MALE	USA	DE
82	5/6/2013	9277389	1		Direct	9	MALE	USA	DE

*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, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, RI=Required Intervention, OT=Other medically significant

4.5.4. FAERS Line Listing of Neuropsychiatric Events Following Montelukast Withdrawal Case Series (n=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	5/22/2018	14996115 †	1		Direct	17.2	F	USA	HO,OT
2	8/28/2018	15341934	1		Direct	10	F	USA	OT

*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, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

†This case is coded as a domestic case, but the events appear to have occurred in the United Kingdom.

Abbreviations: HO=Hospitalization, OT=Other medically significant event

5 Division of Epidemiology Literature Review and Sentinel Analysis

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Literature Review for Leukotriene-Modifying Agents and Neuropsychiatric Events

Date:	September 12, 2019
Reviewer(s):	Veronica Sansing-Foster, PhD, MS Division of Epidemiology II
Team Leader:	Efe Eworuke, PhD Division of Epidemiology II
Division Director:	CAPT David Moeny, R.Ph., MPH, USPHS Division of Epidemiology II
Subject:	Risk of Neuropsychiatric Events for Leukotriene Receptor-Modifying Agents
Drug Name(s):	Montelukast, zafirlukast, zileuton
Application Type/Number:	NDAs: 20829, 020830, 021409 (montelukast); 2054, 22052 (zafirlukast); 020471 (zileuton)
Sponsors:	Multiple
TSI #:	415

** The information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.**

5.1. Literature Review

5.1.1. Executive Summary

The purpose of this literature review is to examine the risk of neuropsychiatric adverse events (NAEs) with montelukast and other leukotriene-modifying agents (LTMAs). On November 11, 2017, the Parents United for Pharmaceutical Safety and Accountability and the montelukast (Singulair) Side Effects Support and Discussion Group submitted a letter to FDA requesting that neuropsychiatric effects in the montelukast label be updated based on a survey conducted by the group. The survey suggested the incidence of neuropsychiatric side effects with montelukast is much more common than is currently reported, particularly in children. In addition, the group cited numerous case series, case reports, as well as a survey study by Bénard et al. (2017), showing an adjusted relative risk of 12.0 (95% confidence interval [CI]: 2–90) for patient reported NAEs and 9 (CI: 1.2-69.5) for adjudicated NAEs with montelukast use as compared to inhaled corticosteroids.[83]

On December 29, 2017, January 5, 2018, and July 1, 2019, the Division of Epidemiology completed three separate literature reviews pertaining to montelukast use, other asthma medications, and NAEs, including suicidality. The literature search resulted in three nested case-control studies (Ali et al., Schumock et al., and Glockler-Lauf et al.) and one survey study (Bénard et al.).[83-86] Although Bénard's study was highly publicized for finding a 9- to 12-fold increased risk of NAE with montelukast use, the study was underpowered and had the opportunity for substantial recall bias which may have resulted in an overestimation of the risk. Glockler-Lauf's study found that cases had twice the odds of being exposed to montelukast compared to controls (adj. odds ratio [OR] 1.91; CI: 1.15 - 3.18); however, the cases may have included psychiatric conditions that existed before asthma medication exposure. Evidence from the two nested-case control studies by Ali (overall OR: 0.96; CI 0.80–1.14) and Schumock (overall OR: 0.70; CI: 0.36-1.39) using LifeLink healthcare claims data were considered high quality and were used to form the basis of the FDA's literature review's conclusions. Schumock found a positive association between montelukast exposure and NAEs in patients age 19-24 years (OR: 5.15; CI: 1.16 – 22.86). Although, the Ali and Schumock case-control studies do not suggest an association between NAEs and montelukast exposure in pediatric patients (≤17 years), these results must be interpreted in the context of the following limitations: 1) The primarily analyses for both studies do not control for concomitant asthma medications which carry their own risk for NAE. 2) The Ali study did not control for multiple comparisons and the positive results may be due to chance. 3) The suicide attempt definition in the Schumock study may not reflect suicidal ideation. 4) The last author of the Schumock study reported a conflict of interest and the positive study result for the 19-24 year old age group was re-evaluated until it was null.

The Schumock data is suggestive of an increased risk of self-harm in patients aged 19-24 years; however, these results have not been duplicated within this age group in other studies. There

is no observational evidence regarding the safety of withdrawal and the long-term implications of adverse reactions.

5.1.2. Introduction

The purpose of this literature review is to examine the risk of neuropsychiatric adverse events (NAEs) with montelukast and other leukotriene-modifying agents (LTMAs). Montelukast (Singulair) is a LTMA for the prevention and treatment of asthma in persons as young as 12 months and the prevention of allergic rhinitis in children as young as 6 months. Other LTMA's include zafirlukast and zileuton. Inhaled corticosteroids are the first line of treatment in children with persistent asthma, while LTMAs, such as montelukast, are second line treatment.

On November 11, 2017, the Parents United for Pharmaceutical Safety and Accountability and the montelukast (Singulair) Side Effects Support and Discussion Group submitted a letter to the FDA to:

- reclassify the neuropsychiatric side effects of montelukast (Singulair) to be 'common' in children, update the label with a warning for the possible delayed onset of side effects and include 'excoriation', 'hyperkinesia' and 'obsessive compulsive disorder' as reported side effects.
- issue a Medication Guide for montelukast (Singulair) due to the life altering and life-threatening potential of its neuropsychiatric effects and consider a black box warning. This will be formally requested in a future submission by the Petitioner.

and to determine:

- the mechanisms for montelukast's neuropsychiatric side effects
- risk factors for an adverse reaction
- the appropriate way to discontinue montelukast ("cold turkey" vs. tapering)
- withdrawal symptoms and long-term implications of an adverse reaction

As evidence, the group cited numerous case reports, studies, and conducted their own online survey by the Facebook (FB) montelukast (Singulair) Side Effect Support and Discussion Group co-managers and the Patients United for Pharmaceutical Safety. The parent group believes the evidence submitted shows the current label does not adequately capture the scope and magnitude of the NAEs and has not adequately informed the public of the risks associated with use and withdrawal from montelukast.

Regulatory History

Montelukast was approved in 1998, followed by zafirlukast in 1999, and zileuton in 2007. In 2008, FDA issued a warning to the healthcare public and revised the montelukast label to include the risk of neuropsychiatric events based on postmarketing pharmacovigilance studies. This warning was later updated to include all LTMAs. The labels of all LTMAs were revised to include information regarding NAEs.

Product Labeling

Below are sections of the current montelukast label pertaining to NAEs. Similar, but not identical, language can be found in the Precautions and Adverse Reaction section of the zafirlukast (Accolate) and zileuton (Zyflo) labels.

Warning and Precautions

Neuropsychiatric events have been reported with SINGULAIR. Instruct subjects to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur (5.4 and 6.2).

Neuropsychiatric Events

5.4 Neuropsychiatric events have been reported in adult, adolescent, and pediatric subjects taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect. Subjects and prescribers should be alert for neuropsychiatric events. Subjects should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of SINGULAIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tremor.

5.1.3. Review Methods and Materials

On December 29, 2017, January 5, 2018, and July 1, 2019, the FDA reviewer searched the National Library of Medicine's Pub Med database, Web of Science, EBSCOHost and Google Scholar Advanced Search using the following search string: (asthma [mesh]) AND (neuropsychia* OR depressi* OR suicid* OR mental OR violen* OR psychiatric or anx* or tremor or behav*) AND (singulair or montelukast or LTRA or "Leukotriene Receptor Antagonist" or LTMA or "leukotriene modifying agent")). The reference sections of the studies were reviewed for additional studies, including landmark studies.

The quality of the studies was reviewed per the Newcastle-Ottawa Scale[q] for cohort and case-control studies, and according to six attributes the reviewer considered critical when assessing montelukast and neuropsychiatric adverse events (NAEs):

1. Control for 2008 Drug Safety Communication (DSC) and subsequent labeling changes to reduce information and channeling bias as failure to do so may result in increased reporting of events post-labeling.
2. Disclosure of conflicts of interest
3. Incident use of montelukast as opposed to prevalent use
4. Adequate power to test association between montelukast and the outcome
5. Assessment of asthma treatment duration or dose to examine dose-response relationship
6. Adjustment for montelukast monotherapy or inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) combination therapy given the additive risk of NAEs with LABA use

5.1.4. Review Results

Literature Search Results

After the removal of duplicates, the literature search included 71 publications (including conference abstracts) written in English, studied in humans, all ages, and published from January 1, 2014 until July 1, 2019. The literature search excluded 67 studies:

- Non-human studies (n=4) [16-19]
- Case reports and case series (n=10) [20-29]
- Clinical studies (n=1) [30]
- Commentaries and reviews (n=13) [31-43]
- Does not include montelukast (n=4) [44-47]
- Did not formally examine an association between montelukast, LTMAs, and the outcomes (n=19) [48-67]
- Ecological study (n=1)[68]
- Examines effectiveness (n=2) [69,70]
- In vitro, in silico, and bench studies (n=7) [71-76]
- Literature review and meta-analysis (n=2) [77,78]
- Sample size <100 (n=2) [79,80]
- Spontaneous reporting system (n=2) [81,82]

In total, four studies provided data analyses germane to the association between montelukast use and neuropsychiatric outcomes:

- Schumock, et al. (2012) - Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study[84]
- Ali, et al. (2015) - Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study[85]

[q] Newcastle-Ottawa scale was used to standardize the evaluation of study quality. The scale has a numeric scoring system, which was not used in this review to avoid quantifying the quality of results.

- Bénard, et al. (2017) - Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice[83]
- Glocker-Lauf, et. al (2019) - Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case–Control Study[86]

The study designs, descriptions and results are provided in Table 20.

Bénard, et al. (2017)[83]

The primary objective of Bénard's survey study was the to determine the incidence and relative risk of neuropsychiatric adverse related drug events (ADRs) leading to discontinuation of montelukast, as compared to ICS, in children ages 1-17 years diagnosed with asthma between February 2011 – April 2016. The secondary objective was to describe the characteristics and determinants of neuropsychiatric ADRs leading to drug cessation. The majority (>85%) of the surveyed participants included parents who consented to participate in another study – the Pediatric Asthma Database and Biobank. Parents of both the ICS and montelukast initiating patients were contacted by telephone in the summers of 2014, 2015, and 2016 using standardized, non-leading interviews to collect demographic, clinical history, drug use history, NAEs, and family clinical history data. There was a median delay of 3 years between drug initiation and the parent interview. After the interviews were complete, a blinded adjudication committee reviewed structured coded reports of all possible NAEs to assess the probability of their drug association (unlikely to definitely) using the Naranjo score.[118] The study controlled for age, sex, ethnicity, asthma control, phenotype, personal and familial predisposing behavioral problems, and time between drug initiation and interview, as well as baseline group differences. The median age of the patients initiating montelukast was 5 years (interquartile range 3-8). The montelukast cohort included montelukast monotherapy (43%), adjunct to ICS only (43%) or ICS/LABA combination (14%) and compared to patients receiving ICS monotherapy. The use of montelukast as adjunct to other asthma treatment, indicates that patients with various levels of asthma severity were included in the montelukast cohort. The adjusted relative risk (RR) of all neuropsychiatric ADRs leading to cessation of montelukast vs. ICS was 12.0 (CI: 1.6 – 90.2), and 9.0 (CI: 1.2 – 69.5) when only probable/definite drug related neuropsychiatric ADRs were evaluated (Table 15). A *post hoc* analysis without matching showed an increased risk of ADRs with montelukast use for of patients on monotherapy only (adj. RR: 5.9; CI: 1.5-22.5) and for patients with monotherapy or adjunct therapy to ICS or ICS/LABA (adj. RR: 7.1; CI 2.1-23.4).

Table 15. Incidence and adjusted relative risk of neuropsychiatric ADR leading to montelukast cessation among montelukast users compared to ICS users in the Bénard et al. study

Montelukast Cohort	MON Incidence, % (95% CI)	ICS Incidence, % (95% CI)	Final Model, Adjusted RR (95% CI)**	NNH‡
Monotherapy or with adjunct therapy: matched*	14 (8-25)	1 (0-8)	12.00 (1.6-90.2)	7.7
Monotherapy or with adjunct therapy: matched (Probably/Definitely Drug Related)§	11 (6-21)	1 (0-8)	9.00 (1.2-69.5)	10
Monotherapy or with adjunct therapy: unmatched	16 (10-26)	2 (1-7)	7.1 (2.1-23.4)	7.1
Monotherapy: unmatched	13 (6-30)	2 (1-7)	5.9 (1.5-22.5)	9.1

KEY: ADR – adverse drug related events, ICS – inhaled corticosteroid, MON – montelukast, mono – monotherapy, NNH – number needed to harm, RR – relative risk

Notes: Adjunct therapy to ICS or ICS/long acting beta agonists

§ Ascertained as definite (⩾9; n=0) or probably (5–8; n=13) drug related on the Naranjo causality scale.

‡ Number needed to harm (NNH) calculated by FDA reviewer as 1/(incident in montelukast – incidence in ICS).

* Nested matched cohort of 84 montelukast exposed and 84 montelukast unexposed patients matched within 90 days of the drug initiation date.

** None of the potential confounders of the patient (age, sex, ethnicity, asthma control, phenotype, personal and familial predisposing behavioral problems) and treatment (delay between drug initiation and interview) were significant determinates in the multivariate logistic model.

Schumock, et al. (2012)[84]

The objective was to examine the association between LTMAs and attempted suicides within the LifeLink Health Plan Claims database. This was a case control study, nested in a cohort of patients aged 5-24 years in with a primary diagnosis of asthma who were new users (using a 6-month pre-index period) of LTMA or other asthma medications between 1997 – 2006. Cases were patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM: E950-959) codes for self-harm after exposure (n=344) and were matched 1:10 to controls at risk for suicide attempts (n=3438) based on age, gender and geographic region. Using conditional logistic regression, the odds ratios for current exposure (exposure overlapping the index date); immediate past exposure (exposure ending within 30 days of the index date); past exposure (exposure ending between 30 and 180 days of the index date) vs. never exposure were obtained. The study controlled for asthma severity (asthma emergency visits, SABA and oral corticosteroid use and asthma exacerbations), prognostic factors of suicide attempts, and drugs associated with an increased risk of suicide attempt. All 19 cases and 219 control subjects exposed to an LTMA received montelukast; 5 controls received zafirlukast. The adjusted OR of suicide attempt with LTMA ever use (any exposure time) was 0.70 (95% CI 0.36-1.39; Table 16), not controlling for other asthma medications. No dose-response relationship was observed. Neither the overall estimate, nor the age stratified estimates demonstrated an increase in suicide attempt risk with LTMA use, with the exception of an increased risk observed in patients age 19-24 years. Cases were more likely than control patients to have greater risk factors for suicide attempts such as previous suicide attempts and

a history of depression (67.2% vs. 5.6%, respectively, p<0.001), other mental disorders (50.0% vs. 6.3%, respectively; p<0.001), receive psychological counseling, and use medications associated with suicide such as antidepressants, antipsychotics, and anticonvulsants.

Table 16. Adjusted odds ratio of leukotriene-modifying agent exposure for experiencing a suicide attempt in the Schumock et al. study

Exposure Categories	Adjusted Odds Ratio (95% Confidence Interval)
Current use	0.70 (0.36 – 1.39)
Immediate Past use	0.95 (0.36 – 2.50)
Past use	0.69 (0.32 – 1.50)
Ever use	0.74 (0.46 - 1.20)
Stratified Analysis by Cumulative dose[a]	
<=60 leukotriene-modifying agent equivalents	0.64 (0.32 - 1.28)
>60 leukotriene-modifying agent equivalents	0.54 (0.23 - 1.30)
Subgroup Analysis by Age for current use	
5-11 years of age	0.78 (0.03 - 18.09)
12-18 years of age	0.47 (0.20 - 1.09)
19-24 years of age	5.15 (1.16 - 22.86)*
19-24 years adjusting for more medication exposure	5.64 (0.87 – 36.66)

* p<0.05

[a] Total cumulative dose in 180 days before index date calculated as LTMA equivalents (1 equivalent equals 10mg montelukast or 40mg zafirlukast or 2400mg zileuton) for the total milligram dispensed.

Ali, et al. (2015)[85]

Ali et al. conducted a matched case control study nested in a cohort of asthma patients to examine the association between asthma and NAEs in a 10% sample of the LifeLink Health Plan Claims database. The study included patients age 1-17 years with a primary diagnosis of asthma between 1998 – 2009. Cohort entry date was the date of the asthma diagnosis; patients were required to have at least 365 days before and after their asthma diagnosis. Patients with a NAE diagnosis at least one year before cohort entry date and those in long-term care or with developmental or developmental disorders were excluded. Cases were defined as subjects with a primary or secondary diagnosis of mental illnesses, extrapyramidal and abnormal movement disorders, or hallucinations (psychiatric disorder diagnosis [PDD]) or receipt of a psychotropic medication within 365 days of cohort entry date (Neuropsychiatric Diagnosis). PDD (excluding psychotropic medications); psychotropic medication receipt was examined separately. A fourth case definition, neuropsychiatric event diagnosis (NED) defined as PDD mapped to a specific labeled disorder (conduct disorders, anxiety disorders, oppositional defiant disorder, attention deficit and hyperactivity disorder, delirium, dementia, amnestic and other cognitive disorders, tic disorders, depressive disorders, suicide and intentional self-inflicted injury, sleep disorders, other extrapyramidal disease and abnormal movement disorders, or hallucinations) was also examined.

Our review focused on NEDs since this outcome was most germane to the literature review's objective. Cases with NED occurring after exposure (n=1007) were matched 1:3 to controls

without a NED (n=3021) based on age, gender and geographic region, and assigned a matching index date within 1 year of the case. The study controlled for asthma severity, low socioeconomic status, and prognostic factors of psychiatric disorders. Patients with any exposure to montelukast in the prior year had an adjusted OR of 0.96 (CI: 0.80 - 1.14) for NED (Table 17). No increased risk was observed when recency of exposure to the index date was considered. There was no consistent dose relationship observed. Patients exposed to high cumulative doses (>1080 mg) of montelukast in the prior year had lower odds (OR: 0.67; CI 0.48 - 0.93) for experiencing NED but no association for the moderate dose (481-1080 mg) (OR: 1.15; CI: 0.83-1.59). The time from montelukast exposure to index date was 0 -7 days in 53% of the cases and controls exposed to montelukast.

Table 17. Adjusted odds ratio of montelukast exposure for experiencing a neuropsychiatric disturbance, psychiatric disorder diagnosis, neuropsychiatric event diagnosis, and a psychotropic medication receipt in the Ali et al. study (select results, only)

	Adjusted Odds Ratio (95% Confidence Interval)			
	Neuropsychiatric Diagnosis (cases = 1920)	**Psychiatric disorder diagnosis (PDD) (cases = 1637)**	**Neuropsychiatric event diagnosis (NED) (cases = 1007)**	**Psychotropic medication receipt (cases = 392)**
Any exposure to montelukast vs. no exposure				
Past 30 days	1.01 (0.86-1.18)	0.99 (0.84-1.18)	1.02 (0.82-1.26)	1.02 (0.71-1.46)
Past 365 days	1.01 (0.88-1.14)	0.99 (0.86-1.14)	0.96 (0.80–1.14)	1.14 (0.85-1.52)
Chronic Cumulative Dose vs. no montelukast exposure [b]				
Moderate dose (481-1080 mg)	1.27 (1.03 – 1.57)*	1.25 (0.99 – 1.57)	1.28 (0.96 – 1.69)	1.49 (0.92 – 2.43)
High dose (>1080 mg)	0.64 (0.50 – 0.82)*	0.64 (0.49 - 0.83)	0.67 (0.48 - 0.93)	0.59 (0.34 – 1.04)
Treatment duration vs. no montelukast exposure				
90-180 days treatment duration	1.06 (0.84 – 1.36)	0.99 (0.76 – 1.28)	1.15 (0.83 – 1.59)	1.87 (1.11 – 3.15)
>180 days treatment duration	0.75 (0.59 - 0.95)*	0.77 (0.60 – 0.99)	0.83 (0.61 – 1.13)	0.61 (0.34– 1.10)

* $p<0.05$

[b] Chronic cumulative dose is the total quantity of montelukast expressed in mg in the 365 days before the case date, the range provided are total dose for NED only.

KEY: CI – confidence interval, OR – odds ratio

Glockler-Lauf, et al. (2019)[86]

The objective of this matched, nested case–control study was to examine the association between montelukast prescription and neuropsychiatric events in children with pharmacologically treated asthma. The study included children aged 5-18 years with physician-diagnosed asthma from April 1, 2004 to March 31, 2015 in the Institute for Clinical Evaluative Services and the Ontario Drug Benefit Database. Cases were defined by the first neuropsychiatric event following the asthma diagnosis, defined as one hospitalization, same-day surgery, or emergency department (ED) visit for substance-related, schizophrenia, anxiety, sleep disturbance, mood and personality disorders, or agitation, regardless of position. Cases (n=898) were matched 1:4 to controls without a neuropsychiatric event (n=3497) by birth year, year of asthma diagnosis, and sex. Both cases and controls had to have at least 1 prescription

of an asthma maintenance medication in the year prior to the index date. The study adjusted for geography, socioeconomic status (SES), number of asthma medication dispensings, number of asthma related hospitalizations, ED visits and physician office visits, and number of oral corticosteroid prescriptions. Children with a new-onset neuropsychiatric event had nearly 2 times the odds of having a montelukast dispensing compared to controls (adj. OR: 1.91; CI: 1.15-3.18). The number of montelukast prescriptions versus none was not significantly associated with new-onset neuropsychiatric events (1 prescription adj. OR: 2.38; CI: 0.98 -5.77; ≥2 prescriptions (adj. OR: 1.74; CI: 0.96 – 3.16; [Table 18]). Observing the direction of the point estimates, a dose response relationship was observed for other asthma medication prescriptions including oral corticosteroids, but not for montelukast.

Table 18. Adjusted odds ratio for new-onset neuropsychiatric diagnosis in the Glockler-Lauf et al. study

Covariates	Adjusted Odds Ratio (95% Confidence Interval)
Montelukast use (reference = none)	1.91 (1.15 - 3.18)
1 prescription	2.38 (0.98 - 5.77)
2+ prescriptions	1.74 (0.96 - 3.16)
Other asthma medication prescriptions (reference = 0 - 1)*	
2 – 3 prescriptions	2.03 (1.53 – 2.68)
4+ prescriptions	9.66 (7.29 – 12.81)
Number of oral corticosteroid prescriptions (reference = 0)	
1 prescription	0.96 (0.72 – 1.26)
2 prescriptions	1.41 (0.99 – 2.02)
Asthma severity (hospitalizations, physician, and ED visits for asthma)	2.09 (1.82 – 2.40)

* Inhaled corticosteroids, long acting beta agonists, short acting beta-2 agonists, anti-IgE, methylxanthines, PDE-4 inhibitors, interleukin-5 inhibitors
KEY: ED – emergency department, SDS – same day surgery

5.1.5. Methodological quality of studies

Evidence from the high-quality studies were used to form the basis of the literature review's conclusions. The nested case-control studies by Ali and Schumock were of high quality as both studies had adequate sample selection, study group comparability, exposure and outcome assessment, and adequate study power (Table 19). Additionally, these studies both examined incident montelukast users and assessed treatment duration. While both studies utilized the LifeLink database, the results were not redundant since each study assessed different outcomes, years, and age groups. Although Bénard's and Glockler-Lauf's studies were well publicized for finding an increased risk of NAEs with montelukast use, the studies had several limitations which warrant further discussion.[119]

Bénard's study found an 9- to 12-fold increased risk of NAEs with montelukast use, but the parent interviews were conducted after the 2008 DSC and labeling changes and approximately three years after the pediatric patients initiated the asthma medications; this created three concerns. First, parents with children on montelukast compared to ICS may be more likely to

detect and recall a neuropsychiatric event or a developmental change, relate it to montelukast use, and cease treatment (recall bias). This is probable since 70% of the events were rated by the adjudicators as mild or "an [NAE] requiring drug cessation." The 2009 label informed prescribers to instruct montelukast users "to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur." The ICS labels did not come with these warnings. Second, the study did not validate the parent reported outcomes; instead, possible causal relationship between the outcome and asthma medication was examined. As a reaction to the 2008 DSC and labeling changes, parents may have been more likely to attribute events to montelukast use, compared to parents with children exposed to ICS. The recall bias from the montelukast parents would result in overestimation of the actual risk between montelukast and NAEs. Validation of the event occurrence between the ICS and montelukast groups would have resulted in a more accurate risk estimate. Finally, although the study was able to detect an increased risk of probable/definite neuropsychiatric ADRs leading to cessation (adj RR=9.0; CI: 1.2 – 69.5), it was not powered to study this association. Eighteen events out of 100 patients exposed to montelukast were required for adequate study power, but only 9 events out of 84 patients occurred. Because of these limitations, the magnitude of the association between montelukast and NAEs is likely overestimated and imprecise, as indicated by the very wide confidence intervals.

Glockler-Lauf's study found that cases had twice the odds of being exposed to montelukast compared to controls, however, the cases may have included psychiatric conditions that existed before asthma medication exposure. The 898 cases were acquired from the inpatient setting (41%), emergency room visits (43%) and same-day surgeries (15%), namely dental, ear, nose and throat surgeries. The study does not specify if the mental diagnosis was the reason for the medical encounter. This is especially of concern since patients presenting for emergency room visits or same day surgeries may report their history of a previously diagnosed mental disorder instead of actually receiving their initial psychiatric diagnosis. Furthermore, the study may have included patients with pre-existing sleep disorders and agitation, since these two conditions were not in the exclusion criteria. As a result, the study could not ensure that the exposure always preceded the initial neuropsychiatric diagnosis. In addition to the inclusion of prevalent cases, montelukast exposure was rare in this study (<9%) since it is second-line therapy for pediatric patients who have failed ICS and LABA (in compliance with Canada's Exceptional Access Program). As a result, the study was not adequately powered to examine the psychiatric event type or the number of montelukast prescriptions.

Table 19. Quality assessment of reviewed studies

Cohort Study	***Bénard (2017)[83]***	**Case-Control Studies**	***Ali (2015)[85]***	***Schumock (2012)[84]***	***Glockler-Lauf (2019)[120]***
Newcastle Ottawa Criteria		***Newcastle Ottawa Criteria***			
Selection		**Selection**			
Representativeness of exposed cohort	X	Adequacy of Case Definition	x	x	
Selection of non-exposed cohort	X	Representativeness of Cases	x	x	x
Ascertainment of exposure	X	Selection of Controls	x	x	x
Study outcome was not present at start of study		Definition of Controls	x	x	
Comparability		**Comparability**			
Adjust for other psychiatric or behavioral disorders	X	Adjust for other psychiatric or behavioral disorders	x	x	x
Adjust for asthma severity	X	Adjust for asthma severity	x	x	x
Outcome		**Exposure**			
Assessment of outcome		Ascertainment of exposure	x	x	x
Was follow-up long enough for outcomes to occur	X	Same methods of ascertainment for cases and controls	x	x	x
Adequacy of follow-up of cohorts		Non-response rate	x	x	
Further Considerations of Reviewer		***Further Considerations of Reviewer***			
Control for 2008 DSC and labeling changes		Control for 2008DSC and labeling changes		x	
No conflicts of interest	x	No conflicts of interest	x		x
Power to test association between montelukast and outcome		Power to test association between montelukast and outcome		x	
Incident use of MON	x	Incident use of montelukast	x	x	
Assess treatment duration		Assess treatment duration	x	x	x
Adjust for monotherapy or ICS/LABA combination therapy in primary analysis	x	Adjust for monotherapy or ICS/LABA combination therapy in primary analyses			x
Association	Positive	**Association**	None	None	Positive

KEY: DSC - Drug Safety Communications, ICS – inhaled corticosteroid, LABA – long-acting beta agonist, LTMA – leukotriene modifying agents, MON – montelukast

5.1.6. Discussion

The objective of the literature review was to examine the association between montelukast use and withdrawal and the outcome of both labeled and unlabeled NAEs. The two highly publicized studies showed an increased risk of NAEs with montelukast exposure, but as previously discussed, both studies have a risk of considerable bias which may have resulted in an overestimation of the risk and deterred from the studies' credibility.[83,86] The remaining two high quality case-control studies showed a null association. However, there are several limitations that should be considered in the interpretation of the studies' findings.

For both studies, the primarily analyses do not control for concomitant asthma medications which carry their own risk for NAEs, resulting in an inaccurate estimation of the risk.

By not controlling for the concomitant asthma medications in the primary risk analyses, the studies failed to consider the additive risk of NAEs due to LABA use. The use of ICS alone has no increased risk of NAEs within the pediatric population. But LABAs, such as salmeterol, carry a labeled warning regarding reports of "[a]gitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children" and "[p]aresthesia, restlessness." Although the risk of NAEs with LABA use is considered rare, it is unknown if concomitant LABA use contributed to the observed risk in the montelukast cohort.

Ali's study failed to control for multiple comparisons.

Ali failed to control for multiple comparisons within the subgroups (i.e. cumulative dose, treatment duration, regency of drug exposure and specific NAE), thus the likelihood of finding a significant result increased due to random sampling error (Type I error). The study had 80 comparisons between varying exposure and outcome categories, of which 7 comparisons were significant. The reviewer cannot rule out that the significance of these values may be due to chance.

The suicide attempt definition in the Schumock *study may not reflect suicidal ideation.*

The authors have relied on diagnosis codes representing self-inflicted injuries to define suicide attempt, the definitions cannot deduce whether these injuries self-inflicted were due to suicidal ideation. Therefore, one cannot rule out inaccurate ascertainment of the outcome.

The last author of the Schumock study has a conflict of interest and the positive study results were re-evaluated until they were null.

T.A. Lee, the last author of the Schumock article, is a consultant for Merck Pharmaceuticals, and Forest Pharmaceuticals (the makers of Montelukast) and has received financial support from Novartis. The study's conclusions are made questionable when the study re-evaluated the positive association between

montelukast and NAEs within the 19-24-year-old population (adj. OR=5.15, 95% CI 1.16 – 22.86) until no further association was seen (adj. OR=5.64, 95% CI 0.87 – 36.66). Specifically, as a *post hoc* analysis, the study "reassessed the covariates included in [the] adjusted model" and added "previous exposure to both other asthma medications and drugs associated with suicide." (Schumock, et al., 2012, pg. 372). The authors do not specifically state what the reassessment of the covariates involved, so the reassessment may not be valid or necessary. It was, however, appropriate to adjust for medications associated with suicide. The study did not re-evaluate any findings that had a null association. Like Ali, et al., there were too few patients (8 cases and 32 controls) to provide an accurate estimation of the risk within this age group.

In summary, the association between NAEs and montelukast exposure in pediatric patients is not well-studied in observational data. None of the reviewed studies were adequately powered to study the effects of montelukast by age (pediatric and adult) or controlled for the effects of the 2008 DSC and labeling changes to montelukast. Furthermore, all studies excluded patients with pre-existing psychiatric disorders, and thus, were not able to examine this measure as a possible confounder in the association between montelukast and neuropsychiatric events. Of the reviewed studies, none reported the long-term effects of montelukast exposure and withdrawal as requested by the parent group. To bridge these gaps, FDA conducted an observational study in the Sentinel Distributed Database (SDD) to investigate the association between NAEs and montelukast exposure. Specifically, our objectives were to determine if 1) there is an increased risk of depressive disorders, self-harm and suicides associated with montelukast use compared to ICS and 2) if the NAEs with montelukast compared to ICS were modified by the 2008 DSC and montelukast labeling changes, age, sex, and psychiatric history in a separate review.

5.1.7. Conclusions

The observational studies do not provide convincing evidence regarding the association between NAEs and montelukast exposure in pediatric patients. The data are suggestive of an increased risk of self-harm in patients aged 19-24 years; however, these results have not been duplicated in other studies. There is no observational evidence regarding the safety of withdrawal and the long-term implications of adverse reactions. Due to limited data, FDA conducted an observational study in the Sentinel Distributed Database to examine risk of serious neuropsychiatric events and suicides associated with montelukast exposure.

5.2. Sentinel Analysis

5.2.1. Regulatory Memo

To: Sally Seymour, Deputy Director for Safety, Division of Pulmonary Allery and Rheumatology Products

From: Veronica Sansing-Foster, Reviewer, Division of Epidemiology II

Through: Efe Eworuke, Team Leader, Division of Epidemiology II
CAPT David Money, R.Ph., MPH, USPHS, Director, Division of Epidemiology II

Drug Names: Singulair (montelukast); NDAs 021409, 020830, 020829; Accolate (zafirlukast); NDA 020547
Zyflo (zileuton); NDA 020471; Zyflo CR (zileuton CR); NDA 022052; Various ANDAs

TSI: 415

Date: September 6, 2019

Subject: Regulatory Recommendations Memo for FDA's Sentinel analysis of montelukast use and neuropsychiatric adverse events

Introduction

The issue of neuropsychiatric events with exposure to montelukast was the subject of the tracked safety issue (TSI) 415 created on March 19, 2008. In preparation for the Pediatric Advisory Committee Meeting on September 27, 2019, DEPI II undertook an observational analysis of neuropsychiatric adverse event risks with montelukast, using the Sentinel Distributed Database (SDD). This memo accompanies the report for the SDD analysis and provides FDA's assessment and regulatory recommendations.

The study team, in addition to this reviewer, included from the Division of Biometrics 7, Yong Ma; from the Division of Epidemiology 1, Andrew Mosholder, and Dinci Pennap; from the Division of Epidemiology 2, Efe Eworuke and Marie Bradley; from the Division of Pharmacovigilance, Ivone Kim; and from the Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston MA, Nicole Haug, Noelle Cocoros, Elizabeth Dee, Ella Pestine, Andrew Petrone, Sengwee Toh, and Jennifer Lyons.

Background

Singular® (montelukast), a leukotriene-modifying agent (LTMA), was approved on February 20, 1998 (oral and chewable tablet) for the treatment of asthma in patients ≥12 months of age and the acute prevention of exercise induced bronchoconstriction in patients ≥6 years of age. The oral granule form was approved on July 26, 2002 for the relief of perennial allergic rhinitis in patients ≥6 months and seasonal allergic rhinitis in patients ≥2 years or age.

In 2007, FDA received an inquiry from New York State Senator Little regarding a 15-year-old who committed suicide 17 days after starting montelukast. In 2008, an FDA review examining the association between mood, cognitive, perception, and sleep adverse events with montelukast use recommended that neuropsychiatric events to be added to the precautions section of the label.[r] In 2008, FDA issued a Drug Safety Communication (DSC) and revised the montelukast label in 2009 to include the risk of neuropsychiatric events: agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

On November 11, 2017, the Parents United for Pharmaceutical Safety and Accountability and the montelukast (Singulair) Side Effects Support and Discussion Group submitted a letter to FDA requesting that neuropsychiatric effects in the montelukast label be updated based on a survey conducted by the group. Specifically, the Parents group requested reclassifying neuropsychiatric events as common, with potential delayed onset. The survey suggested the incidence of neuropsychiatric side effects with montelukast are more common than currently reported, particularly in children. DEPI conducted a literature review of observational studies,[s] and recommended an observational study be conducted in the Sentinel Distributed Database to examine risk of serious neuropsychiatric events and suicides associated with montelukast exposure compared to inhaled corticosteroids (ICS) since the observational studies in the literature did not provide conclusive evidence regarding the association between neuropsychiatric events and montelukast exposure in pediatric subjects.

Review of FDA's Sentinel Analysis:

Using data from the Sentinel Distributed Database (SDD) from January 1, 2010 to September 30, 2015, we investigated if there was an increased risk of depressive disorders, self-harm and suicides associated with montelukast use compared to ICS, and if the risk of neuropsychiatric adverse events (NAEs) with montelukast compared to ICS was modified by the 2008 DSC and subsequent montelukast labeling changes, or is affected by age, sex, or psychiatric history. Patients were age 6 years and older with asthma diagnosed in any care setting and exposure to montelukast or ICS, excluding patients with COPD. Using a propensity score model, montelukast monotherapy initiators were matched 1:1 to ICS monotherapy initiators based on age, gender, index year, psychiatric history, medication usage, prior comorbidities, and measures of asthma severity. Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

We identified 513,519 and 1,332,531 montelukast and ICS users respectively. After propensity score matching, 89.1% and 34.3% of montelukast and ICS initiators (n=457,377) were retained. Of 38,870 NAEs identified during the follow-up period, 37,740 were treated outpatient depressive disorder, 647 inpatient depressive disorder, 219 self-harm, and 264 cases identified

[r] Green L, Mosholder A, Moeny D. AERS Post-marketing Safety Review: Mood, Cognitive, Perception, Sleep and Movement Adverse Events. December 19, 2008.
[s] September 12, 2018 OSE Integrated Pharmacovigilance and Epidemiology Review: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af804b757c

using the modified self-harm algorithm. Most of the outcomes were NAEs with a previous diagnosis of a psychiatric disorder (94.1%) and occurred in patients exposed to the asthma medications after the 2008 DSC and labeling changes. Exposure to montelukast was significantly associated with a decreased risk of treated outpatient depressive disorder (HR: 0.91; CI 0.89-0.93). This decreased risk was seen in among patients with a history of a psychiatric disorder (HR: 0.89; CI: 0.88-0.91), in patients age 12-17 years (HR: 0.82; CI: 0.76-0.89) and age 18 years and above (HR: 0.90; CI: 0.88-0.92) and in both females (HR: 0.90; CI: 0.88-0.93) and males (HR: 0.93; CI: 0.89-0.97). The overall HR for inpatient depressive disorder with montelukast compared to ICS was 1.06 (CI: 0.90-1.24). There was no significant risk associated with montelukast among males (HR: 1.15; CI: 0.84-1.58), females (HR: 1.04; CI: 0.86-1.26), patients 12 years and older, after the 2008 DSC and labeling changes (HR: 1.08; CI: 0.91-1.29) and in patients with a psychiatric history (HR: 1.10; CI: 0.93-1.31). In patients without a psychiatric history, the HR was 0.63 (CI: 0.37-1.07). Exposure to montelukast was also not associated with self-harm (HR: 0.92; CI: 0.69-1.21) or modified self-harm (HR: 0.81; CI: 0.63-1.05). All suicides, 2 exposed to montelukast and 2 exposed to ICS, occurred in patients over the age of 18 with a psychiatric history.

The absence of risk for serious neuropsychiatric events of inpatient depressive disorder and self-harm appear to be consistent with results from clinical trials and observational studies.[84,85,121] The decreased risk observed between montelukast and the treated outpatient depressive disorder was unexpected. Since most of the exposure occurred after the 2008 DSC and labeling changes, montelukast-treated patients could have stopped treatment at the onset of depressive symptoms without presenting for outpatient treatment of depression. In conclusion, we did not find associations between montelukast monotherapy and hospitalizations for depressive disorder, or medical claims for self-harm events when compared to ICS monotherapy. With montelukast users, we did find a reduced risk of treated outpatient depression compared to ICS users in patients with a psychiatric history, but this finding should be interpreted in the context of the above-mentioned limitations.

Regulatory Recommendations:

The absence of risk for serious neuropsychiatric events associated with montelukast use in the Sentinel analysis is corroborated with findings from the clinical trials and well-conducted observational studies. The current montelukast labeling already includes neuropsychiatric events of varying severity, including events studied in both the Sentinel and observational studies. However, the absence of an increased risk in the Sentinel study should not warrant the removal of these safety events from the label because we did not study the less severe labeled outcomes, such as anxiety, sleep disturbances and attention deficit, that could possibly lead to discontinuation of montelukast treatment.

5.2.2. Executive Summary

Using data from the Sentinel Distributed Database (SDD) from January 1, 2000 to September 30, 2015, we investigated if there was an association between depressive disorders, self-harm and suicides with montelukast use compared to inhaled corticosteroids (ICS), and if the risk of neuropsychiatric adverse events (NAEs) with montelukast compared to ICS were modified by the 2008 Drug Safety Communication (DSC) and montelukast labeling changes, or are affected by age, sex, and psychiatric history. Patients (n=457,377) exposed to montelukast or ICS, aged 6 years and older with a diagnosis of asthma were matched 1:1 on propensity scores. Exposure to montelukast was significantly associated with a decreased risk of treated outpatient depressive disorder (Hazard Ratio [HR]: 0.91; 95% confidence interval [CI]: 0.89 - 0.93). The risk of inpatient depressive disorder (HR: 1.06; CI: 0.90 - 1.24), self-harm (HR: 0.92; CI: 0.69 - 1.21) and a modified self-harm algorithm (HR: 0.81; CI: 0.63 - 1.05) associated with montelukast use compared to ICS was not significant. In summary, when compared to use of ICS, we did not find associations between montelukast treatment and hospitalizations for depression, or medical claims for self-harm events. We did find a reduced rate of outpatient treatment for depression among montelukast users compared to ICS users, but this finding should be interpreted cautiously.

5.2.3. Introduction

Singular® (montelukast), a leukotriene-modifying agent (LTMA), is approved for the treatment of asthma in patients ≥12 months of age, the acute prevention of exercise induced bronchoconstriction in patients ≥6 years of age, and the relief of perennial allergic rhinitis in patients ≥6 months and seasonal allergic rhinitis in patients ≥2 years or age. Following its approval, the post-marketing experience section of the montelukast label was updated to include dream abnormalities, irritability, and restlessness (1999), insomnia (2000), hallucinations (2001), agitation including aggressive behavior (2002). Prompted by pharmacovigilance data, FDA issued Drug Safety Communications (DSC) in 2008 and 2009 and updated the "Warnings and Precautions" section of the montelukast label in 2009 to include: agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, dream

abnormalities, hallucinations, insomnia, irritability, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor.

Since the DSC and labeling changes, there have been conflicting results from postmarket observational studies regarding the risk of NAEs with montelukast use.[83-86] These studies were limited in their ability to control for pre-existing psychiatric conditions and concomitant asthma medications that carry a risk of NAEs, such as oral corticosteroids and long-acting beta adrenoceptor agonists (LABA).[122-124] Using data from16 Data Partners contributing to the Sentinel Distributed Database (SDD), we sought to investigate the association between NAEs and montelukast exposure. Specifically, our objectives were to determine if 1) there is an increased risk of depressive disorders, self-harm and completed suicides associated with montelukast use compared to inhaled corticosteroids (ICS) use, and 2) if the NAE risks with montelukast compared to ICS were modified by the 2008 montelukast DSC and labeling changes, or are affected by age, sex, or psychiatric history.

5.2.4. Methods

Data Source

Data from January 1, 2000 to September 30, 2015 from 16 health plans contributing to the SDD were included. The SDD is composed of U.S.-based data partner (DP) sites primarily represented by large national insurers and integrated delivery care networks. Each DP has medical and pharmacy data, including inpatient and outpatient diagnoses and procedures, and retail and mail order prescription records. This study was conducted as part of the Sentinel surveillance activities under the auspices of the Food and Drug Administration, and therefore, was not under the purview of Institutional Review Boards.[125]

Study Cohorts

We included patients aged 6 years and older with continuous enrollment in health plans with both medical and drug coverage for at least 183 days before medication initiation (Figure 7). To accommodate administrative gaps in enrollment as opposed to disenrollment, we allowed enrollment gaps of up to 45 days. From this source population, we identified new users of montelukast monotherapy (primary exposure) and ICS monotherapy (comparator exposure), defined as patients with an index dispensing (index date) of either exposure with no use of montelukast or ICS as single or combination therapy, LABA, or LTMA in the 183-day baseline period prior to index date. Montelukast monotherapy and ICS monotherapy were chosen as the exposure groups since they are both treatment options for mild to moderate asthma severity per the National Asthma Education and Prevention Program Guidelines.[126] Other LTMAs were used relatively infrequently, so they could not serve as a comparator treatment group. We also required all patients to have an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis of asthma[t] in any care setting (i.e., outpatient, inpatient, and emergency), and no diagnosis of COPD during the baseline period; patients with comorbid

[t] For the baseline asthma diagnosis, we only included ICD-9 codes for diagnoses in which montelukast monotherapy and ICS monotherapy were both viable options for initial treatment.

allergic rhinitis, an alternative indication for montelukast use, were not excluded. Index dates with same-day dispensings for both the primary exposure and comparator exposure were not considered.

Outcomes

The following study outcomes were evaluated: 1) inpatient depressive disorder defined as depression in the primary position on an inpatient claim, 2) outpatient depressive disorder requiring psychotherapy or antidepressant use within 30 days following the date of the diagnosis 3) hospitalization due to self-harm, 4) hospitalization due to self-harm or self-harm E-codes (modified self-harm) and 5) death by completed suicide (see Section 5.3.2 for ICD 9 codes and E-codes). Self-harm was defined as a combination of inpatient, outpatient, or emergency room discharge diagnosis of poisoning, toxicity of non-medical substance, asphyxiation or an open wound to the elbow/wrist/forearm and an inpatient discharge diagnosis of depression, personality disorder, mania, adjustment reaction, or an unspecified non-psychotic mental disorder on the same day. The algorithm for self-harm used in our analysis has been modified[u] from a validated algorithm with a positive predictive value of 73%.[2] In order to capture additional cases of self-harm, we also analyzed a composite outcome of the aforementioned self-harm outcomes including E-codes relevant to self-harm (modified self-harm: E950 – E958; Section 5.3.2). Death by completed suicide was only examined in six DPs contributing cause of death data to SDD. Although not a study outcome, we enumerated all-cause mortality to provide context for suicides.

Exposure Episodes for Montelukast and ICS

For inpatient depression, self-harm, suicide and all-cause mortality, we allowed medication gaps of 15 days between dispensings of the exposure drug, plus a 15-day episode extension period after stockpiling overlapping dispensings (of the same generic name) to define continuous exposure (Section 5.3.3). To accommodate the time-period between depression diagnosis and psychotherapy or antidepressant use, we used a 30-day gap and episode extension period to create exposure episodes for the treated outpatient depressive disorder. Only the first treatment episode meeting these requirements were analyzed; patients were not allowed to re-enter the cohort. Episodes beginning with a same-day initiation of both montelukast and ICS were not considered.

Follow-up and Study Design

The index date served as the cohort entry date. Patients who experienced an outcome on the cohort entry date were excluded. Follow-up for events began on the day after the cohort entry date and ended at the earliest of any of the following: exposure end date; dispensing of comparator drug; dispensing of LTRA, LABA, oral corticosteroid, or a combination ICS/LABA product; occurrence of any study outcome; asthma-related hospitalization (asthma diagnosis in the primary position); death; DP end date; query end date (9/30/2015); or disenrollment (Section 5.3.3).

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[u] We modified the self-harm algorithm by adding the outpatient and emergency room discharge diagnoses of poisoning, toxicity of non-medical substance, asphyxiation or an open wound to the elbow/wrist/forearm. The original algorithm only included the inpatient setting for these diagnoses.

Covariates of Interest

We estimated the baseline propensity scores (PS) using logistic regression to predict the probability of initiation of montelukast versus ICS. Specifically, the PS model included age (continuous), sex (female, male), index year, combined comorbidity score, substance abuse, allergic rhinitis, asthma-related hospitalization or emergency visit, or 2 asthma-related outpatient visits, at least two respiratory disorders other than asthma or COPD, oral corticosteroid dispensings, short acting beta agonists (SABAs), other asthma medication dispensings (anticholinergic agents, phosphodiesterase inhibitors), asthma exacerbations and status asthmaticus (yes, no), and a history of psychiatric disorders defined as a composite of psychiatric and psychotropic medication use, self-harm (as defined by the Patrick et al., 2010 algorithm), or any other psychiatric event (Sections 5.3.2 and 5.3.3).[127]

Statistical Analysis

Based on the estimated PS, montelukast initiators were matched to ICS initiators with a 1:1 ratio using the nearest neighbor match (0.05 calipers within each DP) both conditionally and unconditionally. Baseline characteristics were described using means, percentages, and standard deviations, and compared between treatment groups using standardized mean differences (SMD). We obtained unadjusted risk estimates for inpatient depressive disorder, treated outpatient depressive disorder and self-harm separately and using Cox proportional hazards regression model obtained adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) in the unmatched population (adjusting for DP study site only), and separately in the matched population. The rates of all-cause mortality were examined descriptively within these six DPs to provide context for the rates of suicide in the population. We conducted subgroup analyses stratified by age groups (6-11 years, 12-17 years, and ≥18 years), sex, history of psychiatric disorder, and the periods before and after the montelukast DSC and labeling changes (pre: 2000-2007, post: 2008 – 2015). For subgroup analyses, patients that were matched in the main analysis were re-matched within their subgroups using their original propensity scores.

The following sensitivity analyses were conducted for the inpatient depressive disorder only. First, we excluded the 30-day episode extension period, to examine if risk estimate attenuated. Then, given the potential of ICS to be underused as compared to montelukast, we compared ICS users with a 30-day gap and extension period to montelukast users with a 15-day gap and 15-day extension period.[128] The analytical process, including propensity score calculation and effect estimation, was completed using the Sentinel Propensity Score tool, version 7.3.3, a pre-tested, validated analytic program.[129]

5.2.5. Results

Patient Baseline Characteristics

From January 1, 2000 to September 30, 2015, we identified 513,519 and 1,332,531 montelukast and ICS patients with a diagnosis of asthma in the 6 months prior (Table 21). We conducted analyses within the matched conditional and matched-unconditional cohorts, but have presented the matched-unconditional results, only, as these analyses provided a greater

number of events. The direction and magnitude of the estimates of matched-conditional cohort results did not materially differ from the matched-unconditional cohort results.

After propensity score matching, 89.1% and 34.3% of montelukast and ICS initiators (n=457,377 in each exposure group) were retained. Patient characteristics in the matched and unmatched cohorts differed. Compared to the unmatched ICS cohort, the matched ICS include more patients with allergic rhinitis (43.4% vs. 27.4%); psychiatric disorder (36.8% vs. 31.6%); and history of oral corticosteroid use (20.6% vs. 14.5%). The unmatched and matched montelukast cohorts were more similar on baseline psychiatric disorders; however, the matched montelukast cohort included more patients who previously used SABAs (63.0% vs. 57.7%). Despite differences noted between matched and unmatched cohorts, the covariates were well-balanced between the treatment groups after matching. In the matched cohorts, most participants were female (62%), with a mean age of 38.5 years. Approximately a third of the patients had a history of a psychiatric disorder (37%). Less than half the patients had a concomitant diagnosis of allergic rhinitis (43%) and other respiratory disorders besides asthma and COPD (~48%). Most patients received their asthma medications after the 2008 DSC and labeling changes (89.9%).

Depressive Disorders and Self-Harm

There was a total of 38,870 NAEs identified during the follow-up period. Of these, 37,740 were treated outpatient depressive disorder, 647 inpatient depressive disorder, 219 self-harm, and 264 cases identified using the modified self-harm algorithm (Table 22). Most of the outcomes were NAEs with a previous diagnosis of a psychiatric disorder (94.1%). The average length of follow-up until censoring for each outcome ranged from 81-100 days for montelukast patients and 54-70 days for ICS patients.

The HR for inpatient depressive disorder with montelukast compared to ICS was 1.06 (CI: 0.90-1.24; Figure 8). Hazard ratios were not statistically significant in patients with a psychiatric history (HR: 1.10; CI: 0.93-1.31), males (HR: 1.15; CI: 0.84-1.58), females (HR: 1.04; CI: 0.86-1.26), patients 12 years and older, and after the 2008 DSC and labeling changes (HR: 1.08; CI: 0.91-1.29). In patients without a psychiatric history, the HR was 0.63 (CI: 0.37-1.07). Exposure to montelukast was significantly associated with a decreased risk of for treated outpatient depressive disorder (HR: 0.91; CI 0.89-0.93; Figure 9). This decreased risk was observed among patients with a history of a psychiatric disorder or psychotropic drug use (HR: 0.89; CI: 0.88-0.91) and in patients age 12-17 years (HR: 0.82; CI: 0.76-0.89) and age 18 years and above (HR: 0.90; CI: 0.88-0.92). The decreased risk was similar between females (HR: 0.90; CI: 0.88-0.93) and males (HR: 0.93; CI: 0.84-0.97). The magnitude and direction of risk did not change between the DSC and labeling change periods.

Exposure to montelukast was not associated with self-harm (HR: 0.92; CI: 0.69-1.21; Figure 10) and the modified self-harm outcome (HR:0.81; CI 0.63-1.05; Figure 11). Montelukast was also not associated with self-harm in patients without a history of psychiatric disorder (HR: 1.34; CI: 0.38-4.71), among males (HR: 1.16; CI: 0.58-2.36) and before the DSC and labeling changes (HR:

1.16; CI: 0.49-2.74). For modified self-harm, there was no association before the DSC and labeling changes (HR: 1.06; CI: 0.53-2.15).

In the sensitivity analyses, the direction and magnitude of the HRs for inpatient depression for the analyses without an extension period (adj. HR: 1.07; CI: 0.89 - 1.28) and 30-day gap for ICS episodes (adj. HR: 1.04; CI: 0.90 - 1.20) were not substantially different from the primary analyses.

Upon reviewing the results from the primary analyses, we observed the proportional hazards assumption was not met. Therefore, we evaluated the HR for all study outcomes censored at 365 days of follow-up in a *post-hoc* analysis. These results were consistent with the primary analyses. There was no risk associated with montelukast for the inpatient depressive disorder (1-year HR: 1.06; CI: 0.90 - 1.25; Figure 12) and a decreased risk of treated outpatient depressive disorder (1-year HR: 0.91; CI: 0.89 - 0.93) compared to ICS patients at the end of 1-year follow-up.

Suicide Analyses

Within the six data partners reporting cause of death data, there were 57,167 montelukast patients and 222,016 ICS patients. After 1:1 PS matching, the final patient population for the analyses was comprised of 49,800 montelukast and ICS initiators (Table 23). Among the matched patients, there were no suicides among ICS patients, but two suicides within the montelukast cohort (1.2 events per 10,000 new users). Both events occurred within female patients over the age of 18 with a history of a psychiatric disorder. For all-cause mortality in the unmatched patient population, 2 out of the 29 montelukast users who died committed suicide (7%), and 2 out of the 125 ICS users who died committed suicide (2%).

5.2.6. Discussion

Our study did not find any associations between montelukast and severe NAEs (inpatient depressive disorder and self-harm) in the overall analyses and across age, sex, or calendar time strata. On the contrary, we observed a significantly decreased risk of treated outpatient depressive disorder with montelukast compared with ICS.

The absence of risk for serious neuropsychiatric events appear to be consistent with results from clinical trials and observational studies.[84,85,121] A retrospective analysis of 46 placebo-controlled trials by the manufacturer of montelukast which examined the association between montelukast and NAEs of varying severity resulted in an OR of 1.12 (CI: 0.93-1.36).[121] Among the more serious events, the authors note no difference between montelukast and placebo groups (0.03% in each treatment group). Differences in reporting of NAEs between the individual trials, either investigator or patient-reported, could have impacted outcome ascertainment. Ali et al. (2015) used a matched nested-case control study design to examine the association between asthma and a neuropsychiatric event diagnosis in patients age 1- 17

years and found no association with any exposure to montelukast in the prior year (adjusted odds ratio [OR]: 1.02; CI: 0.82-1.26).[85] Schumock and colleagues (2012) also used a matched case-control study design to examine the association between LTMAs and attempted suicides (referred to in our study as self-harm) in patients aged 5 – 24 years and found no association any exposure to LTMAs within the 180 days prior (adjusted OR: 0.70; CI: 0.36 – 1.39).[84] No dose-response relationship was observed, although an increased risk of suicide attempts with montelukast exposure was observed in patients aged 19-24 years (OR: 5.15; CI: 1.16 – 22.86).

The decreased risk between treated outpatient depressive disorder and montelukast and was unexpected. However, there are plausible explanations for the estimates observed. First, the majority (90%) of our patient population was exposed to montelukast and ICS after the 2008 DSC and labeling change. The 2009 label informed prescribers to instruct montelukast users "to be alert for neuropsychiatric events. Evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur." Therefore, montelukast-treated patients could have stopped treatment at the onset of depressive symptoms without presenting for outpatient treatment of depression. Additionally, patients already receiving treatment for depression may have been more likely to have received ICS than montelukast after the 2008 DSC and labeling changes. Second, it is also possible our definition of outpatient depressive disorder (outpatient diagnosis plus psychotherapy or psychotropic drug prescription within 30 days of diagnosis) may have captured a high proportion of continuing outpatient treatment episodes for pre-existing outpatient depressive disorder, complicating its interpretation as a treatment-emergent outcome during follow-up. The decreased risk of NAEs with montelukast was not present in the subgroup without a prior psychiatric disorder, which excluded patients receiving treatment for depression. Finally, we acknowledge the possibility that ICS use could be associated with depressive symptoms, given that oral corticosteroids are well-known to be associated with psychiatric disorders, and a portion of the ICS dose is systemically absorbed.[130] We also noted a reduction in inpatient depression with montelukast, though it was not significant and was only in the subgroup of patients without a psychiatric history.

Strengths of our study included a large patient population from 16 different data partners of varying insured patient populations, the balancing of covariates after PS matching, and the ability to study patients exposed to montelukast before and after the DSC and labeling changes. Our suicide data was extracted from records that the data partners deemed "excellent," thus ensuring high specificity for this outcome. A post-hoc power calculation showed that our study had 80% power to detect a hazard ratio >= 1.25 for inpatient depression and a hazard ratio >= 1.46 for self-harm outcomes.

Our study had several limitations. First, it could be argued that ICS may not be the best comparator for montelukast due to the relatively poor adherence to ICS compared to montelukast creating disparate at-risk times between the exposure groups.[131] However, our sensitivity analysis that elongated the gap and extension period between dispensings to include patients who were likely to refill ICS regularly was comparable to the primary analyses. Second, we were unable to adjust for socioeconomic status (SES), but we did not have any evidence that montelukast and ICS are prescribed disproportionally to patients of varying SES.[132] Patients

with relatively higher SES may be more likely to seek asthma management through outpatient visits, resulting in increased surveillance for NAEs.[132] Relative to lower SES patients, this increased surveillance can either result in increased NAE diagnosis or decrease NAE diagnoses due to early intervention. Third, while we observed non-proportionality of the hazards for the study outcomes, our post-hoc analyses truncating follow-up to 1 year after treatment did not substantially change the study's findings. Finally, we were only able to study outcomes that resulted in healthcare claims. Conceivably, some NAEs may have been handled by discontinuation of the drug without a healthcare encounter, such as intervention through non-medical professionals (i.e. family members, religious leaders, etc.).

5.2.7. Conclusions

When compared to ICS monotherapy, we did not find associations between montelukast monotherapy and hospitalizations for depressive disorder, or medical claims for self-harm events. We did find a reduced risk of outpatient treatment for depression among montelukast users compared to ICS users, but this finding should be interpreted cautiously.

5.3. Supplements

5.3.1. Additional Tables and Figures

Table 20. Summary of reviewed studies

Cohort Studies					
First Author (Year) Conflicts of Interest	**Exposure (type)**	**Outcome**	**Exposed (N) Unexposed (N)**	**Risk Estimates (95% Confidence Intervals)**	**Comments**
Bénard (2017) No disclosed conflicts of interest	MON	Neuropsychiatric adverse drug reactions	84 on montelukast monotherapy, combination ICS therapy, and ICS/LABA combination therapy vs. 84 on ICS monotherapy	Adj. HR = 12.0 (1.6-90.2) Adj. HR of probable/definite events = 9.0 (1.2-69.5)	Well-publicized, but: ▪ Imprecise estimates (very wide confidence intervals). ▪ Entire study conducted after 2008 DSC and labeling changes ▪ MON users instructed to be vigilant of NAEs and to consider drug cessation. ▪ Interviews by proxy conducted 3 years after drug initiation. ▪ The occurrence of study outcomes was unvalidated. ▪ Asthma severity is a confounder since MON cohort includes monotherapy and combination therapy
Nested Case-Control Studies					
First Author (Year) Conflicts of Interest	**Exposure**	**Outcome**	**Case (N) Control (N)**	**Risk Estimates (95% Confidence Intervals)**	**Comments**
Schumock (2012) Merck, Forest Pharmaceuticals	LTMAs	Suicide Attempts	344 cases 3438 matched controls	Adj. OR: 0.70 (0.36-1.39)	▪ The last author received funding from Merck ▪ Positive association in patients age 19-24 re-evaluated. until it was null; no other null findings were re-evaluated. ▪ Study failed to control for combination therapy with LABAs.
Ali (2015) No disclosed conflicts of interest	MON	Neuropsychiatric disturbance, psychiatric disorder diagnosis, neuropsychiatric event diagnosis, psychotropic medication receipt	1920 cases 5760 matched controls	Adj. OR: 0.96 (0.80–1.14)	▪ Study failed to control for combination therapy with LABAs.

Glockler-Lauf (2019) No disclosed conflicts of interest	MON	New onset substance-related disorders, schizophrenia, anxiety, sleep disturbance, mood and personality disorders, agitation	898 cases 3497 matched controls	Adj. OR: 1.91 (1.15-3.18)	Well-publicized but: ▪ A substantial proportion of new-onset cases may contain prevalent cases (outcome may precede exposure). ▪ Underpowered to test association between montelukast and NAE within subgroups.

KEY: adj. – adjusted, ICS – inhaled corticosteroid, LABA – long acting beta antagonist, LTMA - leukotriene receptor-modifying agents, MON – Montelukast, NAEs – neuropsychiatric adverse events, OR – odds ratio

Table 21. Baseline characteristics for inpatient depressive disorder, treated outpatient depressive disorder, self-harm, and modified self-harm before and after propensity score matching

	Before Matching					After Matching			
	MON		ICS			MON		ICS	
Characteristic[1]	**N**	**%**	**N**	**SD**	**SMD**	**N**	**%**	**N**	**%**
Number of unique patients	513,519	100.0	1,332,531	100.0		457,377	89.1	457,377	34.3
Demographics	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**Mean**	**SD**	**Mean**	**SD**
Mean age (years)	38.9	18.3	37.0	19.8	0.1	38.5	18.3	38.5	19.3
	N	**%**	**N**	**%**	**SMD**	**N**	**%**	**N**	**%**
Age group (years)									
6-11	92,294	18.0	269,772	21.1	-0.06	83,372	18.2	96,887	21.2
12-17	61,854	12.0	152,571	13.5	0.02	56,576	12.4	50,311	11.0
18+	359,371	70.0	910,188	65.4	0.04	318,009	69.4	310,759	67.9
Female	321,937	62.7	789,900	60.4	0.07	283,584	61.9	283,502	61.9
Male	191,582	37.3	542,631	39.6	-0.07	174,373	38.1	174,455	38.1
Pre-DSC/labeling change (2000 - 2007)	53,082	10.3	380,780	46.0	-1.27	45,949	10.0	45,405	10.2
Post-DSC/labeling change (2008 - 2015)	460,437	89.7	951,751	54.0	0.58	412,008	90.0	411,497	89.9
Recorded history of:	**Mean**	**SD**	**Mean**	**SD**	**SMD**	**Mean**	**SD**	**Mean**	**SD**
Combined comorbidity score (mean/SD)	1.2	1.1	1.2	0.8	0.06	1.3	1.1	1.3	1.1
	N	**%**	**N**	**%**	**SMD**	**N**	**%**	**N**	**%**
Psychiatric Disorder	191,922	37.4	421,649	34.7	0.12	168,654	36.8	168,435	36.8
Any Other Psych Event	136,101	26.5	300,278	25.4	0.09	119,790	26.2	120,723	26.4
Self-harm	366	0.1	774	0.1	0.01	337	0.1	328	0.1
Psychiatric and Psychotropic Drugs	151,108	29.4	325,423	26.5	0.11	132,614	30.0	131,852	28.8
Substance Abuse	3,607	0.7	15,230	2.1	-0.05	3,310	0.7	3,256	0.7
Allergic Rhinitis	249,160	48.5	366,987	23.8	0.44	198,702	43.4	198,406	43.3
At Least 2 Other Respiratory Disorders (not COPD or asthma)	260,341	50.7	465,933	34.7	0.32	221,671	48.4	220,988	48.3
Asthma – Emergency	42,512	8.3	89,980	9.1	0.06	2,001	0.4	1,992	0.4
Asthma - Inpatient Primary	2,190	0.4	4,443	0.5	0.02	17,113	3.7	17,067	3.7
Asthma - Inpatient Secondary/Unknown	19,003	3.7	40,224	3.0	0.04	134,486	29.4	135,549	29.6
Asthma – Outpatient	149,886	29.2	308,554	23.4	0.14	52,674	11.5	52,385	11.4
Asthma Exacerbation	55,780	10.9	147,857	13.8	-0.01	2,001	0.4	1,992	0.4
History of Other Asthma Medications									
Oral Corticosteroids	109,785	21.4	193,116	16.7	0.18	94,602	20.7	94,240	20.6
Short Acting Beta-agonists	296,329	57.7	1,041,200	82.5	-0.45	288,348	63.0	287,982	62.9
Anticholinergic Agents	5,578	1.1	7,904	0.3	0.05	4,984	1.1	5,008	1.1

Phosphodiesterase Inhibitors	3,039	0.6	6,091	0.9	0.02	2,583	0.6	2,589	0.6

KEY: COPD – chronic obstructive pulmonary disease, SMD – standardized mean difference, SD – standard deviation

Table 22. Depressive disorder and self-harm outcomes among montelukast (MON) monotherapy and inhaled corticosteroid (ICS) monotherapy initiators

	Average Person Days at Risk	Number of Events (N=38,870)	No Psych History (N=2,266) n (%)	Psych History (N=36,210) n (%)
Inpatient Depressive Disorder		**647**	**58 (10.0)**	**581 (90.0)**
MON	81.5	381	26 (6.8)	350 (91.9)
ICS	54.0	266	32 (12.0)	231 (86.8)
Treated Outpatient Depressive Disorder		**37,740**	**2,178 (6.2)**	**35,182 (93.8)**
MON	100.0	19,598	1,325 (6.8)	18,077 (92.2)
ICS	69.7	18,142	853 (4.7)	17,105 (94.3)
Self-Harm		**219**	**11 (5.4)**	**205 (94.6)**
MON	81.5	124	7 (5.6)	115 (92.7)
ICS	54.1	95	4 (4.2)	90 (94.7)
Modified Self-harm		**264**	**19 (7.9)**	**242 (92.1)**
MON	81.5	142	10 (7.0)	130 (91.5)
ICS	54.1	122	9 (7.4)	112 (91.8)

Table 23. Baseline demographics for suicide in the six data partners with cause of death data - unmatched and matched patient population*

	Unmatched				Matched			
	MON		ICS		MON		ICS	
Characteristics[1]	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of unique patients	62,343	100.0	225,798	100.0	49,800	87.1	49,800	22.4
Demographics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Mean age (years)	22.5	16.3	33.1	19.8	23.4	16.9	23.3	16.7
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age group (years)								
6-11	23,487	37.7	47,550	21.1	18,013	36.2	18,145	36.4
12-17	13,738	22.0	30,559	13.5	10,454	21.0	9,248	18.6
18+	25,118	40.3	147,689	65.4	21,333	42.8	22,407	45.0
Female	35,068	56.3	136,383	60.4	28,482	57.2	28,471	57.2
Male	27,275	43.7	89,415	39.6	21,318	42.8	21,329	42.8
Pre-DSC/labeling change (2000 - 2007)	26,462	42.4	103,766	46.0	20,709	41.6	20,946	42.1
Post-DSC/labeling change (2008 - 2015)	35,881	57.6	122,032	54.0	29,091	58.4	28,854	57.9
Recorded history of:	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Combined comorbidity score (mean/SD)	1.1	0.6	1.1	0.8	1.1	0.7	1.1	0.7
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Psychiatric Disorder	21,120	33.9	78,383	34.7	17,128	34.4	17,037	34.2
Any Other Psych Event	16,390	26.3	57,289	25.4	13,197	26.5	13,284	26.7
Self-harm	68	0.1	195	0.1	58	0.1	44	0.1
Psychiatric and Psychotropic Drugs	15,527	24.9	59,943	26.5	12,599	25.3	12,544	25.2
Substance Abuse	991	1.6	4,653	2.1	848	1.7	832	1.7
Allergic Rhinitis	24,307	39.0	53,828	23.8	18,119	36.4	18,196	36.5
At Least 2 Other Respiratory Disorders (not COPD or asthma)	27,898	44.7	78,343	34.7	21,717	43.6	21,733	43.6
Asthma – Emergency	10,778	17.3	20,445	9.1	8,122	16.3	8,139	16.3
Asthma - Inpatient Primary	449	0.7	1,136	0.5	389	0.8	388	0.8
Asthma - Inpatient Secondary/Unknown	1,962	3.1	6,788	3.0	1,568	3.1	1,591	3.2
Asthma – Outpatient	13,440	21.6	52,811	23.4	11,245	22.6	11,463	23.0
Asthma Exacerbation	8,005	12.8	31,112	13.8	6,647	13.3	6,592	13.2
History of Other Asthma Medications								
Oral Corticosteroids	11,733	18.8	37,672	16.7	9,664	19.4	9,654	19.4
Short acting beta-agonist	46,200	74.1	186,189	82.5	38,750	77.8	38,708	77.7
Anticholinergic Agents	299	0.5	676	0.3	245	0.5	227	0.5

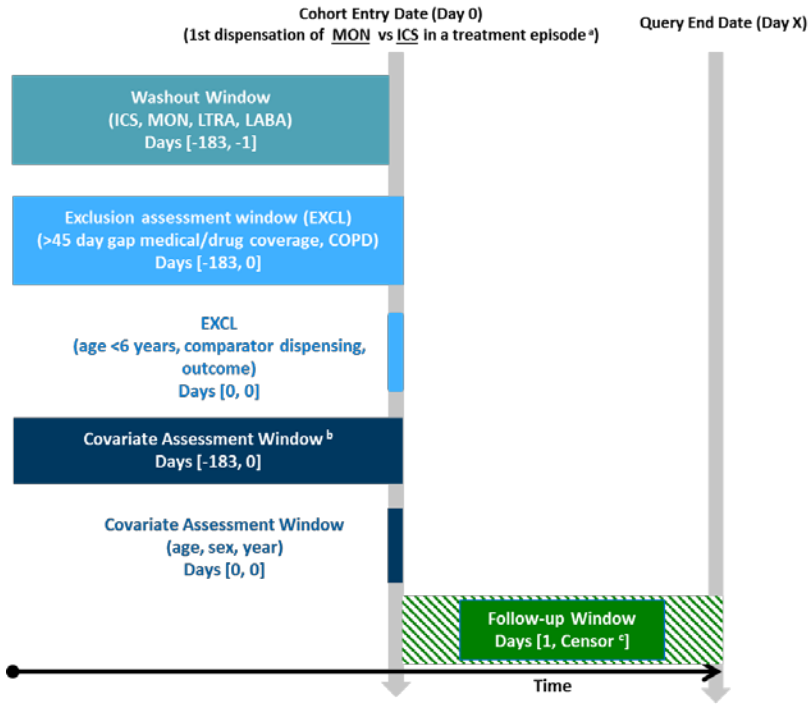
Phosphodiesterase Inhibitor	696	1.1	1,931	0.9	539	1.1	549	1.1

KEY: COPD – chronic obstructive pulmonary disease, SD – standard deviation

* We described all-cause mortality among the unmatched cohorts to contextualize the results from the analysis of the association between montelukast use compared to inhaled corticosteroid use and suicide. The unmatched patient population also contains patients who contributed time to both the montelukast and inhaled corticosteroid groups, while the matched population does not. See Section 5.3.4 for the table of unmatched patient population that comprised the matched patient population.

[1]All metrics are based on total number of episodes per group, except for sex which is based on total number of unique patients

Figure 7. Design diagram for analysis



KEY: ICS – inhaled corticosteroid, LABA – long acting beta- agonist, MON – montelukast, LTRA – leukotriene receptor antagonists

a. Gaps of <15 days between end of days supply and next dispensation were bridged for inpatient depressive disorder, suicide, and self-harm outcomes (30 days for treated outpatient depressive disorder). 15 days was added to the last dispensation's days supply in an exposure episode for inpatient depressive disorder suicide, and self-harm outcomes (30 days for outpatient depressive disorder).

b. Covariates: comorbidity score, history of psych disorder, psychiatric and psychotropic drugs, self-harm (inpatient), any other psychiatric event, substance abuse, allergic rhinitis, respiratory disorder (≥ 2 codes), asthma (emergency department), asthma (inpatient primary position), asthma (outpatient), asthma exacerbations or status asthmaticus, oral corticosteroids, short acting beta-agonists, anticholinergic agents, phosphodiesterase inhibitors

c. Censoring: dispensing of ICS monotherapy, LABAs, ICS combination therapies or LTRAs, dispensing of oral corticosteroid, asthma related hospitalization in the primary position, death, data partner end date, query end date, disenrollment, outcome, end of treatment episode

Figure 8. Forest plots of hazard ratios and 95% confidence intervals for inpatient depressive disorder

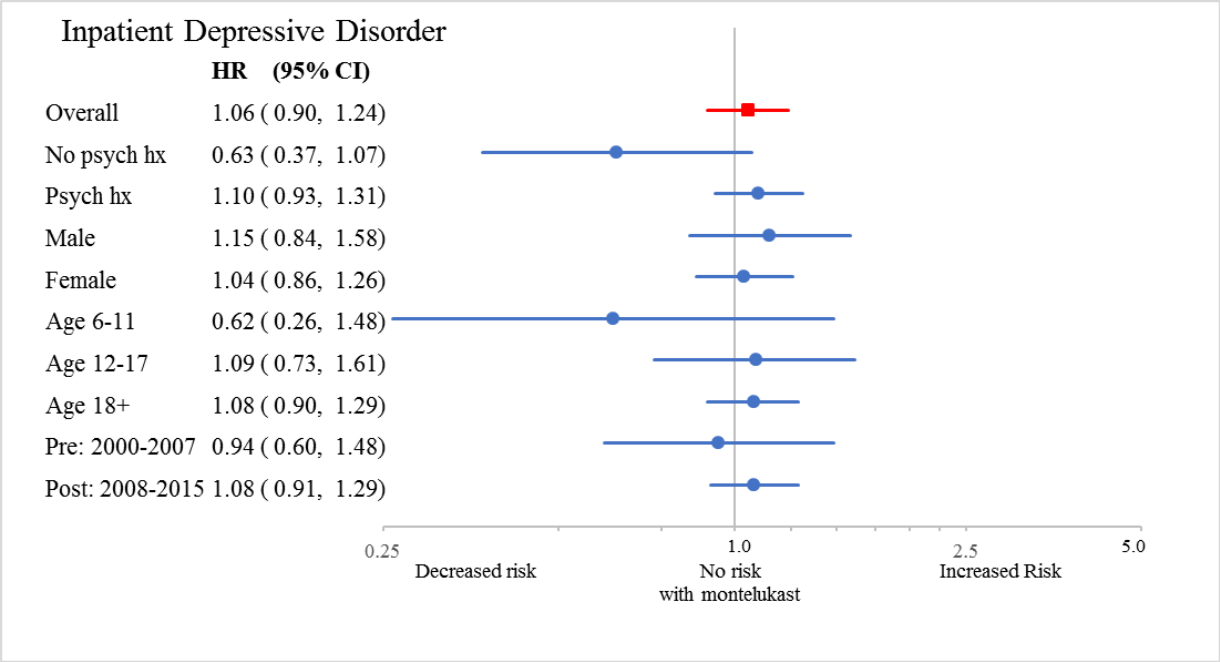
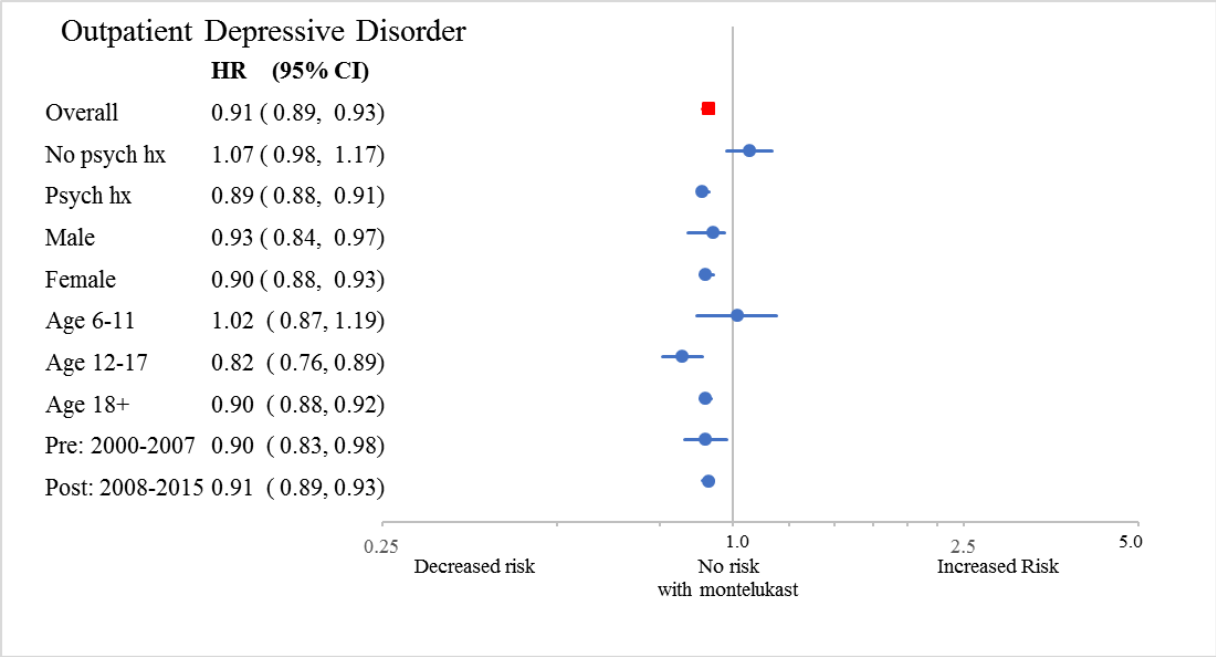


Figure 9. Forest plots of hazard ratios and 95% confidence intervals for treated outpatient depressive disorder



KEY: CI – confidence interval, HR – hazard ratio, hx – history, pre – before drug safety communications and labeling changes, post – after drug safety communications and labeling changes

Figure 10. Forest plots of hazard ratios and 95% confidence intervals for self-harm

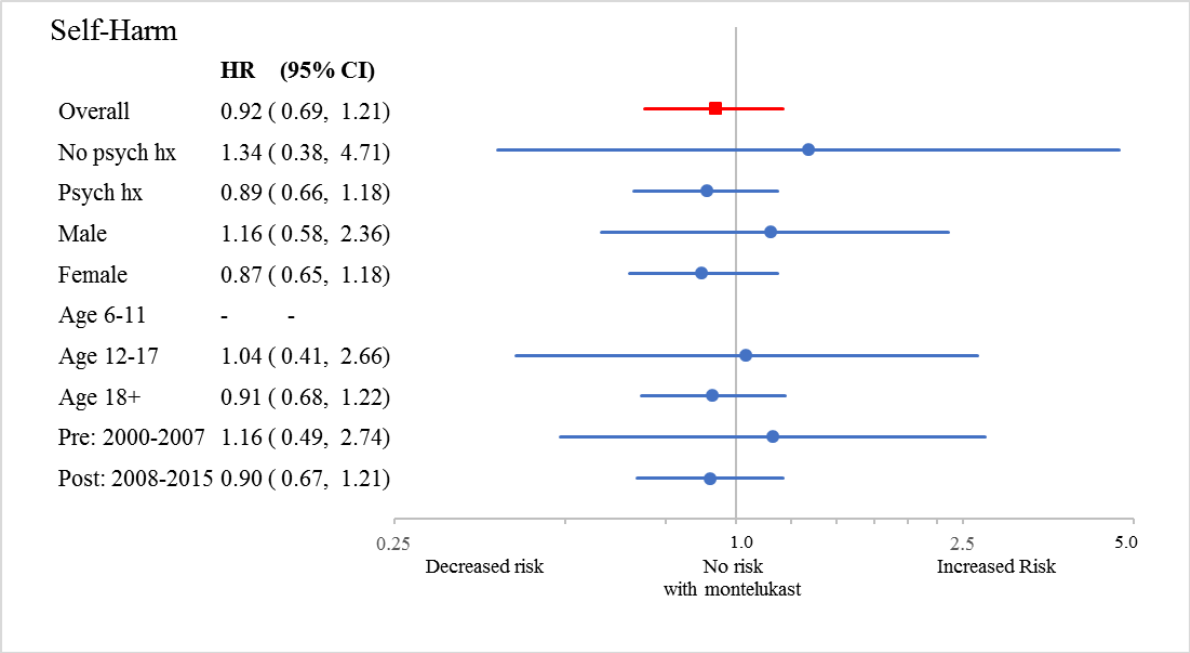
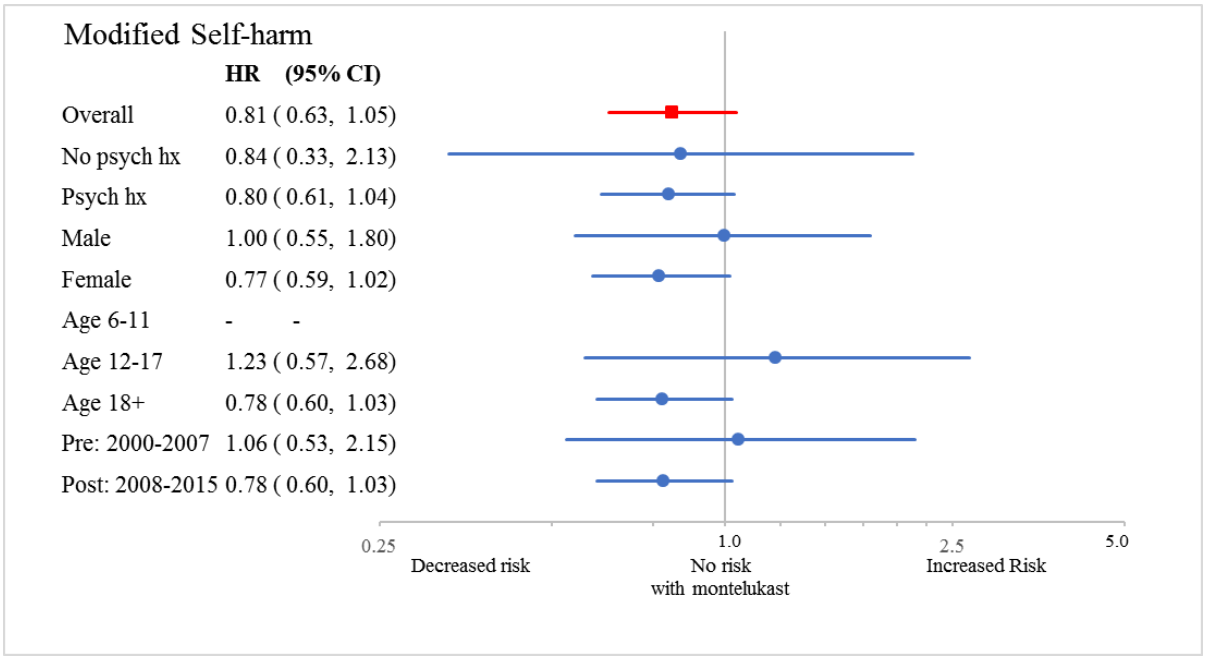


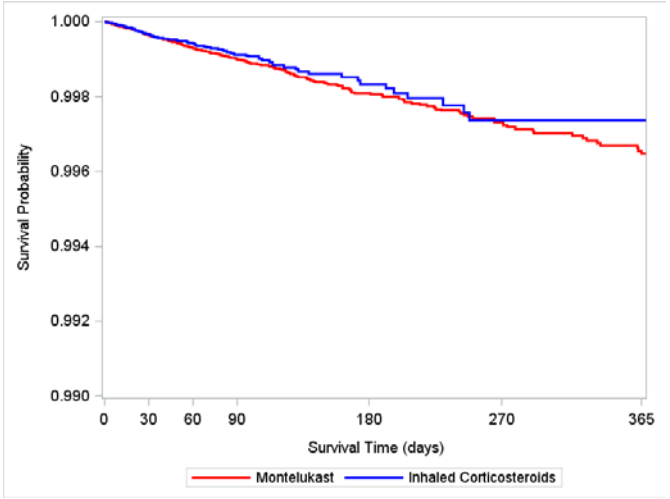
Figure 11. Forest plots of hazard ratios and 95% confidence intervals for modified self-harm



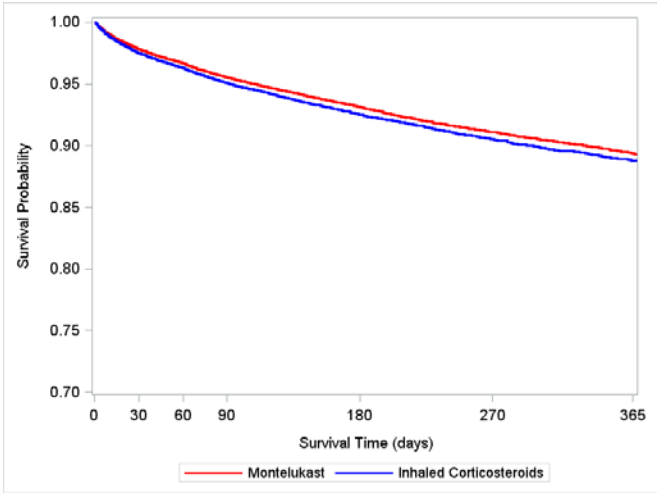
KEY: CI – confidence interval, HR – hazard ratio, hx – history, pre – before drug safety communications and labeling changes, post – after drug safety communications and labeling changes

Figure 12. One-year event free survival for inpatient depressive disorder, treated outpatient depressive disorder, self-harm and self-harm with E-codes

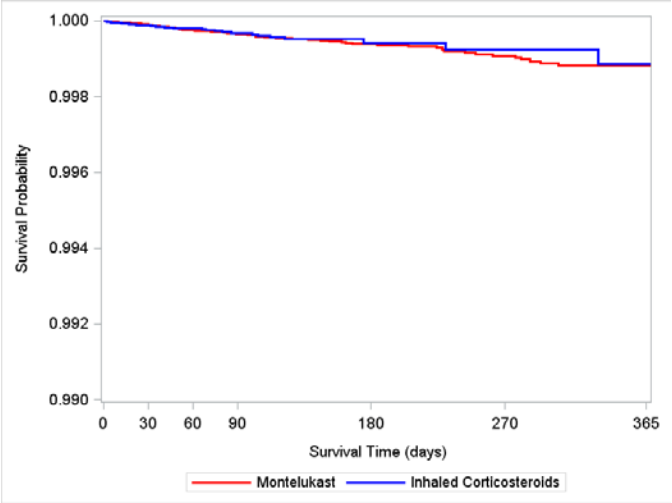
Inpatient Depressive Disorder (HR: 1.06; CI: 0.90 – 1.25)



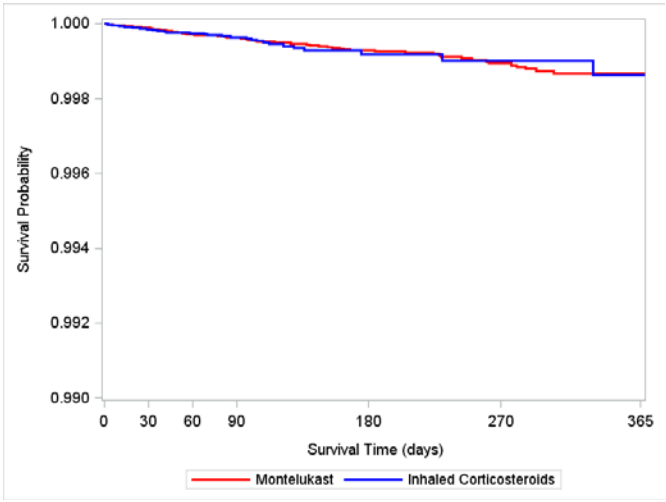
Outpatient Depressive Disorder (HR: 0.91; CI: 0.89 – 0.93)



Self-Harm (HR: 0.96; CI: 0.72 - 1.26)



Modified Self-Harm (HR: 0.86; CI: 0.67 - 1.11)



KEY: CI – confidence interval, HR – hazard ratio

5.3.2. Codes Used in Analyses (Alphabetical Order)

Allergic Rhinitis

ICD-9 codes: 472.0, 477, 477.0, 477.1, 477.2, 477.8, 477.9

Asthma

ICD-9 codes: 493.0, 493.00, 493.02, 493.1, 493.10, 493.12, 493.8, 493.81, 493.82, 493.9, 493.90, 493.92

Asthma Exacerbation and Status Asthmaticus

ICD-9 codes: 493.92, 493.11, 4893.91, 493.01

Chronic Obstructive Pulmonary Disease

ICD-9 codes: 490, 491, 491.0, 491.1, 491.20, 491.2, 491.21, 491.22, 491.8, 491.9, 492, 492.0, 492.8, 493.2, 493.20, 493.21, 493.22, 494, 494.0, 494.1

Depression

ICD-9 codes: 311, 293.83, 296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.90, 298.0, 300.4, 301.12, 309.0, 309.1, 309.28

Other Psychiatric Events

ICD-9 codes: 333.99, 296.0, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.1, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.4, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.6, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.8, 296.80, 296.81, 296.82, 296.89, 296.99, 300.02, 300.0, 300.00, 300.09, 300.2, 300.20, 300.22, 300.29, 300.01, 300.21, 300.3, 309.81, 295, 295.0, 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.1, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.2, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.3, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.4, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.5, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.6, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.7, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.8, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.9, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 300.23, 291, 291.1, 291.2, 291.3, 291.4, 291.5, 291.8, 291.81, 291.82, 291.89, 291.9, 292.0, 292.1, 292.11, 292.12, 292.2, 292.8, 292.89, 292.9, 303.0, 303.00, 303.01, 303.02, 303.03, 303.9, 303.90, 303.91, 303.92, 303.93, 304.0, 304.00, 304.01, 304.02, 304.03, 304.1, 304.10, 304.11, 304.12, 304.13, 304.2, 304.20, 304.21, 304.22, 304.23, 304.3, 304.30, 304.31, 304.32, 304.33, 304.4, 304.40, 304.41, 304.42, 304.43, 304.5, 304.50, 304.51, 304.52, 304.53, 304.6, 304.60, 304.61, 304.62, 304.63, 304.7, 304.70, 304.71, 304.72, 304.73, 304.8, 304.80, 304.81, 304.82, 304.83, 304.9, 304.90, 304.91, 304.92, 304.93, 305.0, 305.00, 305.01, 305.02, 305.03, 305.2, 305.20, 305.21, 305.22, 305.23, 305.3, 305.30, 305.31, 305.32, 305.33, 305.4, 305.40, 305.41, 305.42, 305.43, 305.5, 305.50, 305.51, 305.52, 305.53, 305.6, 305.60, 305.61, 305.62, 305.63, 305.7, 305.70, 305.71, 305.72, 305.73, 305.8, 305.80, 305.81, 305.82, 305.83, 305.9, 305.90, 305.91, 305.92, 305.93, 307.4, 307.40, 307.41, 307.42, 307.43, 307.44, 307.45, 307.46,

307.47, 307.48, 307.49, 347, 347.0, 347.00, 347.01, 347.1, 347.10, 347.11, 780.5, 780.50, 780.51, 780.52, 780.53, 780.54, 780.55, 780.56, 780.57, 780.58, 780.59, 312, 312.0, 312.00, 312.01, 312.02, 312.03, 312.1, 312.10, 312.11, 312.12, 312.13, 312.2, 312.20, 312.21, 312.22, 312.23, 312.3, 312.30, 312.31, 312.32, 312.33, 312.34, 312.35, 312.39, 312.4, 312.8, 312.81, 312.82, 312.89, 312.9, 314, 314.0, 314.00, 314.01, 314.1, 314.2, 314.8, 314.9, 290.8, 290.9, 297, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9, 299, 299.0, 299.00, 299.01, 299.1, 299.10, 299.11, 299.8, 299.80, 299.81, 299.9, 299.90, 299.91, 780.1, 294, 294.0, 294.1, 294.10, 294.11, 294.2, 294.20, 294.21, 294.8, 294.9, 330, 330.0, 330.1, 330.2, 330.3, 330.8, 330.9, 331, 331.0, 331.1, 331.11, 331.19, 331.2, 331.3, 331.4, 331.5, 331.6, 331.7, 331.8, 331.81, 331.82, 331.83, 331.89, 331.9, 291.0, 292.81, 293, 293.0, 293.1, 293.8, 293.81, 293.82, 293.83, 293.84, 293.89, 293.9, 348.3, 348.30, 348.31, 348.39, 301, 301.0, 301.1, 301.10, 301.11, 301.12, 301.13, 301.2, 301.20, 301.21, 301.22, 301.3, 301.4, 301.5, 301.50, 301.51, 301.59, 301.6, 301.7, 301.8, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9, 300.1, 300.10, 300.11, 300.12, 300.13, 300.14, 300.15, 300.16, 300.19, 300.5, 300.6, 300.7, 300.8, 300.81, 300.82, 300.89, 300.9, 302, 302.0, 302.1, 302.2, 302.3, 302.4, 302.5, 302.50, 302.51, 302.52, 302.53, 302.6, 302.7, 302.70, 302.71, 302.72, 302.73, 302.74, 302.75, 302.76, 302.79, 302.8, 302.81, 302.82, 302.83, 302.84, 302.85, 302.89, 302.9, 306, 306.0, 306.1, 306.2, 306.3, 306.4, 306.5, 306.50, 306.51, 306.52, 306.53, 306.59, 306.6, 306.7, 306.8, 306.9, 307, 307.0, 307.1, 307.2, 307.20, 307.21, 307.22, 307.23, 307.3, 307.5, 307.50, 307.51, 307.52, 307.53, 307.54, 307.59, 307.6, 307.7, 307.8, 307.80, 307.81, 307.89, 307.9, 308, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.2, 309.21, 309.22, 309.23, 309.24, 309.28, 309.29, 309.3, 309.4, 309.8, 309.82, 309.83, 309.89, 309.9, 310, 310.0, 310.1, 310.2, 310.8, 310.81, 310.89, 310.9, 313, 313.0, 313.1, 313.2, 313.21, 313.22, 313.23, 313.3, 313.8, 313.81, 313.82, 313.83, 313.89, 313.9, 315, 315.0, 315.00, 315.01, 315.02, 315.09, 315.1, 315.2, 315.3, 315.31, 315.32, 315.34, 315.35, 315.39, 315.4, 315.5, 315.8, 315.9, 316, 61885, 61886, 61888, 64553, 64568, 64569, 64570, 64585, 95970, 95971, 95974, 95975, L8679, L8680, L8681, L8682, L8683, L8685, L8686, L8687, L8688, L8689, 90870, 90871, 90867, 90868, 90869, 311, 296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.90, 300.4, 309.0, 309.1, 960, 960.0, 960.1, 960.2, 960.3, 960.4, 960.5, 960.6, 960.7, 960.8, 960.9, 961, 961.0, 961.1, 961.2, 961.3, 961.4, 961.5, 961.6, 961.7, 961.8, 961.9, 962, 962.0, 962.1, 962.2, 962.3, 962.4, 962.5, 962.6, 962.7, 962.8, 962.9, 963, 963.0, 963.1, 963.2, 963.3, 963.4, 963.5, 963.8, 963.9, 964, 964.0, 964.1, 964.2, 964.3, 964.4, 964.5, 964.6, 964.7, 964.8, 964.9, 965, 965.0, 965.00, 965.01, 965.02, 965.09, 965.1, 965.4, 965.5, 965.6, 965.61, 965.69, 965.7, 965.8, 965.9, 966, 966.0, 966.1, 966.2, 966.3, 966.4, 967, 967.0, 967.1, 967.2, 967.3, 967.4, 967.5, 967.6, 967.8, 967.9, 968, 968.0, 968.1, 968.2, 968.3, 968.4, 968.5, 968.6, 968.7, 968.9, 969, 969.0, 969.00, 969.01, 969.02, 969.03, 969.04, 969.05, 969.09, 969.1, 969.2, 969.3, 969.4, 969.5, 969.6, 969.7, 969.70, 969.71, 969.72, 969.73, 969.79, 969.8, 969.9, 881, 980, 980.0, 980.1, 980.2, 980.3, 980.8, 980.9, 981, 982, 982.0, 982.1, 982.2, 982.3, 982.4, 982.8, 983, 983.0, 983.1, 983.2, 983.9, 984, 984.0, 984.1, 984.8, 984.9, 985, 985.0, 985.1, 985.2, 985.3, 985.4, 985.5, 985.6, 985.8, 985.9, 986, 987, 987.0, 987.1, 987.2, 987.3, 987.4, 987.5, 987.6, 987.7, 987.8, 987.9, 988, 988.0, 988.1, 988.2,

988.8, 988.9, 989, 989.0, 989.1, 989.2, 989.3, 989.4, 989.5, 989.6, 989.7, 989.8, 989.81, 989.82, 989.83, 989.84, 989.89, 989.9, 994.7

Psychotherapy

ICD-9 codes: 94.31, 94.32, 94.33, 94.35, 94.36, 94.37, 94.38, 94.39, 94.43, 94.44,
Procedure codes (C4): 90815, 90823, 90824, 90826, 90827, 90828, 90829, 90832, 90833, 90834, 90836, 90837, 90838, 90839, 90840, 90845, 90853, 90857

Self-Harm

Psychological ICD-9 Codes

Depression: 293.83, 296.2, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.90, 298.0, 300.4, 309.0, 309.1, 309.28, 311

Mania: 296.0, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.1, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.4, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.5, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.6, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.8, 296.80, 296.81, 296.82, 296.89, 296.99

Personality Disorder: 301.0, 301.1, 301.10, 301.11, 301.12, 301.13, 301.2, 301.20, 301.21, 301.22, 301.3, 301.4, 301.5, 301.50, 301.51, 301.59, 301.6, 301.7, 301.8, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9

Adjustment reaction: 309.2, 309.21, 309.22, 309.23, 309.24, 309.29, 309.3, 309.4, 309.8, 309.81, 309.82, 309.83, 309.89, 309.9

Unspecified non-psychotic mental disorder: 300.9

Physical ICD-9 codes

Poisoning: 960, 960.0, 960.1, 960.2, 960.3, 960.4, 960.5, 960.6, 960.7, 960.8, 960.9, 961, 961.0, 961.1, 961.2, 961.3, 961.4, 961.5, 961.6, 961.7, 961.8, 961.9, 962, 962.0, 962.1, 962.2, 962.3, 962.4, 962.5, 962.6, 962.7, 962.8, 962.9, 963, 963.0, 963.1, 963.2, 963.3, 963.4, 963.5, 963.8, 963.9, 964, 964.0, 964.1, 964.2, 964.3, 964.4, 964.5, 964.6, 964.7, 964.8, 964.9, 965, 965.0, 965.00, 965.01, 965.02, 965.09, 965.1, 965.4, 965.5, 965.6, 965.61, 965.69, 965.7, 965.8, 965.9, 966, 966.0, 966.1, 966.2, 966.3, 966.4, 967, 967.0, 967.1, 967.2, 967.3, 967.4, 967.5, 967.6, 967.8, 967.9, 968, 968.0, 968.1, 968.2, 968.3, 968.4, 968.5, 968.6, 968.7, 968.9, 969, 969.0, 969.00, 969.01, 969.02, 969.03, 969.04, 969.05, 969.09, 969.1, 969.2, 969.3, 969.4, 969.5, 969.6, 969.7, 969.70, 969.71, 969.72, 969.73, 969.79, 969.8, 969.9, 970, 970.0, 970.1, 970.8, 970.9, 971, 971.0, 971.1, 971.2, 971.3, 971.9, 972, 972.0, 972.1, 972.2, 972.3, 972.4, 972.5, 972.6, 972.7, 972.8, 972.9, 973, 973.0, 973.1, 973.2, 973.3, 973.4, 973.5, 973.6, 973.8, 973.9, 974, 974.0, 974.1, 974.2, 974.3, 974.4, 974.5, 974.6, 974.7, 975, 975.0, 975.1, 975.2, 975.3, 975.4, 975.5, 975.6, 975.7, 975.8, 976, 976.0, 976.1, 976.2, 976.3, 976.4, 976.5, 976.6, 976.7, 976.8, 976.9, 977, 977.0, 977.1, 977.2, 977.3, 977.4, 977.8, 977.9, 978, 978.0, 978.1, 978.2, 978.3, 978.4, 978.5, 978.6, 978.8, 978.9, 979, 979.0, 979.1, 979.2, 979.3, 979.4, 979.5, 979.6, 979.7, 979.9

Toxicity: 980, 980.0, 980.1, 980.2, 980.3, 980.8, 980.9, 981, 982, 982.0, 982.1, 982.2, 982.3, 982.4, 982.8, 983, 983.0, 983.1, 983.2, 983.9, 984, 984.0, 984.1, 984.8, 984.9, 985, 985.0, 985.1, 985.2, 985.3, 985.4, 985.5, 985.6, 985.8, 985.9,

986, 987, 987.0, 987.1, 987.2, 987.3, 987.4, 987.5, 987.6, 987.7, 987.8, 987.9, 988, 988.0, 988.1, 988.2, 988.8, 988.9, 989, 989.0, 989.1, 989.2, 989.3, 989.4, 989.5, 989.6, 989.7, 989.8, 989.81, 989.82, 989.83, 989.84, 989.89, 989.9

Asphyxiation: 994.7

Open wound to elbow, forearm, or wrist: 881

Self-harm E-codes

Suicide and self-inflicted injury: E950 – E958

Other Respiratory Disorders

ICD-9 codes: 003.22, 020.3, 020.4, 020.5, 021.2, 022.1, 031.0, 032.0, 032.1, 032.2, 032.3, 034.0, 039.1, 052.1, 055.1, 073.0, 083.0, 112.4, 114.0, 114.4, 114.5, 115.05, 115.15, 115.95, 122, 122.0, 122.1, 122.2, 122.3, 122.4, 122.5, 122.6, 122.7, 122.8, 122.9, 123, 123.0, 123.1, 123.2, 123.3, 123.4, 123.5, 123.6, 123.8, 123.9, 124, 125, 125.0, 125.1, 125.2, 125.3, 125.4, 125.5, 125.6, 125.7, 125.9, 126, 126.0, 126.1, 126.2, 126.3, 126.8, 126.9, 127, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128, 128.0, 128.1, 128.8, 128.9, 129, 130, 130.0, 130.1, 130.2, 130.3, 130.4, 130.5, 130.7, 130.8, 130.9, 131, 131.0, 131.00, 131.01, 131.02, 131.03, 131.09, 131.8, 131.9, 132, 132.0, 132.1, 132.2, 132.3, 132.9, 133, 133.0, 133.8, 133.9, 134, 134.0, 134.1, 134.2, 134.8, 134.9, 136.3, 460, 461.0, 461.1, 461.2, 461.3, 461.8, 461.9, 462, 463, 464.0, 464.00, 464.01, 464.10, 464.11, 464.20, 464.21, 464.30, 464.31, 464.4, 464.50, 464.51, 465.0, 465.8, 465.9, 466.0, 466.1, 466.11, 466.19, 470, 471.0, 471.1, 471.8, 471.9, 472.0, 472.1, 472.2, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9, 474.0, 474.00, 474.01, 474.02, 474.10, 474.11, 474.12, 474.2, 474.8, 474.9, 475, 476.0, 476.1, 477.0, 477.2, 477.8, 477.9, 478.0, 478.1, 478.11, 478.19, 478.20, 478.21, 478.22, 478.24, 478.25, 478.26, 478.29, 478.30, 478.31, 478.32, 478.33, 478.34, 478.4, 478.5, 478.6, 478.70, 478.71, 478.74, 478.75, 478.79, 478.8, 478.9, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.3, 482.30, 482.31, 482.32, 482.39, 482.4, 482.40, 482.41, 482.42, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487.0, 487.1, 487.8, 488, 488.0, 488.01, 488.02, 488.09, 488.1, 488.11, 488.12, 488.19, 488.81, 488.82, 488.89, 495.0, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8, 495.9, 496, 500, 501, 502, 503, 504, 505, 506.0, 506.1, 506.2, 506.3, 506.4, 506.9, 507.0, 507.1, 507.8, 508.0, 508.1, 508.2, 508.8, 508.9, 510.0, 510.9, 511.0, 511.1, 511.8, 511.89, 511.9, 512.0, 512.8, 512.81, 512.82, 512.83, 512.84, 512.89, 513.0, 513.1, 514, 515, 516.0, 516.1, 516.2, 516.3, 516.30, 516.31, 516.32, 516.33, 516.34, 516.35, 516.36, 516.37, 516.4, 516.5, 516.61, 516.62, 516.63, 516.64, 516.69, 516.8, 516.9, 517.1, 517.2, 517.3, 517.8, 518.0, 518.1, 518.2, 518.3, 518.4, 518.5, 518.51, 518.52, 518.53, 518.81, 518.82, 518.83, 518.84, 518.89, 519.1, 519.11, 519.19, 519.2, 519.3, 519.4, 519.8, 519.9, 782.5, 784.1, 784.40, 784.41, 784.42, 784.43, 784.44, 784.49, 784.7, 784.8, 784.9, 784.91, 784.99, 786.00, 786.01, 786.02, 786.03, 786.04, 786.05, 786.06, 786.07, 786.09, 786.1, 786.2, 786.3, 786.30, 786.31, 786.39, 786.4, 786.52, 786.6, 786.7, 786.8, 786.9, 793.1, 793.11, 793.19, 794.2, 799.1, V12.6, V12.60, V12.61, V12.69, V41.4, V42.6, V44.0, V46.1, V46.11, V46.12, V46.13, V46.14, V46.2, V55.0

Substance Abuse

ICD-9 codes: 305.3, 305.30, 305.31, 305.32, 305.33, 305.4, 305.40, 305.41, 305.42, 305.43, 305.5, 305.50, 305.51, 305.52, 305.53, 305.6, 305.60, 305.61, 305.62, 305.63, 305.7, 305.70, 305.71, 305.72, 305.73, 305.8, 305.80, 305.81, 305.82, 305.83, 305.9, 305.90, 305.91, 305.92, 305.93

Suicide

ICD-9 codes: X60, X61, X62, X63, X64, X65, X66, X67, X68, X69, X70, X71, X72, X73, X74, X75, X76, X77, X78, X79, X80, X81, X82, X83, X84, Y870

5.3.3. Medications

EXPOSURE: [Montelukast]
montelukast sodium
COMPARATOR: [Corticosteroids (inhaled)]
beclomethasone dipropionate
budesonide
ciclesonide
flunisolide
fluticasone furoate
fluticasone propionate
mometasone furoate
triamcinolone acetonide
WASHOUT AND CENSORING: LABA
arformoterol tartrate
formoterol fumarate
formoterol fumarate dihydrate, micronized
indacaterol maleate
indacaterol maleate/glycopyrrolate
olodaterol HCl
salmeterol xinafoate
tiotropium bromide/olodaterol HCl
WASHOUT AND CENSORING: ICS Combination Products
budesonide/formoterol fumarate
flunisolide/menthol
fluticasone furoate/vilanterol trifenatate
fluticasone propionate/salmeterol xinafoate
mometasone furoate/formoterol fumarate
COVARIATE: Anticholinergic agents
tiotropium bromide
COVARIATE: SABA
albuterol
albuterol sulfate
levalbuterol HCl
levalbuterol tartrate
metaproterenol sulfate
pirbuterol acetate
ipratropium bromide/albuterol sulfate
terbutaline sulfate
WASHOUT AND CENSORING: LTRA
zafirlukast
zileuton
CENSORING: [Corticosteroids (oral)]
cortisone acetate
dexamethasone
methylprednisolone
prednisolone
prednisone
COVARIATE: Phosphodiesterase inhibitors
aminophylline
aminophylline/ephedrine/potassium iodide/phenobarbital
dyphylline
guaifenesin/dyphylline
guaifenesin/dyphylline/ephedrine/phenobarbital
guaifenesin/theophylline
guaifenesin/theophylline anhydrous/pseudoephedrine
theophylline anhydrous
theophylline in dextrose 5 % in water
theophylline/caffeine/AA no.13/cinnamon/herbal 135
theophylline/dietary supplement,misc.comb.no.9
theophylline/ephedrine HCl/phenobarbital
theophylline/ephedrine/potassium iodide/phenobarbital
theophylline/potassium iodide
COVARIATE: Psychiatric and Psychotropic Drugs
alprazolam
alprazolam/dietary supplement,misc combo no.17
amitriptyline HCl
amitriptyline HCl/chlordiazepoxide
amobarbital sodium/secobarbital sodium
amoxapine
aripiprazole
asenapine maleate
aspirin/meprobamate
atomoxetine HCl
brexpiprazole
bupropion HBr
bupropion HCl
bupropion HCl/dietary supplement combination no.15
bupropion HCl/dietary supplement combination no.16
buspirone HCl
butabarbital sodium
carbamazepine
cariprazine HCl
chloral hydrate
chlordiazepoxide HCl
chlordiazepoxide HCl/methscopolamine nitrate
chlordiazepoxide/clidinium bromide
chlorpromazine HCl
citalopram hydrobromide
clomipramine HCl
clonazepam
clorazepate dipotassium
clozapine
desipramine HCl
desvenlafaxine
desvenlafaxine fumarate
desvenlafaxine succinate
dexmethylphenidate HCl
dextroamphetamine sulfate
dextroamphetamine sulf-saccharate/amphetamine sulf-aspartate
diazepam
diazepam (in soybean oil)
divalproex sodium
doxepin HCl
droperidol
duloxetine HCl
escitalopram oxalate
estazolam
eszopiclone
ethchlorvynol
fluoxetine HCl
fluoxetine HCl/dietary supplement no.17
fluoxetine HCl/dietary supplement no.8
fluphenazine decanoate
fluphenazine enanthate

fluphenazine HCl
flurazepam HCl
fluvoxamine maleate
guanfacine HCl
halazepam
haloperidol
haloperidol decanoate
haloperidol lactate
iloperidone
imipramine HCl
imipramine pamoate
isocarboxazid
lamotrigine
levomilnacipran HCl
lisdexamfetamine dimesylate
lithium carbonate
lithium citrate
lithium citrate tetrahydrate
lorazepam
lorazepam in 0.9 % sodium chloride
lorazepam in 5 % dextrose and water
loxapine
loxapine HCl
loxapine succinate
lurasidone HCl
maprotiline HCl
mephobarbital
meprobamate
mesoridazine besylate
methamphetamine HCl
methylphenidate
methylphenidate HCl
mirtazapine
molindone HCl
naltrexone HCl/bupropion HCl
nefazodone HCl
nortriptyline HCl
olanzapine
olanzapine pamoate
olanzapine/fluoxetine HCl
oxazepam
oxcarbazepine
paliperidone
paliperidone palmitate
paroxetine HCl
paroxetine mesylate
pemoline
pentobarbital sodium
perphenazine
perphenazine/amitriptyline HCl
phenelzine sulfate
pimozide
quazepam
quetiapine fumarate
ramelteon
risperidone
risperidone microspheres
secobarbital sodium
selegiline
selegiline HCl
sertraline HCl
suvorexant
temazepam
temazepam/dietary supplement no.8
thioridazine HCl
thiothixene
thiothixene HCl
tranylcypromine sulfate
trazodone HCl/dietary supplement no.8
triazolam
trifluoperazine HCl
trimipramine maleate
valproic acid
valproic acid (as sodium salt) (valproate sodium)
venlafaxine HCl
vilazodone HCl
vortioxetine hydrobromide
zaleplon
ziprasidone HCl
ziprasidone mesylate
zolpidem tartrate

5.3.4. Baseline characteristics of unmatched patient population used to form the matched population for the suicide outcome

	Before Matching				
	MON		ICS		
Characteristic[1]	**N**	**%**	**N**	**%**	**SMD**
Number of unique patients	57,167	100	222,016	--	
Demographics	**Mean**	**SD**	**Mean**	**SD**	**SMD**
Mean age (years)	22.20	16.3	33.30	19.9	-0.61
	N	**%**	**N**	**%**	**SMD**
Age group (years)					
6-11	22,333	39.1	46,623	21.0	0.40
12-17	12,293	21.5	29,462	13.3	0.22
18+	22,541	39.4	145,931	65.7	-0.55
Female	31,988	56.0	134,204	60.4	-0.09
Male	25,179	44.0	87,812	39.6	0.09
Pre-DSC/labeling change (2000 - 2007)	24,747	43.3	103,009	46.4	-3.11
Post-DSC/labeling change (2008 - 2015)	32,420	56.7	119,007	53.60	3.11
Recorded history of:	**Mean**	**SD**	**Mean**	**SD**	**SMD**
Combined comorbidity score (mean/SD)	1.10	0.60	1.10	0.80	-0.04
	N	**%**	**N**	**%**	**SMD**
Psychiatric Disorder	19,123	33.5	76,933	34.7	-0.03
Any Other Psych Event	14,837	26.0	56,096	25.3	0.02
Self-harm	64.00	0.1	194.00	0.1	0.01
Psychiatric and Psychotropic Drugs	14,008	24.5	58,947	26.6	-0.05
Substance Abuse	878.00	1.5	4,560	2.1	-0.04
Allergic Rhinitis	22,267	39.0	52,733	23.8	0.33
At Least 2 Other Respiratory Disorders (not COPD or asthma)	25,700	45.0	76,900	34.6	0.21
Asthma – Emergency	9,715	17.0	19,614	8.8	0.25
Asthma - Inpatient Primary	416.00	0.7	1,110	0.5	0.03
Asthma - Inpatient Secondary/Unknown	1,762	3.1	6,658	3.0	0.01
Asthma – Outpatient	12,015	21.0	51,768	23.3	-0.06
Asthma Exacerbation	7,215	12.6	30,417	13.7	-0.03
History of Other Asthma Medications					
Oral Corticosteroids	10,653	18.6	36,799	16.6	0.05
Short Acting Beta-agonists	42,362	74.1	182,980	82.4	-0.20
Anticholinergic Agents	269.00	0.5	659.00	0.3	0.03
Phosphodiesterase Inhibitors	645.00	1.1	1,915	0.9	0.03

KEY: COPD – chronic obstructive pulmonary disease, SMD – standardized mean difference, SD – standard deviation

6 Appendices

6.1. References

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6.2. Correspondence from Parents United for Pharmaceutical Safety and Accountability and the Montelukast (Singulair) Side Effects Support and Discussion Group

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RE: Neuropsychiatric Side Effects of Asthma Medication Montelukast (Singulair)

Dear Ms. Brill,

Parents United for Pharmaceutical Safety and Accountability and **The Montelukast (Singulair) Side Effects Support and Discussion Group**, (a Facebook group of over 3,280 parents of affected children and adults) raise awareness of and provide support to parents of children and adults who have suffered from the side effects of Montelukast (Singulair). We presented and submitted testimonials at the September 2014 FDA Pediatric Advisory Committee (PAC) meeting about our members' experiences with neuropsychiatric side effects from Montelukast (Singulair).

Based on continued daily reports from parents of children (and affected adults) to both our groups, we feel compelled to contact you. We have had more than 200 members join in just the last month; this is possibly due to three recently published scientific studies on Montelukast pointing to a higher incidence of neuropsychiatric side effects than was previously recognized.

We believe the incidence of neuropsychiatric side effects is much more common than is currently reported and that without an understanding of how Montelukast causes these side effects, the well-being of those who use this medication is at risk, particularly children.

We respectfully request that the FDA immediately prioritize investigations to determine:

- the mechanisms for Montelukast's neuropsychiatric side effects
- risk factors for an adverse reaction
- the appropriate way to discontinue Montelukast ("cold turkey" vs. tapering)
- withdrawal symptoms and long-term implications of an adverse reaction

so that healthcare providers may better care for their patients who take or have previously taken this medication.

In addition, we ask that the FDA reclassify the neuropsychiatric side effects of Montelukast (Singulair) to be 'common' in children, update the label with a warning for the possible delayed onset of side effects and include 'excoriation', 'hyperkinesia' and 'obsessive compulsive disorder' as reported side effects.

We also request that the FDA issue a Medication Guide for Montelukast (Singulair) due to the *life altering and life-threatening potential* of its neuropsychiatric effects and consider a black box warning. Our groups will be providing you with an official petition, requesting a black box warning in the coming months.

As of August 31, 2017, the FDA Adverse Events Reporting System (FAERS) Public Dashboard** shows the following serious adverse event cases reported between 1998 and 2017: (Safety reports submitted to FDA do not necessarily reflect a conclusion by FDA that the information in the reports constitutes an admission that the drug caused or contributed to an adverse event.)

	Total Adverse Event Cases	Serious Cases	Death Cases
Singulair	12,424	9,037	482
Montelukast	1,865	1,518	128
Montelukast Sodium	15,738	11,667	649
TOTAL	**30,027**	**22,222**	**1259**

During the past nine years, our groups have encouraged parents and adults who have contacted us to ask their doctors to report these adverse events. Disconcertingly, our members continue to report a general reluctance by their healthcare providers to file Adverse Event Reports with the FDA, which tells us that these cases are underreported.

Bernard, et al, (2017) reported a >10% incidence of neuropsychiatric side effects in the children they studied (most frequently observed were irritability, aggressiveness, and sleep disturbances) and a "notable risk of neuropsychiatric ADRs, leading to drug cessation, that is significantly higher than that associated with ICS". (Page1)

> *"In conclusion, in our real-life practice, >10% of children initiated on montelukast developed neuropsychiatric symptoms leading to drug cessation by parents. Risk factors predisposing to neuropsychiatric ADRs remain to be clarified"*[1] (Page 9)

** https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis

[1] Bernard, Brigitte & Bastien, Valérie & Vinet, Benjamin & Yang, Roger & Krajinovic, Maja & M. Ducharme, Francine. (2017). Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. European Respiratory Journal. 50. . 10.1183/13993003.00148-2017.
http://erj.ersjournals.com/content/50/2/1700148?ijkey=6bbfbe438acb30ce40548c38e47195c116dd7dd8&keytype2=tf_ipsecsha
http://erj.ersjournals.com/content/erj/50/2/1700148.full.pdf

Erdem et. al. also concluded that “the side effects of LTRAs were common in children. Therefore, patients must be informed at the beginning of the treatment and they must be evaluated at certain intervals.” [2] (Page1)

This suggests that the incidence of these side effects require reclassification to "common" in the label.

The Bernard et, al study also points to the delayed onset of side effects which is not specified in the label.

> *“The time to ADR occurrence may be contingent on specific neuropsychiatric ADRs, with sleep disorders, agitation, nervousness and psychotic disorders developing within hours to a few days, whereas depression and suicidal behavior occurred within months or years of treatment.”* (Page 8)

These findings reflect what we have suspected for years, and Ernst et. al further confirm the need for larger studies and that the risks need to be better communicated to the medical community. We believe the FDA should be instrumental in doing so.

> *“There are several implications of the study by BENARD et al. [4]. Firstly, clinical trials do not, by themselves, adequately assess the occurrence of adverse effects of medications. It remains the responsibility of the treating physician to have easy access to up-to-date online tools to check for reported adverse events and to engage patients actively to report possible adverse drug effects. At a meeting of the Pediatric Advisory Committee of the FDA held in September 2014, it was suggested that many healthcare professionals were unaware of the neuropsychiatric adverse events related to use of montelukast and that steps to increase awareness were required. Given that neuropsychiatric symptoms in children may be attributed to a wide variety of conditions and possible triggers, it is imperative that knowledge of this common ADR of montelukast be disseminated not only to paediatric respirologists but also to paediatricians and primary care providers. However, physician education alone is unlikely to result in sustained change in prescribing practices. Monitoring for neuropsychiatric ADRs should be integrated into existing asthma guidelines and individual clinics should explore ways to remind physicians to ask families about this important ADR. Moreover, patients should not only be asked about common ADRs at follow-up visits but there also needs to be a system in place for families to report new concerns to their physician as they arise. The transition to electronic medical records in*

---

[2] Erdem SB, Nacaroglu HT, Unsal Karkiner CS, Gunay I, Can D. Side Effects of Leukotriene Receptor Antagonists in Asthmatic Children. Iranian Journal of Pediatrics. 2015;25(5):e3313. doi:10.5812/ijp.3313. (Page 1)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610338/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4610338/pdf/ijp-25-3313.pdf

outpatient clinics will provide great opportunities for ongoing ADR surveillance and automated physician alerts. Most importantly, empowering families to report common ADRs on an ongoing basis would allow their physician to adjust their treatment plan sooner and may improve compliance, in addition to overall patient satisfaction.

As for the use of montelukast in children, adverse neuropsychiatric effects are sufficiently common and potentially difficult to recognize in young children to require that parents be informed of these at the initiation of treatment. Notably, the current study included only a small number of adolescents, such that the risk of suicidal behaviour in adolescents reported with montelukast cannot be quantified by the study by Benard et al. [4]. However, it may be prudent to discuss the possibility of mood changes as well as warning signs for suicidality with both adolescents and their parents when initiating treatment. Finally, it would be helpful to have larger studies that would permit the identification of individual predictors of neuro-psychiatric adverse events related to montelukast" [3] *(Page 2)*

Most recently Harmaan et. al explored adverse events reported in the Netherlands Pharmacovigilance Centre and the WHO Global ICSR database, VigiBase. Depression (n=1188) was the most frequently reported side effect in VigiBase and aggression (n=808) was the most reported in children. Nightmares were often reported in both adults and children and suicidal ideation was reported in 1046 cases. Concerns were also raised about the reports of allergic granulomatous angitis (Churg-Strauss syndrome) in people using Montelukast (n=8).

The study emphasizes that the "clinician must discuss the possibility of these adverse events with the patient and the parents" and that "further research is required to reveal the mechanism for the higher incidence of neuropsychiatric symptoms in patients using Montelukast in comparison with other medications." *(P,. 6)*

"Our data indicate that neuropsychiatric symptoms, such as depression, aggression, suicidal ideation, abnormal behavior, and nightmares, were significantly frequently reported in children and in adults in both the Dutch and the global database. The RORs found in these adverse events were high, pointing to a strong relationship." *(Page 6)*

In addition, Haarman et. al report that, in the Netherlands Pharmacovigilance Center spontaneous reporting database, **excoriation** (dermatillomania) was reported as a 'serious' adverse event.

"In 16 patients, the adverse event was called serious because of angioedema, hypersensitivity, fatigue, epilepsy, aggression, pain in extremity, immune system disorder, confusional state, hemorrhage, abnormal dreams, excoriation, eosinophil count increased, and abdominal pain." [4] (Page 2-3)

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[3] Ernst P, Ernst G. Neuropsychiatric adverse effects of montelukast in children. Eur Respir J 2017; 50: 1701020 [https://doi.org/10.1183/13993003.01020-2017] http://erj.ersjournals.com/content/erj/50/2/1701020.full.pdf

[4] M. G. Haarman, F. van Hunsel, T. W de Vries, Pharmacology Research and Perspectives, 20 September 2017. http://onlinelibrary.wiley.com/doi/10.1002/prp2.341/full http://onlinelibrary.wiley.com/doi/10.1002/prp2.341/epdf

Excoriation (dermatillomania), a chronic skin-picking disorder that can occur in response to anxiety or depression, is important to acknowledge due to its close ties to Obsessive Compulsive Disorder (OCD). Excoriation and other OCD behaviors have been regularly reported within our support group. Excoriation and obsessive-compulsive disorder are not listed in the Product Information (PI)[5] or the Patient Product Information for Singulair (Montelukast) [6].

Hyperkinesia was also listed as a "common adverse event in children" in the Harmaan study. Hyperkinetic symptoms (attention problems, uncharacteristic hyperactivity or restlessness, and tics/uncontrolled movements) have been reported consistently by our members as side effects. These symptoms are listed in the label as possible side effects but the word "hyperkinesia" (which was at one time listed on the Canadian monograph) is not specifically listed in the US Product Information (PI) or the Patient Product Information for Singulair (Montelukast). Members report that doctors are not connecting hyperkinetic symptoms *that started during treatment* and later result in the diagnosis of ADHD, Tics and/or Tourettes with Montelukast (Singulair).

> *"Most common adverse events in children (1–10% of all users) according to the SmPC are headaches, abdominal pain, rash, thirst, hyperkinesia, asthma, and eczema (Dutch Children's Formulary, 2016). Recent studies have also reported adverse events such as sleeping disorders and psychiatric disorders (Calapai et al. 2014). In addition, allergic granulomatous angiitis (Churg-Strauss syndrome) may also be associated with the use of montelukast (Calapai et al. 2014)."*[7] (Page 1-2)

Furthermore, based on what parents and affected adults are reporting to our groups, there may be very serious **unrecognized long-term implications** on the brain, gut and body after having an adverse reaction to Singulair. We continue to receive reports about an **intense 4-6 week withdrawal period** after discontinuation among those who are seriously affected, where heightened emotions and suicidal actions and thoughts can intensify or appear with sudden onset. Parents and affected adults tell us that they are not taken seriously by their healthcare providers when reporting withdrawal and/or lingering "side effect" symptoms that started during treatment and continued after discontinuation. Perhaps this is because there currently is no scientific/medical guidance on how to help those affected with these issues.

We recently conducted a survey about Montelukast's adverse side effects among parents of affected children and affected adults. We received 390 responses across 22 nations (including 190 from the US). A summary of our observations Annex A and a copy of the survey and the collective results are attached as Annex B, C and D.

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[5] Singulair PI - https://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf

[6] Singulair PPI - http://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_ppi.pdf

[7] M. G. Haarman, F. van Hunsel, T. W de Vries, Pharmacology Research and Perspectives, 20 September 2017. http://onlinelibrary.wiley.com/doi/10.1002/prp2.341/full

Among our thousands of members, the long-term implications are a common theme **(see Annex B and C)**. Healthcare providers and parents need information on how to recover in the long term after having a serious adverse reaction to Montelukast (Singulair). **Recognition of withdrawal and long-term implications is urgently required.**

We are available to answer any questions you may have and continue to collect additional information from our members. We invite you to join our Facebook group https://www.facebook.com/groups/189006057954150/ to be in real time contact with the parents and affected adults who are posting questions and sharing their experiences with this drug.

We hope that the Food and Drug Administration will consider this important information and agree that urgent action needs to be taken to make Montelukast (Singulair) safer to use.

Best regards,

Montelukast (Singulair) Side Effects Support and Discussion Group

(Previously known as Making the Side Effects of Singulair Aware to Parents of Children & Teens) https://www.facebook.com/groups/189006057954150/

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Vanessa Sellick
Stacy Stowe Schick
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Parents United for Pharmaceutical Safety and Accountability
www.parentsforsafety.org

Jenna Markle
Lynne Faraone
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Kate Belden Miller

Annex A – *Observations of Montelukast (Singulair) Side Effects*
Annex B – *Statistics at a Glance* – Results of Survey into Montelukast (Singulair) Adverse Side Effects
Annex C – *Graphs and Open Comments* - Results of Survey into Montelukast (Singulair) Adverse Side Effects with Attachments 1 to 5
Annex D – Copy of *Survey on Montelukast (Singulair) Adverse Side Effects*

CC: Members of the FDA Pediatric Advisory Committee (listed on following page)
Michael R. Cohen, President, Institute of Safe Medication Practices
Robert Weissman, President, Public Citizen
Amy Whicker - Director of Administration and Governance, Asthma and Allergy Foundation of America
Anita Everett, M.D., President, American Psychiatric Association

The Honorable Greg Hunt - Australian Minister for Health
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6.3. DPV-I and DEPI-II 2018 Joint Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance and Epidemiology Review

Date:	September 12, 2018
Reviewer(s):	Dipti Kalra, RPh, Safety Evaluator Division of Pharmacovigilance I Ivone Kim, MD, Medical Officer (Pediatrician) Division of Pharmacovigilance I Veronica Sansing-Foster, Epidemiologist Division of Epidemiology II
Team Leader(s):	Lisa Harinstein, PharmD, Safety Evaluator Team Leader Division of Pharmacovigilance I Efe Eworuke, PhD Division of Epidemiology II
Deputy Division Director:	Monica Muñoz, PharmD, MS, BCPS, Deputy Director, Division of Pharmacovigilance I Lockwood Taylor, PhD, MPH Division of Epidemiology II
Product Name(s):	Leukotriene modifiers: Singulair (montelukast), Accolate (zafirlukast), Zyflo (zileuton)
Subject:	Hyperkinesia, excoriation, obsessive compulsive disorder, and withdrawal neuropsychiatric adverse events following discontinuation of leukotriene modifiers
Application Type/Number:	Singulair NDA 021409, NDA 020830, NDA 020829 Accolate NDA 020547 Zyflo NDA 020471, Zyflo CR NDA 022052 Various ANDAs
Applicant/Sponsor:	Merck Consumer Care, Inc. Merck & Co, Inc. Par Pharm Inc Chiesi USA Inc
OSE RCM #:	2017-2297
TSI #:	415

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EXECUTIVE SUMMARY

This joint review between the Divisions of Pharmacovigilance I (DPV-I) and Epidemiology II (DEPI) in Office of Surveillance and Epidemiology (OSE) review is in response to a consult request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the safety concerns raised in a letter sent to the Office of Pediatric Therapeutics (OPT) by the Parents United for Pharmaceutical Safety and the Facebook Montelukast Side Effects Support and Discussion Group (herein referred to as the Parents and Facebook Groups) to determine if regulatory action is warranted.

At the December 29, 2017 planning meeting, DPARP requested DPV-I to provide an analysis of case reports in the FDA Adverse Event Reporting System (FAERS) database and the published medical literature for an association between leukotriene-modifying agents (LTMAs) and hyperkinesia, excoriation, obsessive-compulsive disorder (OCD), and adverse events related to drug withdrawal. DPARP requested the Division of Epidemiology II (DEPI-II) to review the epidemiologic data contained in the letter to OPT and to review the observational literature to determine if there is new information related to the association between LTMAs and neuropsychiatric events.

DPARP also requested the sponsor examine the clinical and postmarketing data from market introduction (July 31, 1997) to January 5, 2018 for an association between montelukast and excoriation, hyperkinesia, OCD, and adverse events not limited to neuropsychiatric events that persisted for more than 14 days following the last dose of montelukast.

The discussion section details OSE's assessment of the issues raised in the consult.

In summary, OSE recommends updating the montelukast labeling to include obsessive-compulsive symptoms based on data from the Sponsor's IR and FAERS. Given the constellation of neuropsychiatric symptoms with montelukast use, we recommend adding the phrase "including, but not limited to" as a precursor to sections of the label which describe neuropsychiatric adverse events. DEPI is conducting an analysis in Sentinel (expected completion late 2018) to examine the clinically relevant determinants that may increase the risk of neuropsychiatric events in montelukast users.

1 INTRODUCTION

This joint review between the Divisions of Pharmacovigilance I (DPV-I) and Epidemiology II (DEPI-II) in the Office of Surveillance and Epidemiology (OSE) is in response to a consult request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to review the safety concerns raised in a letter sent to the Office of Pediatric Therapeutics (OPT) by the Parents United for Pharmaceutical Safety and the Facebook Montelukast Side Effects Support and Discussion Group (herein referred to as the Parents and Facebook Groups) to determine if regulatory action is warranted.

Specifically, DPARP requested DPV-I in OSE to provide an analysis of case reports in the FDA Adverse Event Reporting System (FAERS) database and the published medical literature for an association between leukotriene-modifying agents (LTMAs) and four adverse events of interest: 1) hyperkinesia, 2) excoriation, 3) obsessive-compulsive disorder (OCD), and 4) adverse events related to drug withdrawal. DPARP requested DEPI-II in OSE to review the epidemiologic data contained in the letter to OPT and to review the observational literature to determine if there is new information related to the association between LTMAs and neuropsychiatric events. The LTMAs included in this review are Singulair (montelukast), Accolate (zafirlukast), and Zyflo (zileuton).

1.1 BACKGROUND

LTMAs are a class of medications used to treat asthma by blocking the bronchoconstrictor effects and proinflammatory activity of cysteinyl leukotrienes within the asthmatic airway. There are currently three LTMAs approved in the United States. Information related to the different products is contained in Table 1 below.

Table 1. U.S. Product Information for LTMAs

Proprietary Name	Active Ingredient	NDA*	Original Approval Date	Mechanism	Indication for Use
Accolate	Zafirlukast	020547	9/26/96	Leukotriene receptor antagonist (LTD_4 and LTE_4)	Prophylaxis and chronic treatment of asthma in adults and children ≥ 5 years of age
Singulair	Montelukast	020829 (oral tablet)	2/20/98	Leukotriene receptor antagonist (LTD_4)	Prophylaxis and chronic treatment of asthma in patients ≥ 12 months of age
		020830 (chewable tablet)	2/20/98		Acute prevention of exercise-induced bronchoconstriction (EIB) in patients ≥ 6 years of age
		021409 (oral granule)	7/26/02		Relief of symptoms of allergic rhinitis: seasonal allergic rhinitis in patients ≥ 2 years of age, and perennial allergic rhinitis in patients ≥ 6 months of age

Zyflo Zyflo CR	Zileuton Zileuton CR	020471 022052	12/9/96 5/30/07	Inhibitor of 5-lipoxygenase, which inhibits leukotriene (LTB_4, LTC_4, LTD_4, and LTE_4) formation	Prophylaxis and chronic treatment of asthma in adults and children ≥ 12 years of age
* There is one FDA approved ANDA for zafirlukast and zileuton and multiple FDA approved ANDAs for montelukast.					

DPARP and OSE have reviewed the association between montelukast and neuropsychiatric events previously as part of tracked safety issue (TSI) #415 after Merck submitted supplements in 2007 to add several different neuropsychiatric events to the postmarketing adverse event section of the montelukast prescribing information (OSE's reviews are summarized below in Section 1.2). Additionally, on October 22, 2007, correspondence was received by FDA from New York State Senator Elizabeth Little, requesting FDA to review the safety of montelukast after a 15-year-old within her district committed suicide 17 days after starting montelukast. The OSE and DPARP reviews resulted in the addition of neuropsychiatric events to the PRECAUTIONS section (currently WARNINGS AND PRECAUTIONS section, see section 1.4 of this review) of the montelukast prescribing information and patient information sheet. Several Drug Safety Communications (DSCs) were also posted on the FDA internet to inform healthcare professionals and patients of the new safety information.[1,2]

On September 28, 2008, the safety of montelukast was further reviewed after a Citizen Petition was submitted by the Parents United for Pharmaceutical Safety and Accountability (FDA-2009-P-0039). The Citizen Petition requested FDA to remove the indication for montelukast use in children and requested labeling changes for the following adverse events: seizures, neurological damage, neuropsychiatric events, and Churg-Strauss Syndrome. DPARP and OSE opened TSI #837 for the Petition and reviewed these safety issues. The reviewers found the montelukast labeling to be adequate for the concerns raised by the Petition.[3] FDA denied the Petitioner's request to remove the indication for use in children, but added Henoch-Schönlein purpura, a form of systemic vasculitis, to the ADVERSE REACTIONS *Post-Marketing Experience* section of the label.

On September 23, 2014, the Pediatric Advisory Committee reviewed the current montelukast labeling regarding the risk of neuropsychiatric events. Ultimately, the committee felt that the patient information was clear, but the physician labeling might be strengthened.[4]

On November 3, 2017, the Parents and Facebook Groups submitted a letter to OPT asserting that the incidence of neuropsychiatric side effects with montelukast is much more common than currently reported, particularly in children. As evidence, the letter contained an analysis of the FAERS Public Dashboard (30,027 total adverse event cases with Singulair, montelukast, and montelukast sodium from 1998 and 2017 as of August 31, 2017), citations of numerous case reports and studies, and an online survey by the Parents and Facebook Groups. The letter requested the FDA to do the following:

1. determine the mechanisms for montelukast's neuropsychiatric side effects.
2. determine risk factors for an adverse reaction.
3. determine the appropriate way to discontinue montelukast ("cold turkey" vs. tapering).
4. determine withdrawal symptoms and long-term implications of an adverse reaction.

5. reclassify the neuropsychiatric side effects of montelukast (Singulair) to be 'common' in children.
6. update the label with a warning for the possible delayed-onset of side effects and include 'excoriation', 'hyperkinesia,' and 'obsessive compulsive disorder (OCD)' as reported side effects.
7. issue a Medication Guide for montelukast due to the life altering and life-threatening potential of its neuropsychiatric effects.
8. consider a black box warning.

On December 6, 2017, DPARP consulted DEPI-II in OSE to provide a review of the letter sent to OPT (issues 1-6) and an assessment of the survey methods and data. Additionally, DPARP requested a brief review of the observational literature to evaluate whether there appears to be any new information related to the association of montelukast and neuropsychiatric events such as frequency, risk factors, withdrawal symptoms, and mechanistic information.

On December 16, 2017, TSI #415 was re-opened for the safety issue of neuropsychiatric events with LTMAs.

On December 29, 2017, DPARP consulted DPV-I in OSE to provide a review of the FAERS database for cases of hyperkinesia, excoriation, OCD, and symptoms following withdrawal, including neuropsychiatric events, associated with montelukast use to address the issues in the letter sent to OPT. Given that montelukast is a LTMA, it was requested to expand the analysis to zafirlukast and zileuton for completeness.

On January 2, 2018, DPARP sent an information request (IR) to the Sponsor of Singulair (montelukast), requesting the following information:

1. an assessment of whether excoriation, hyperkinesia, and OCD are associated with use of Singulair.
2. an assessment of whether there are any risk factors for neuropsychiatric adverse reactions with Singulair.
3. an assessment of continued or worsening symptoms including but not limited to neuropsychiatric symptoms, following discontinuation of Singulair and whether the method of discontinuation of Singulair (e.g., tapering or sudden withdrawal) had an impact on symptoms.

On April 26, 2018, DPARP received the IR response from the Sponsor. The Sponsor analyzed clinical and postmarketing data from market introduction (July 31, 1997) to January 5, 2018 for an association between montelukast and excoriation, hyperkinesia, OCD, and adverse events not limited to neuropsychiatric events that persisted for more than 14 days following the last dose of montelukast. Based on the data, the Sponsor intends to update the montelukast Prescribing Information to include information related to obsessive-compulsive symptoms (see Section 1.4 for a high-level overview of the Sponsor's IR response).

1.2 REGULATORY HISTORY

Below are previous reviews by OSE related to the safety issues put forth in letter to OPT:

- 12/19/08 (RCM # 2008-474) OSE AERS Postmarketing Safety Review: Mood, Cognitive, Perception, Sleep and Movement Adverse Events:[5] This review examined the association between mood (including suicide and suicidal ideation), cognitive, perception, and sleep adverse events with montelukast use. This review was initiated by an inquiry to FDA from New York State Senator Little regarding a 15-year-old who committed suicide, in August 2007, while taking montelukast to treat allergic rhinitis. The review recommended neuropsychiatric events to be added to the PRECAUTIONS section (currently WARNINGS AND PRECAUTIONS section) of the label.
- 06/30/10 (RCM# 2010-1209) OSE Review of Labeling Submission for 'Disorientation':[6] This review examined the association between disorientation and montelukast use. It was recommended to add disorientation to the label based on data provided in a Changes Being Effected supplement.
- 05/14/11 (RCM #2009-1006) OSE Response to Citizen Petition:[7] A consult was received from the Office of Regulatory Policy. The Petitioner requested the removal the montelukast indication for use in children, changes to the product labeling, implement requirements that adverse events are reported by physicians, and that all labeling changes are communicated to consumers. This OSE review evaluated neuropsychiatric events (vocal and motor tics, seizures and brain damage, status epilepticus, death) and vasculitis (vasculitides, deaths, Churg-Strauss syndrome) with montelukast use. The reviewer recommended no labeling changes to the product labeling at that time.
- 02/27/13 (RCM# 2012-1478) OSE Review of Association Between LTMA Use and Suicide:[8] This epidemiology review evaluated a newly published nested case-control study which examined the association between suicide/suicide attempt and LTMA use. The reviewer concluded that the risk of suicide cannot be quantified based on the epidemiologic studies and regulatory action by FDA was not warranted.
- 02/21/14 (RCM#2013-2360) OSE Review of Neuropsychiatric events and Churg-Strauss Syndrome:[9] This review did not identify any new safety issues that have not been previously recognized and reviewed by the FDA. The neuropsychiatric events appear to be adequately labeled in the proposed over-the-counter (OTC) montelukast Drug Facts label submitted with NDA 204804; however, the proposed OTC montelukast Drug Facts label lacked information about the potential association between montelukast use and Churg-Strauss Syndrome.
- 09/02/14 (RCM# 2014-585) OSE Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review for Singulair:[10] This review did not identify any new safety concerns in children 0 to <17 years old treated with montelukast.

1.3 SELECTED PRODUCT LABELING[11,12,13]

The specific adverse events of interest in this review (OCD, excoriation, hyperkinesia, and withdrawal adverse events) are not contained in the product labeling for any of the LTMAs. The current montelukast product label dated 12/2016 contains information regarding neuropsychiatric events in the WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS *Post-marketing Experience*, and PATIENT COUNSELING INFORMATION sections. The current zafirlukast product label dated 11/2013 contains neuropsychiatric events in the PRECAUTIONS and ADVERSE REACTIONS sections. The current zileuton product label dated 6/2012 contains

neuropsychiatric events in the PRECAUTIONS and ADVERSE REACTIONS *Post-marketing Experience* sections. Select labeling sections regarding neuropsychiatric events with montelukast is shown below.

----------5 WARNINGS AND PRECAUTIONS----------
5.4 Neuropsychiatric Events
Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking SINGULAIR. Post-marketing reports with SINGULAIR use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The clinical details of some post-marketing reports involving SINGULAIR appear consistent with a drug-induced effect.

Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with SINGULAIR if such events occur *[see Adverse Reactions (6.2)]*.

----------6 ADVERSE REACTIONS----------
6.2 Post-Marketing Experience
Psychiatric disorders: agitation including aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor *[see Warnings and Precautions (5.4)]*.

----------17 PATIENT COUNSELING INFORMATION----------
Patients should be instructed to notify their physician if neuropsychiatric events occur while using SINGULAIR.

These events are also described in the FDA approved Patient Information sheet for Singulair below.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:

o agitation including aggressive behavior or hostility o attention problems o bad or vivid dreams o depression o disorientation (confusion) o feeling anxious o hallucinations (seeing or hearing things that are not really there)	o irritability o memory problems o restlessness o sleep walking o suicidal thoughts and actions (including suicide) o tremor o trouble sleeping o uncontrolled muscle movements

1.4 SPONSOR'S IR RESPONSE

On April 26, 2018, the Sponsor of Singulair (montelukast) completed an analysis of clinical trial and postmarketing data for an association between montelukast and the adverse events of excoriation, hyperkinesia, OCD, and persistent adverse events. The Sponsor reviewed a large pooled clinical dataset (42 interventional clinical trials) to provide an assessment of whether excoriation, hyperkinesia, and OCD are associated with the use of montelukast. Hyperkinesis was observed in a single pediatric individual treated with montelukast in the controlled clinical studies and was assessed as definitely not related by the investigator. The adverse event of OCD was reported from one subject who was 5-years-old; the event occurred after 179 days of therapy

and was assessed as definitely not related by the investigator. Fifteen events of excoriation were reported in 15 subjects. All 15 events were reported as nonserious and the events were assessed as not related by the investigator. The study drug was continued, and all events had resolved prior to the end of the trial.

The Sponsor searched their safety database for spontaneous and non-interventional study reports with the Preferred Terms (PTs) of excoriation, hyperkinesia, and OCD received from healthcare providers, regulatory agencies, and consumers from market introduction (July 31, 1997) to January 5, 2018. The Sponsor found low numbers of excoriation and hyperkinesia cases in the postmarketing database. The Sponsor identified 85 cases with the PT Obsessive-compulsive disorder, of which 26 contained evidence of positive dechallenge. Of the 26 positive dechallenge cases, three contained evidence of positive rechallenge and one contained evidence of negative rechallenge. Many of the 26 positive dechallenge cases contained minimal, if any, descriptive information to support the diagnosis of OCD.[a] The remaining 59 cases lacked sufficient information such as start and stop dates of therapy, start dates for the event of OCD, medical history and concurrent medical conditions, and diagnostic information making a meaningful assessment of the case difficult.

In their analysis of persistent adverse events, the Sponsor searched for cases of continued or worsening symptoms including, but not limited to neuropsychiatric symptoms, that did not resolve after 2 or more weeks following montelukast discontinuation in the clinical trial data. The Sponsor identified an overall low number of cases. The 10 most frequently reported adverse events identified among the cases were then evaluated in the Sponsor's postmarketing database. Of the 10 most frequently reported adverse events that did not resolve after 2 or more weeks following montelukast discontinuation, seven were from either the Nervous system disorders System Organ Class (SOC) or the Psychiatric disorders SOC; the seven adverse events were abnormal behavior, aggression, anxiety, depression, headache, insomnia, and paraesthesia.[b] Abnormal behavior was noted by the Sponsor to be the only term not contained in the montelukast U.S. prescribing information (USPI). However, many terms were already contained in the USPI that were suggestive of abnormal behavior such as disorientation, disturbance in attention, and hallucinations. The Sponsor concluded that the low number of cases in the clinical trials with the limited information from the postmarketing database make it difficult to assess montelukast's role in the events. The most frequently reported adverse events were labeled in the montelukast USPI, therefore, no new safety concerns regarding persistent adverse events after withdrawal of montelukast were identified.

Based on the review of the data, the Sponsor concluded that obsessive-compulsive symptoms should be added to the USPI for montelukast, and that there was insufficient evidence to support the addition of the other three adverse events to the USPI.

[a] Three cases of positive dechallenge and two cases of positive rechallenge were not retrieved in our search of the FAERS database in section 2.1.3. The cases likely were submitted as paper periodic submissions or foreign reports with nonserious outcome. The case details were submitted by the Sponsor in the IR response; we reviewed the cases and concluded that they would not have met our case selection criteria in section 2.1.1 because they did not indicate a diagnosis of OCD by a healthcare provider or did not contain signs and symptoms consistent with OCD.
[b] The three other adverse events analyzed were rash, pruritis, and eosinophilic granulomatosis with polyangiitis

2 METHODS AND MATERIALS

2.1 FAERS AND CASE REPORT LITERATURE – DPV

2.1.1 Case Selection Criteria

Inclusion Criteria*:*

OCD

- A report that contains a diagnosis of OCD by a healthcare provider or contains signs and symptoms consistent with OCD (such as repetitive hand washing or repeating words silently).

Excoriation

- A report that contains a diagnosis of excoriation disorder by a healthcare provider or describes recurrent or excessive picking, scratching, or rubbing of normal skin.[c]

Hyperkinesia

- A report that contains a diagnosis of hyperkinesia by a healthcare provider or describes involuntary or excessive spontaneous movements.

Neuropsychiatric adverse events after drug withdrawal

- A report of new-onset neuropsychiatric adverse events or continued or recurrence of existing neuropsychiatric adverse events after withdrawal[d] or discontinuation of a drug.

2.1.2 Causality Assessment

Cases of OCD, excoriation, hyperkinesia, and neuropsychiatric adverse events after drug withdrawal were assessed for a causal relationship with montelukast, zafirlukast, and zileuton using the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) classification system as shown in Table 2.[14] Cases were excluded from the case series if their causality assessment was deemed to be "unlikely" or "unassessable."

Table 2. Causality Classification and Criteria based on the WHO-UMC System

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs

[c] Adapted from the Diagnostic and Statistic Manual of Mental Disorders V criteria for excoriation disorder.
[d] Withdrawal is defined as tapering the dose or missing doses of LTMAs.

	• Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely*	• Event or laboratory test abnormality, with a time to drug intake that makes relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable*	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
*Excluded from further analysis in the case series	

2.1.3 FAERS Search Strategy

DPV-I searched the FAERS database with the strategy described in Table 3. We first searched the FAERS database for all reports of neuropsychiatric events associated with LTMA use to provide context (high level analysis) and then searched for reports that contained the four adverse events of interest with the three LTMAs (detailed analysis).

Table 3. FAERS Search Strategy*

	Search 1 **All LTMA Reports (High Level Analysis)**	**Search 2** **Adverse Events of Interest (Detailed Analysis)**	**Search 3** **Adverse Events of Interest (Detailed Analysis)**
Date of Search	January 16, 2018		
Time Period of Search	February 20, 1998† - January 16, 2018		
Search Type	Product-Manufacturer Reporting Summary	Quick Query	
Product Terms	Product active ingredient: montelukast sodium, montelukast/montelukast sodium, zafirlukast, and zileuton‡		
MedDRA Search Terms (Version 20)	a. System Organ Class (SOC): All b. SOC: Psychiatric disorders, Nervous system disorders	Preferred Term (PT): Hyperkinesia, Excoriation, OCD	Higher Level Term (HLT): Withdrawal and rebound effects
* See Appendix A for description of the FAERS database. † U.S. approval date for montelukast, as this was the product specified in the letter to OPT. We also searched from the approval date for zafirlukast, the first approved LTMA on September 26, 1966, and did not retrieve any additional reports. ‡ FAERS search by product active ingredient retrieves reports for Singulair, Accolate, and Zyflo in the FAERS product dictionary.			

2.1.4 Literature Search for Case Reports

DPV-I searched the medical literature with the strategy described in Table 4 to identify case reports of the four adverse events of interest with the three LTMAs.

Table 4. Literature search strategy for case reports

	Search 1	Search 2	Search 3
Date of Search	January 23, 2018		
Database	PubMed@FDA	Google Scholar	EMBASE
Search Terms	(((“montelukast”) OR “zafirlukast”) OR “zileuton”) AND neuropsychiatric [All Fields] AND "humans"[MeSH Terms] (((((“montelukast"[Supplementary Concept] OR "montelukast"[All Fields]) OR ("zafirlukast"[Supplementary Concept] OR "zafirlukast"[All Fields])) OR ("zileuton"[Supplementary Concept] OR "zileuton"[All Fields])) AND ("hyperkinesis"[MeSH Terms] OR "hyperkinesis"[All Fields] OR "hyperkinesia"[All Fields])) OR excoriation[All Fields]) AND ("case reports"[Publication Type] OR "case report"[All Fields])	“Montelukast zafirlukast zileuton hyperkinesia” “Montelukast zafirlukast zileuton excoriation” “Montelukast zafirlukast zileuton neuropsychiatric withdrawal effects”	('montelukast'/exp OR montelukast OR 'zafirlukast'/exp OR zafirlukast OR 'zileuton'/exp OR zileuton) AND ('drug withdrawal'/exp OR 'drug withdrawal') AND ('neuropsychiatric symptom'/exp OR 'neuropsychiatric symptom') AND [english]/lim AND [humans]/lim ('montelukast'/exp OR montelukast OR 'zafirlukast'/exp OR zafirlukast OR 'zileuton'/exp OR zileuton) AND ('hyperkinesia'/exp OR hyperkinesia) AND [english]/lim AND [humans]/lim ('montelukast'/exp OR montelukast OR 'zafirlukast'/exp OR zafirlukast OR 'zileuton'/exp OR zileuton) AND ('excoriation'/exp OR excoriation) AND [english]/lim AND [humans]/lim
Years Included	All years		
Limits	Human; Case study; Case series; English		

2.2 OBSERVATIONAL LITERATURE AND DATA – DEPI-II

2.2.1 Literature Search for Observational Data

On December 29, 2017 and January 5, 2018, the DEPI-II reviewer and the FDA Library, respectively, conducted a search of the National Library of Medicine’s Pub Med database, Web of Science, EBSCOHost and Google Scholar Advanced Search. The following search string was used: (asthma [mesh]) AND (((neuropsychia* OR depressi* OR suicid* OR mental OR violen*

OR psychiatric or anx* or tremor or behav*)) AND (singulair or montelukast or LTRA or "Leukotriene Receptor Antagonist")). The final search included studies from January 1, 2012, to January 5, 2018, written in English, pertaining to humans, and all ages (see Section 3.3 for more details). The reference sections of the studies were reviewed for additional studies, especially landmark studies.

The quality of the studies was reviewed per the Newcastle-Ottawa Scale[e] for cohort and case-control studies, and according to six attributes the reviewer considered critical for further internal validity when assessing montelukast and neuropsychiatric events[15]:

1. Control for 2008 labeling changes to reduce information and channeling bias
2. Disclosure of no relationship with manufacturers of asthma medications
3. Incident use of montelukast as opposed to prevalent use
4. Adequate power to test association between montelukast and the outcome
5. Assessment of montelukast treatment duration or dosage to examine dose-response relationship
6. Adjustment of inhaled corticosteroid (ICS)/long-acting beta-agonist (LABA) combination therapy given the risk of neuropsychiatric events with LABA use

2.2.2 Parents and Facebook Groups' Survey

DEPI-II contacted Doris Auth and Shelly Harris in the Division of Risk Management (DRISK) in OSE on December 14, 2017, to provide feedback regarding the design and validity of the survey conducted by the Parents and Facebook Groups.

The primary objective was to describe the types of adverse drug events experienced by Singular users during and after use. This was an international, internet survey conducted by the Parents and Facebook Groups. The survey was conducted through Facebook January 2017 through March 2017.

The survey targeted adults and parents of children who use Singulair for asthma control. The respondents were primarily members of the Singular Facebook Discussion Group. There were no exclusion criteria. Patients with current or past use (withdrawal) of montelukast were asked to answer the survey.

The primary serious adverse events collected in the survey pertained to labeled neuropsychological events, including agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), tic, and tremor. The survey also captured unlabeled neurological side effects.

There were no formal statistical analyses – all results are presented as frequencies and percentages.

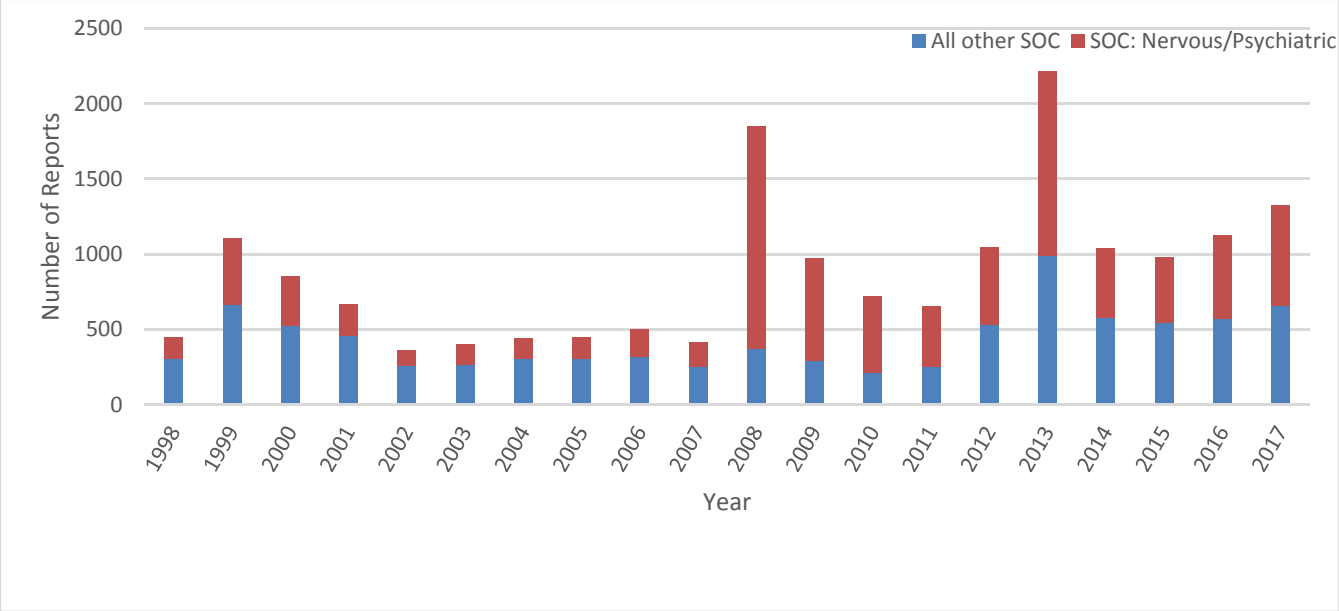
3 RESULTS

[e] Newcastle-Ottawa scale was used as a standardized method of analyzing study quality. The scale has a numeric scoring system, which was not used in this review to avoid quantifying the quality of results. See the references for more information regarding the scoring system for case-control studies and cohort studies.

3.1 FAERS

Figure 1 below depicts the total number of montelukast, zafirlukast, and zileuton reports contained in the FAERS database from February 20, 1998 (U.S. approval date for montelukast), through December 31, 2017 by FDA received year. The reports are further broken down into those coded with a MedDRA PT in the Nervous system disorders or Psychiatric disorders SOC and those coded with a PT in all other SOCs.

Figure 1. All Montelukast, Zafirlukast, and Zileuton FAERS Reports* by FDA Received Year between 1998-2017*



*May include duplicates and reports not assessed for causality

Reviewer comment: ***Figure 1*** *above shows that a total of 17,576 reports (montelukast n=16,290, zafirlukast n=1,074, zileuton n=212) related to the use of LTMAs were identified in the FAERS database from 1998 to 2017; this number may include duplicates. Of the 17,576 total reports, 51% (n=8,915) reported events in the Nervous system disorders SOC or Psychiatric disorders SOC. There was a sharp increase in reports in 2008 when FDA first alerted healthcare professionals and patients about a possible association between the use of LTMAs and neuropsychiatric events. Another spike occurred in 2013, which coincided with an influx of reports that have been received from a line listing from the Adverse Event Reporting System (AERS)[f](approximately 857duplicate reports resulting from a Freedom of Information Act request) database.*

The letter to OPT stated that as of August 31, 2017, the FAERS Public Dashboard contained a total of 30,027 adverse event cases for Singulair (n=12,424), montelukast (n=1,865), and montelukast sodium (n=15,738). The total of 30,027 cases is incorrect because the product term

[f] The FAERS database deployed in September 2012

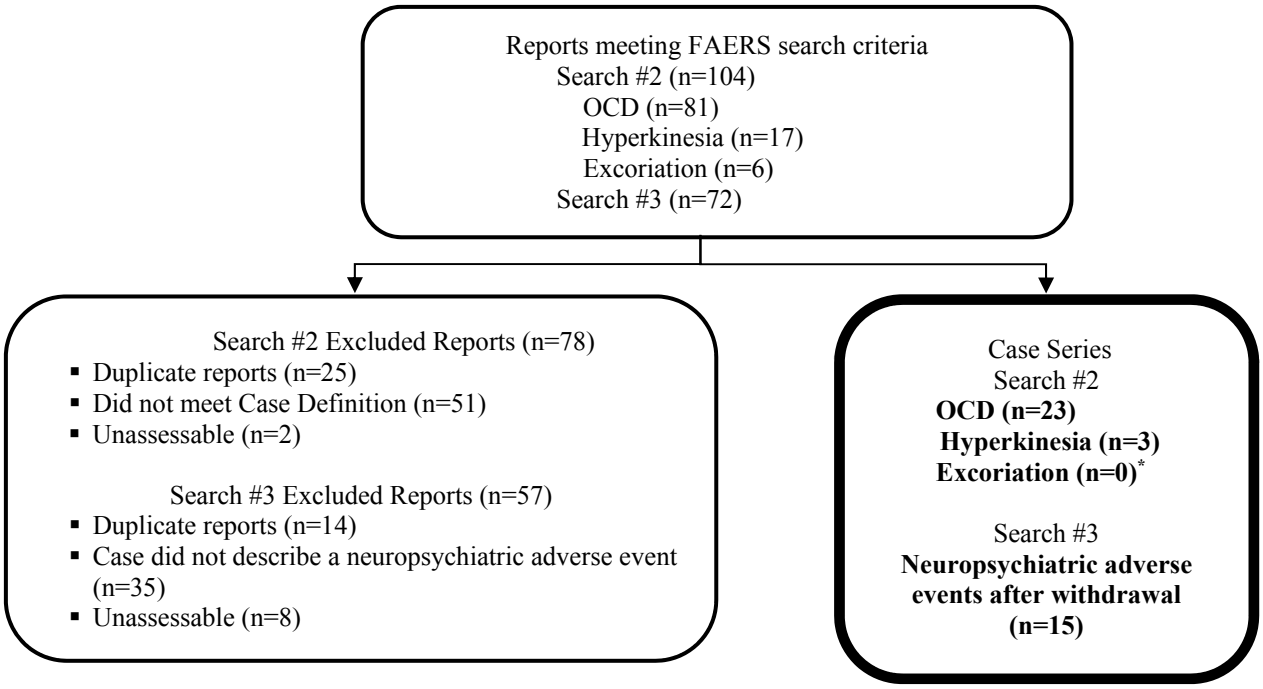
"montelukast sodium" retrieves all reports for Singulair, montelukast, and montelukast sodium in the FAERS Public Dashboard. Therefore, the true total in the public dashboard through August 31, 2017, was 15,738.

Figure 2 below depicts FAERS search strategies 2 and 3 (detailed analysis) and the FAERS case selection. The FAERS searches retrieved in total 176 reports with montelukast and no reports for zafirlukast and zileuton.

Search 2: The FAERS search for excoriation, hyperkinesia, and OCD with LTMAs retrieved 104 reports; all reports involved montelukast and no reports involved zafirlukast or zileuton. After accounting for duplicate reports (n=25), reports that did not meet the case definition (n=51), and reports that were unassessable (n=2), 26 cases were included in the case series of OCD (n=23), hyperkinesia (n=3), and excoriation (n=0) reported with montelukast use (see Figure 2). Appendix C contains a line listing of all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 26 cases in this case series.

Search 3: The FAERS search for neuropsychiatric withdrawal symptoms with LTMAs retrieved 72 reports; all reports involved montelukast and no reports involved zafirlukast or zileuton. After accounting for duplicate reports (n=14), reports that did not contain the adverse events of interest (n=35), and reports that were unassessable (n=8), 15 cases were included in the case series of neuropsychiatric adverse events after withdrawal of montelukast.

Figure 2. FAERS Case Selection



* Excoriation will not be discussed any further in the results because we did not identify any cases.

3.1.1 OCD

Table 5 summarizes the 23 FAERS cases of OCD reported with montelukast use for this case series.

Table 5. Characteristics of OCD Cases Reported with Montelukast Use in FAERS, Received by FDA from February 20, 1998, to January 16, 2018

Sex	Male			16
	Female			7
Age (years) (n=21)	Mean			11
	Median			9
	Range			3-61
FDA received year	2001	1	2011	1
	2003	1	2012	4
	2008	10	2013	1
	2009	3	2015	1
	2010	1		
Serious outcome* (n=20)	Other serious			16
	Hospitalization†			1
	Life-threatening			3
	Disability			2
	Required intervention			1
Country	United States			22
	Foreign			1
Report type	Direct			16
	Expedited			6
	Periodic			1
Report source	Health professional			5
	Consumer			18
Time to onset (n=10) (weeks)	Mean			19
	Median			4
	Range			1-104
Comorbid neuropsychiatric condition(s) at baseline	Yes			2
	Not reported			21
Dechallenge (n=8) ‡	Positive dechallenge			8
	Negative dechallenge			1
Rechallenge (n=1)	Positive rechallenge			1
WHO-UMC causality assessment	Probable			9
	Possible			14

* 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 one or more outcome.

† There was one additional case with a serious outcome of hospitalization; after review of the case narrative, it was determined that hospitalization did not occur, and the case was miscoded.

‡ One case reported positive dechallenge, then positive rechallenge, followed by negative DE challenge to montelukast and the occurrence of OCD.

Reviewer comment: *The majority of cases of OCD associated with montelukast use occurred in the United States (22/23) and were received after 2008 (21/23), which was when FDA first alerted healthcare providers and patients about a possible association between the use of LTMAs and neuropsychiatric events. The majority (18/23) of cases were reported by consumers to FDA, which coupled with the date of submission, suggests that some reports may have been*

stimulated in response to the FDA alerts and labeling changes. Patients may have submitted a report if they recently observed media coverage regarding the FDA warning. A substantial amount of media reporting has purported that montelukast may have a causal role in the development of the types of neuropsychiatric symptoms described in the postmarketing cases. The influx of cases may be helpful in assessing the association between montelukast and the reported adverse events but may also affect the internal validity of the case series analysis because of the introduction of bias.

We utilized strict case selection criteria to improve the validity of our case series and required a case submitted by a consumer to contain information about the signs and symptoms of OCD. However, most cases did not provide evidence of an evaluation by a healthcare professional to confirm the diagnosis of OCD or to rule out other causes for the neuropsychiatric events. This strict case selection criteria also resulted in a smaller case series when compared to the Sponsor's analysis in the IR response.

Overall, the cases lacked sufficient clinical detail to determine the role of montelukast in the adverse events. The cases contained other potential etiologies such as comorbid conditions and concomitant medications; the cases were missing information about dates of medication administration, past medical history, and diagnostic information to accurately assess causality.

The narratives of select OCD cases that report dechallenge or rechallenge to montelukast are summarized below.

FAERS Case #3654488, Non-serious outcome, U.S., 2001: A physician reported that an 11-year-old male was initiated on montelukast 10 mg for the treatment of asthma and cough. The patient's concomitant therapy included cetirizine, triamcinolone acetonide, budesonide, and albuterol. The patient developed OCD disorder characterized by constantly washing his hands until they became dry, red, and cracked. Therapy with montelukast was interrupted and the patient's hand washing stopped within a few days. Subsequently, the patient was given one tablet of montelukast and his OCD reoccurred. Therapy was permanently discontinued, but at the time of the report (approximately 7 months later), the patient's OCD persisted.

FAERS Case #8467820, Other serious important medical event, U.S., 2012: A consumer reported that her 3-year-old son was prescribed montelukast for asthma and has been taking it for about 15 months. In the beginning, he had night terrors so montelukast was given in the morning and night terrors dissipated; however, the patient became a very restless sleeper and got up numerous times at night. The patient then began having symptoms of OCD. He was constantly repeating words and other motions. He started to gag himself and could not stop or control it and was very upset and scared that he could not stop his hand. After discontinuing the medication, about 2 to 3 days later, the bad behavior completely stopped.

Medical officer comment: *OCD is characterized by obsessive or compulsive thoughts or actions and is closely related to other anxiety disorders. Children with persistent asthma have demonstrated a higher prevalence of comorbid anxiety disorders and behavioral problems than non-asthmatic youths.[16] The immediacy of the patients' resolution of symptoms following montelukast discontinuation in both cases makes a compelling argument for possible causation.*

According to the Diagnostic and Statistic Manual V (DSM-V), a constellation of symptoms that is attributable to the physiological effects of a substance does not meet criteria for diagnosis of OCD.[17] Thus, the adverse events reported do not represent OCD, but rather, OCD-like behaviors (see Appendix B for DSM-V criteria for OCD diagnosis).

We acknowledge that FAERS cases #3654488 and #8467820 do not report medical or psychiatric evaluation for the reported symptoms and lack explicit information about the patient's social history, medical history, and information on whether concomitant medications were discontinued. Additionally, the only case that reports positive rechallenge (FAERS case #3654488) presents mixed information because the first episode of symptoms that are OCD-like resolved within a few days, but the second episode was ongoing 7 months after the second discontinuation. It is possible that the OCD-like symptoms could persist despite montelukast discontinuation, but no other cases in our OCD-like behaviors case series support this hypothesis.

3.1.2 Hyperkinesia

There were three cases of hyperkinesia, of which two were associated with a serious outcome reported as other serious important medical event. All hyperkinesia cases reported additional adverse events including mood swings, sleep terror, and psychomotor hyperactivity following montelukast use. The three case narratives of hyperkinesia accompanying montelukast use are summarized below.

FAERS Case #8710423, Non-serious outcome, U.S., 2012: A consumer reported that his 22-month-old son with allergies and ear tubes in both ears was placed on therapy with montelukast sodium 5 mg chewable tablet once a day for the treatment of cough due to allergies. Concomitant therapy included mometasone furoate nasal spray. One evening, the patient experienced night terrors. The patient woke up every 2 hours, screaming, crying, and exhibiting hyperkinesia (movement of the arms and legs during sleep). The reporter sought medical attention by calling the doctor. No treatment was given to the patient. No lab test was done. Therapy with montelukast sodium was discontinued and not reintroduced.

Medical officer comment: *Benign sleep myoclonus is a brief, sudden, and involuntary twitching or jerking movement. This is common in the neonatal period and in infancy.[18] Excess of movement is common in children and during normal play, behavioral outbursts, and in moments of anxiety. Hyperkinesia, secondary to other pathological conditions, often has sustained duration, rhythmic quality, recurrence, and stereotyped form.[19] The narrative does not provide information to discern if the infant's movements represent normal conditions such as myoclonus or typical movements of upset infants, or if these movements represent other pathologic conditions or reactions.*

FAERS Case #4130975, Other serious important medical event, Foreign, 2004: A physician reported that a 2.5-year-old male was placed on therapy with montelukast sodium 4 mg chewable tablet once a day for the treatment of asthma. Subsequently, the dose of montelukast was switched to 5 mg. Concomitant therapy included budesonide and albuterol. Approximately 2 to 3 months after starting therapy with montelukast, the patient experienced attention decreased, hyperactivity, and later experienced hyperkinesia. The reporting physician stated that therapy

with montelukast was interrupted during the summer and then was restarted approximately a few months later; the physician could not remember if the patient improved from hyperactivity and attention decreased when montelukast was interrupted. The patient needed psychiatric treatment with several drugs, but hyperactivity and attention decreased persisted. Subsequently, the therapy with montelukast was discontinued approximately three months later and the patient recovered from attention decrease, hyperkinesia, and hyperactivity at an unknown time.

Medical officer comment: *The case involves a young child of an age marked by behavioral outbursts, opposition, and sometimes apparent difficulty with attention; for this child's age, the described behaviors may be typical.[20] This case contains insufficient information to determine the cause of the attention decreased, hyperactivity, and hyperkinesia. The differential for the described behaviors is broad and includes, but is not limited to, montelukast, typical behavior for age, or other disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). ASD refers to a group of complex neurodevelopment disorders characterized by difficulties with behavior and social development; increased awareness has led to the diagnosis of ASD in very young children.[21] ADHD is marked by symptoms of impulsivity, hyperactivity, inattention, and possibly impaired functioning. Clinical practice guidelines for the evaluation and management of ADHD from the American Academy of Pediatrics focuses on the diagnosis of children 4 years and older.[22] The diagnosis for ADHD in young children remains difficult because of the possibility of other diagnoses such as ASD and development-associated behaviors of early childhood.*

The narrative reports the child required psychiatric treatment and medication, but no additional detail is provided (such as developmental history, psychiatric treatment received) to assess the causal relationship between the behaviors, including hyperkinesis, and montelukast.

FAERS Case #7093416, Other serious important medical event, U.S., 2009: A consumer reported that her 3-year-old daughter started taking montelukast and immediately began to exhibit signs of hyperkinesia and mood swings. The patient had always been very articulate, happy, and agreeable. She began to have trouble controlling her movements and emotions. She developed completely uncontrollable anger and fear of many things; she had never been afraid before. She also became unreasonable. The doctors said it couldn't be the montelukast. The patient was on montelukast for two years then discontinued it. The patient is improving although she has not fully recovered.

Medical officer comment*: The narrative lacks further information about the nature of the patient's movements to infer any information about the etiology of movements. Without further information about the child's developmental history, social history, and past medical history, it is difficult to develop a meaningful causality assessment.*

Reviewer comment: *The two best representative cases above (FAERS case #4130975 and 7093416) report hyperkinesia in the context of other adverse events such as hyperactivity, decreased attention, and mood swings. Some of these terms or related terms are already captured in the current labeling of montelukast. The inconsistency of adverse events in the limited number of cases does not allow us to appropriately establish the relationship between hyperkinesia and montelukast use.*

3.1.3 Neuropsychiatric adverse events after drug withdrawal

Table 6 summarizes the 15 FAERS cases of neuropsychiatric adverse events reported after withdrawal of montelukast included in the case series. Two case narratives are presented afterwards.

Table 6. Characteristics of Neuropsychiatric Adverse Events Reported After Withdrawal of Montelukast in FAERS, Received by FDA from February 20, 1998, to January 16, 2018

Sex	Male Female	8 7
Age (years)	Mean Median Range	20 11 3-56
FDA received year	2008 1 2012 2 2009 2 2013 2 2010 2 2015 3 2011 1 2017 2	
Outcome* (n=10)	Other serious Life-threatening Disability	9 1 1
Country	United States Foreign	14 1
Report type	Direct Expedited Periodic	10 3 2
Report source	Health professional Consumer	5 10
Duration of montelukast use prior to discontinuation (n=13)	0-6 months 2 years 3 years 4 years 5 years 8 years	7 1 2 1 1 1
Time to onset of symptoms after montelukast discontinuation, days (n=5)	Mean Median Range	3.8 5 0-8
New or continued neuropsychiatric symptoms after montelukast discontinuation†	New Continued	6 9
Cases reporting neuropsychiatric symptom resolution after restarting montelukast (n=2)	Yes	2
Cases reporting neuropsychiatric symptom recurrence after repeat montelukast discontinuation (n=1)	Yes	1
Mention of stimulated reporting (n=7)‡	Yes	7

Reported PTs associated with more than 2 reports	Withdrawal syndrome§	11
	Anxiety	10
	Abnormal behaviour	6
	Aggression	5
	Fear	5
	Drug withdrawal syndrome§	4
	Emotional disorder	4
	Suicidal ideation	4
	Crying	3
	Feeling abnormal	3
WHO-UMC causality assessment	Probable	1
	Possible	1
	Unassessable	13¶

* 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 report may have one or more serious outcome.

† "New" was defined as onset of neuropsychiatric symptoms after montelukast discontinuation. "Continued" was defined as neuropsychiatric symptoms during montelukast therapy that persisted or recurred after montelukast discontinuation.

‡ A case was assessed as stimulated if a consumer reported that montelukast had a potential causative role in the development of adverse event due to information received outside a health care setting. Some cases specified that the information linking montelukast to neuropsychiatric withdrawal symptoms was derived from the internet (n=2) and other unspecified sources (e.g. "news reports" n=4).

§ These reports described a constellation of symptoms that included symptoms that were neuropsychiatric in nature.

¶ We were unable to assess causality in cases due to insufficient information including information regarding clinical course, dechallenge trials, rechallenge trials, temporality, neurodevelopmental history, family history, concomitant mediations, or diagnostic evaluation.

Medical officer comment: *We identified 15 cases of neuropsychiatric symptoms after montelukast withdrawal. Six of the 15 cases described patients who developed new-onset neuropsychiatric symptoms after montelukast discontinuation and nine described patients who developed symptoms during montelukast use which continued or recurred after montelukast discontinuation. Of the 15 cases, two reported that montelukast was restarted after the patient developed neuropsychiatric withdrawal symptoms and both had symptom resolution (positive dechallenge). One of the two cases (case 8522762) discontinued montelukast again and developed recurrent neuropsychiatric symptoms (positive rechallenge). The cases demonstrated a temporal association with montelukast discontinuation with the time to onset of neuropsychiatric symptoms ranging from 0 to 9 days after montelukast discontinuation.*

Most cases were reported by consumers after the 2008 labeling change that included neuropsychiatric events to the WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS section of the montelukast product label. Seven cases reported by consumers noted that montelukast was suspected in the events after obtaining information outside of the health care setting. Two of the seven cases involved patients who used montelukast for prolonged periods (2 years n=1, 5 years n=1) and the remainder (5/7 cases) involved patients who took montelukast for less than 4 months.

The most common neuropsychiatric symptoms reported after montelukast discontinuation included anxiety, abnormal behavior, aggression, fear, suicidal ideation, crying, and feeling abnormal. These symptoms are consistent with the information provided in the current montelukast product labeling, however, the labeling does not specify timing of neuropsychiatric symptom onset relative to time of drug use. Nine cases suggested that the patient sought medical evaluation after symptom onset (new onset n=5, continued onset n=4), but did not provide details of the specific workup for the neuropsychiatric events. None of the cases provided information about the patient's social and neuropsychiatric history which would help strengthen the causality assessments.

FAERS Case #7006890, Other serious important medical event, Foreign, 2009: A physician reported that a 9-year-old boy with a history of dyslexia and asthma experienced neuropsychiatric symptoms with the use of montelukast. The patient started montelukast 5 mg chewable tablet and fluticasone proprionate for the indication of asthma. One month later, he experienced anxiety and stomach aches and began to be sent home from school every morning. Two months after initiating montelukast, he discontinued both montelukast and fluticasone for an unspecified reason but had to resume therapy with both medications because of asthma exacerbations; there is no information regarding the patient's symptoms during the period off medication. Allergy testing at the time revealed a significant reaction to grass and fungi. The patient experienced depression, suicidal ideation, separation anxiety, and extreme situational anxiety in dark environments which prevented him from sleeping. Symptoms did not abate with incentives such as a new puppy or Christmas presents. Four months after montelukast initiation, he stopped going to school due to symptoms and could not engage in simple conversation as he complained he "could not think straight," therefore would feel frustrated and cry. His parents put him on "suicide watch" as he spoke of death and suicide daily. Five months after montelukast initiation, the parents read reports of other children with similar symptoms with montelukast use and they discontinued the patient's montelukast therapy after discussion with the patient's primary care doctor. Within three days of montelukast discontinuation, the patient was smiling again and able to sleep. On day five of montelukast discontinuation, the patient appeared to "shut down," was sad, and began screaming that "he could not control his head," and reported visual hallucinations. The withdrawal symptoms resolved the next day and the patient's condition continued to improve over three weeks after medication discontinuation. The patient started attending school again two months after montelukast discontinuation without further complications.

Reviewer comment: *This case described a patient who developed neuropsychiatric symptoms during montelukast therapy that initially improved once montelukast was discontinued. However, the patient's neuropsychiatric symptoms returned a few days later. The case narrative does not offer details about the patient's reaction to his first trial of montelukast discontinuation 2 months after the start of therapy. This case lacks information on the physician's clinical evaluation or diagnostic workup to help rule out differential diagnoses (e.g. underlying anxiety disorder, maladjustment to family changes, poor sleep quality).*

FAERS Case #8522762, Other serious important medical event, USA, 2012: A mother reported that her 5-year-old son started montelukast therapy for nasal congestion and inflammation. The patient tolerated montelukast well. The patient missed one dose of the

montelukast one night and developed visual hallucinations of bugs crawling on his skin and an acute and severe anxiety episode. The same symptoms recurred when the patient missed a dose of montelukast on two separate occasions. Information about the patient's past medical history and developmental history was unavailable. The patient's mother contacted the prescribing allergist, but no workup was performed.

Reviewer comment: *The patient developed neuropsychiatric symptoms of hallucinations and anxiety with missed montelukast doses. The case does not provide details about the timing of montelukast administration and the number of hours that elapsed prior to the development of hallucinations and anxiety, which is important when evaluating the case.*

3.2 CASE REPORTS LITERATURE RESULTS

Our literature search did not yield any published case reports meeting the case definition in Section 2.1.1.

The letter to OPT referred to one publication by Haarman et al.[g], which retrospectively explored adverse events in children and adults reported to the Netherlands Pharmacovigilance Centre Lareb and the WHO Global Individual Case Study Report (ICSR) database, Vigibase, until 2016.[23] The aim of the study was to obtain insight into the safety profile of montelukast by describing the reports in the two databases and performing disproportionality analyses to identify signals. Causality between a drug and adverse event cannot be inferred from disproportionality analyses. The Netherlands Pharmacovigilance Centre Lareb database contained 331 adverse events reported with montelukast; the database contained at least one serious report of excoriation, however no additional information is provided on the report (this report is specifically mentioned in the letter to OPT). VigiBase contained 17,723 reports with montelukast. Disproportionality analyses revealed high reporting odd ratios (RORs) for neuropsychiatric adverse events (such as depression, aggression, suicidal ideation, abnormal behavior, and nightmares). However, the identified adverse events are already contained in LTMA product labeling and findings from this study do not add to the discussion of the adverse events of interest in this review.

3.3 OBSERVATIONAL LITERATURE RESULTS

The original search examined articles published from January 1, 2014, as a continuation of RCM# 2014-585, until January 5, 2018. After the removal of duplicates, the literature searches included 59 publications (including conference abstracts). The literature search excluded 57 studies:

- Non-human studies (n=4) [24-27]
- Case reports and case series (n=7) [28-34]
- Clinical studies (n=1) [35]
- Commentaries and reviews (n=11) [36-46]
- Does not include montelukast (n=4) [47-50]

[g] This study was not retrieved in our literature search because we restricted the search to retrieve case studies or case series only.

- Did not formally examine an association between montelukast, LTMAs, and the outcomes (n=17) [51-65]
- Ecological study (n=1)[66]
- Examines effectiveness (n=2) [67,68]
- In vitro, in silico, and bench studies (n=6) [69-74]
- Literature review and meta-analysis (n=2) [75,76]
- Sample size <100 (n=2) [77,78]
- Spontaneous reporting system (n=2) [79,80]

Upon review of references, the literature review by Law et al. (2017) and a paper by Schumock et al. (2012) were often cited as providing important evidence in the association between montelukast and NE.[81,82] Although our original search was limited to 2014, the Schumock paper was later included despite being published in 2012. An additional search of PubMed and Web of Science for articles published between January 1, 2012 and December 31, 2013 resulted in six additional articles, none which met the literature review criteria.[65,83-87] Jick et al. (2009) was also a frequently cited article, but this study provided only crude incidence rates and did not formally study an association between montelukast and neuropsychiatric events.[88]

In total, four studies provided data analysis germane to the association between montelukast use and neuropsychiatric outcomes:

- Schumock et al. (2012) - Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study[82]
- Chen et al. (2014) - Asthma and self-harm: a population-based cohort study in Taiwan[89]
- Ali et al. (2015) - Exploring the possible association between Montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study[90]
- Bénard et al. (2017) - Neuropsychiatric adverse drug reactions in children initiated on Montelukast in real-life practice[91]

The study designs, descriptions and results are provided in Appendices D and E.

3.3.1 Cohort Studies

3.3.1.1 Chen et al. (2014) [89]

3.3.1.1.1 Methods

3.3.1.1.1.1 Study conduct

This study was conducted at the Chung Shan Medical University Medical Hospital. No IRB approval was needed. Authors disclosed no conflict of interest.

3.3.1.1.1.2 Objectives

The primary objective of Chen et al.'s study was to examine the association between asthma and risk of non-fatal self-harm.

3.3.1.1.1.3 Design, data source, and population

They conducted a retrospective national cohort study using data from Taiwan National Health Insurance Database. Eligible subjects were age 10 years and above presenting with asthma between 2000-2008. Incident asthma subjects were defined by at least two ICD-9-CM code (493.xx), within a year in the outpatient setting, excluding patients with any asthma diagnosis claim from 1997 to 1999. Non-asthma patients were selected from the database between 2000-2008 and matched 5:1 to asthma patients by sex, age within 1 year. Non-asthma subjects were assigned the diagnosis date of the matched asthma patient (Appendix E). The date of asthma diagnosis or matching served as the index date.

3.3.1.1.1.4 Exposure

Prevalent montelukast usage cumulative defined daily dose (cDDD) was categorized as 0-90 cDDD and ≥90 cDDD. Montelukast exposure was a covariate.

3.3.1.1.1.5 Outcome

The study outcome was self-harm defined by the ICD-9-CM codes E590-E959 (self-harm causes) and E980-E989 (undetermined causes). Deaths within 2 weeks of self-harm were classified as suicides and excluded from the analysis (n=2).

3.3.1.1.1.6 Follow-up

The matched asthma and non-asthma subjects were followed from index date to outcomes, death, migration or end of study.

3.3.1.1.1.7 Statistical Analysis

The risk of self-harm between the asthma and non-asthma patients was analyzed using modified cox regression analysis (using the Fine and Gray method) to accommodate the issue of competing risk with death. Since death was a censoring criterion, the experience of self-harm was not observed if a patient was censored on death. Competing risk adjusted hazard ratios with 95% confidence intervals for montelukast and the other covariates were calculated. The study results were stratified on the following covariates: age, sex, ethnicity, urban/rural, insurance premium (low SES), montelukast treatment, personal psychiatric disease, and Charlson Comorbidity Index (CCS). The study did not control for asthma severity or asthma control.

3.3.1.1.2 Results

There were 27,781 subjects with asthma and 138,905 age- and sex- matched controls. Asthma subjects were more likely to be sicker (higher CCS) and have a history of mental disorder than the non-asthma controls. Four hundred forty-five subjects reported self-harm; 133 (0.5%) were asthma cases and 312 (0.2%) were non-asthma controls. Of the asthma subjects, 710 (2.6%) used montelukast ≥90 cDDD compared to 16 (0.01%) in the non-asthma controls. The mean follow-up for all subjects was 5.8 (standard deviation [sd]: 2.4) years.

The crude risk of self-harm comparing asthma patients to non-asthma patients was 2.03 (95% CI = 1.94 – 2.5) and 2.12 (95% CI = 0.68 - 6.62) for subjects on montelukast ≥90 cDDD compared to patients 0-90 cDDD. In the fully adjusted Cox regression model for competing risk analysis, asthma was positively associated with self-harm (hazard ratio [HR]= 1.70, 95% CI = 1.35–2.14), but montelukast use ≥90 cDDD was not associated with self-harm (adjusted HR=0.92; 95% CI =

0.29 – 2.91). Additional factors associated with self-harm incidence were rural residence, psychiatric disorder diagnosis and higher CCS.

No significant interactions were found between asthma and age group on self-harm (p=0.108). No analyses were conducted regarding the association between montelukast and self-harm by age groups.

3.3.1.2 Bénard et al. (2017)[91]

3.3.1.2.1 Study conduct

The study was funded and conducted by the Sainte-Justine University Health Centre (Canada). The study was approved the IRB. Subjects' parents provided consent to enroll in the Pediatric Asthma Database and Biobank and additional consent to be interviewed.

3.3.1.2.2 Objective

The primary objective of Bénard et al.'s study was to determine the incidence and relative risk of "neuropsychiatric adverse drug reactions" (ADRs) leading to discontinuation of montelukast as compared to ICS, in children with asthma. The secondary objective was to describe the characteristics and determinants of neuropsychiatric ADRs leading to drug cessation.

3.3.1.2.3 Design, data source, and population

Bénard conducted a survey within a population of subjects previously exposed to montelukast and ICS at the Sainte-Justine University Health Centre, Canada. Eligible subjects were ages of 1-17 years with a physician-confirmed diagnosis of asthma between February 2011 – April 2016. Parents of both the ICS and montelukast subjects were contacted by telephone in the summers of 2014, 2015, and 2016 using standardized, non-leading interviews to collect demographic, clinical history, drug use history, neuropsychiatric events, and family clinical history data. After the interviews were complete, a blinded adjudication committee reviewed structured coded reports of all possible neuropsychiatric events to assess the probability of their drug association (unlikely to definitely) using the Naranjo score.[92]

3.3.1.2.4 Exposure

Montelukast initiators were defined as subjects initiating montelukast as monotherapy or adjunct therapy to ICS or ICS (beclomethasone, fluticasone, ciclesonide or budesonide) with LABA. ICS monotherapy initiators were selected from the database between the same timeframe.

3.3.1.2.5 Outcome

The study outcome, identified from the questionnaires, was neuropsychiatric adverse drug reactions (ADR) leading to discontinuation of the drug (dechallenge) and after restarting the drug (rechallenge). The secondary outcomes included the incidence and characteristics of all neuropsychiatric ADRs.

3.3.1.2.6 Statistical analysis

Within the montelukast cohort, the study assessed the incidence of neuropsychiatric events leading to cessation. Using modified multivariate logistic regression, the study assessed the relative risk (RR) of neuropsychiatric events leading to cessation in the montelukast subjects vs.

the ICS subjects. The study controlled for age, sex, ethnicity, asthma control, phenotype, personal and family predisposing behavioral problems, and time between drug initiation and interview as well as baseline group differences.

A *post hoc* analysis within unmatched nested cohort was conducted between ICS patients and 1) montelukast monotherapy patients and 2) montelukast adjunct therapy to ICS or ICS/LABA patients. A sample of 100 montelukast initiators would allow the study to detect a ≤18% incidence with a two-sided 95% CI width of 0.15. The primary outcome to the cohort study with a 95% CI was analyzed using Poisson regression. Three sensitivity analyses were conducted, including an analysis of definite and probable drug related cases.

3.3.1.2.7 Study Results

There was a median delay of 3 years between drug initiation and the parent interview. Of 223 subjects who initiated montelukast, 106 had parents who completed the interview. Non-responder and responders were roughly comparable, except responders were more likely to be Caucasian. The median age of the subjects was 5 (IQR – 3-8) years old. More than a third (37%) of children initiating montelukast had predisposing conditions, namely attention deficit hyperactivity disorder (ADHD) (20%) and depression (6%). In total, there were 106 subjects on montelukast (84 were matched; 22 patients with adjunct ICS therapy were not matched) and 132 on ICS (84 were matched).

Twenty-five subjects reported neuropsychiatric ADRs (24%) with the most frequent being irritability (n=9), aggressiveness (n=8) and sleep disturbances (n=7; Appendix C). Seventeen (16%) subjects stopped montelukast due to neuropsychiatric ADRs; 13 (12%) were adjudicated as definite/probably related. The average neuropsychiatric event was very mild to mild and there were no reports of suicidal ideation. The median time from treatment to ADR onset was 7 (interquartile range [IQR] 2-14) days and disappeared within 2 (IQR 0 – 3.5) days of initiation.

When adjusting for potential confounders with the nested-matched controlled population, the relative risk (RR) of neuropsychiatric ADRs leading to cessation in montelukast overall vs. ICS was 12.0 (95% CI = 1.6 – 90.2) and 9.0 (95% CI = 1.2 – 69.5) when only probable/definite drug related events were evaluated (Table 7). The *post hoc* analysis within unmatched nested cohorts showed the RR of ADR-related cessation was 5.9 (95% CI = 1.5-22.5) with montelukast as monotherapy, and 7.1 (95% CI = 2.1 – 23.4) with adjunct therapy compared to ICS monotherapy (**Table 8**). None of the potential confounders (i.e. age, race, asthma control, predisposing condition) were significant risk factors in any of the nested cohort analyses.

Children in whom neuropsychiatric ADRs were probably or definitely associated with montelukast use, non-Caucasian race (adj. RR = 3.38; 95% CI = 1.15 – 9.96) and cotreatment with ICS and LABA (6.77; 95% CI = 1.84 – 24.91) significantly increased the odds. No other potential confounders, including age, were significant.

Table 7. Risk of neuropsychiatric events per study analyses

	Chen (2014) Adjusted HR (95% CI)	Bénard (2017) Adjusted RR (95% CI)
Outcome	Self-harm	Neuropsychiatric ADR leading to drug cessation
Population, N	27,781 asthma subjects vs. 138,905 non-asthma subjects	84 montelukast users vs. 84 ICS monotherapy users
MON Use ≥90 cDDD vs. <90 cDDD (Chen)		
MON Use vs. ICS monotherapy (Bénard)	0.92 (0.29 - 2.91)	9.00 (1.2 – 69.5)
Asthma vs. No asthma	1.70 (1.35 – 2.14)	all subjects had asthma
Age vs. 10-24 years (Chen)		n.s. per 1 year increment
25-44	1.18 (0.84 – 1.65)	
45-64	0.77 (0.55 – 1.08)	
≥65	0.49 (0.33 – 0.72)*	
Personal psychiatric or behavioral problems	2.01 (1.37 - 3.93)*	n.s.
Rural vs. Urban	1.41 (1.13 - 1.76)*	not examined
CCS per 1 unit increase	1.07 (1.02 - 1.11)*	not examined
Female vs. males	n.s.	n.s.
Non-Caucasian vs. Caucasian race	Taiwanese population	n.s.
Asthma control or severity	not examined	n.s.
Phenotype	not examined	n.s.
Family psychiatric or behavioral problems	not examined	n.s.
Low income vs. highest income	n.s.	not examined

KEY: ADR – adverse drug reaction, CI – confidence interval, HR – hazard ratio, ICS – inhaled corticosteroid, MON – Montelukast, CCS – Charlson Comorbidity Index, n.s. not significant
* P<0.05

Table 8. Incidence and Adjusted Relative Risk of Neuropsychiatric ADR leading to montelukast cessation in the Bénard study

Use of Montelukast	MON Incidence, % (95% CI)	ICS monotherapy Incidence, % (95% CI)	Final Model, Adjusted RR (95% CI)**	NNH‡
MON mono or adjunct therapy with matching*	14 (8-25)	1 (0-8)	12.00 (1.6-90.2)	7.7
MON mono or adjunct therapy with matching (Probably/Definitely Drug Related)§	11 (6-21)	1 (0-8)	9.00 (1.2-69.5)	10
MON mono or adjunct therapy without matching	16 (10-26)	2 (1-7)	7.1 (2.1-23.4)	7.1
MON monotherapy without matching	13 (6-30)	2 (1-7)	5.9 (1.5-22.5)	9.1

KEY: ADR – adverse drug reaction, ICS – inhaled corticosteroid, MON – Montelukast, NNH – number needed to harm, RR – relative risk
Notes: Adjunct therapy to ICS or ICS/LABA
§ Ascertained as definite (⩾9; n=0) or probably (5–8; n=13) drug related on the Naranjo causality scale.
‡ Number needed to harm (NNH) calculated by OSE reviewer.
* Nested matched cohort of 84 montelukast exposed and 84 montelukast unexposed subjects matched within 90 days of the drug initiation date.
** None of the potential confounder of the subject (age, sex, ethnicity, asthma control, phenotype, personal and family predisposing behavioral problems) and treatment- (delay between drug initiation and interview) were significant determinates in the multivariate logistic model.

3.3.2 Nested-Case Control Studies

3.3.2.1 Schumock et al. (2012)[82]

3.3.2.1.1 Study conduct

This study was conducted at the University of Illinois at Chicago. The co-author, T.A. Lee, is a consultant for Merck and Forest Pharmaceuticals and has received research support from Novartis.

3.3.2.1.2 Objective

The objective was to examine the association between asthma and attempted suicides.

3.3.2.1.3 Design, data source, and population

Schumock et al. conducted a retrospective cohort study with a matched nested-case control study in subjects age 5-24 years in the LifeLink Health Plan Claims database within the US. A cohort of subjects with a primary diagnosis of asthma who were new users of LTMA or other asthma medications between 1997 – 2006 were identified.

Asthma was defined by at least one ICD-9-CM code (493.xx). The date of the first claim for the asthma controller medication was the index date. Within this cohort were patients with self-harm (cases) matched to controls (those at risk for self-harm; see section 3.3.2.1.5).

3.3.2.1.4 Exposure

LTMA exposure was described by at least 1 prescription claim for ICS, LTMAs, LABAs, methylxanthines, immunomodulators, mast cell stabilizers, and inhaled anticholinergics 1 to 180 days before index date. Because LTMAs are also prescribed for allergic rhinitis or off-label indications, subjects were excluded if there were more than 30 days between the asthma diagnosis date and prescription index date.

3.3.2.1.5 Cases and controls

Cases were defined as subjects with self-harm events occurring at least 1 day after the index date. The following IDC-9-CM codes defined self-harm:

- E950 to E952: self-inflicted poisoning
- E953: self-inflicted injury by hanging
- E954: drowning
- E955: self-inflicted injury by firearms
- E956: self-inflicted injury by cutting
- E957: self-inflicted injury by jumping from high places
- E958: other/unspecified self-inflicted injury
- E959: late effects of self-inflicted injury

Ten controls at risk for a neuropsychiatric event on the same date as the corresponding case were matched without replacement to each case based on age groups (5-11, 12-18, and 19-24 years), gender and geographic region (East, Midwest, South and West), and assigned a matching index date of the case (Appendix E).

3.3.2.1.6 Statistical analysis

Conditional logistic regression was used to estimate unadjusted and adjusted odds ratio (OR) and 95% CI. The study controlled for asthma severity, prognostic factors of self-harm (substance abuse disorders, bipolar disorder, depression, schizophrenia, other mental disorders, human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), malignant neoplasm/cancer, epilepsy, irritable bowel disease, migraine headaches, multiple sclerosis, renal disease, lupus, chronic pain, and allergic rhinitis). The study also controlled for drugs associated with an increased risk of self-harm: anticonvulsants, antidepressants, antipsychotics, hypnotics, anxiolytics, and isotretinoin.

3.3.2.1.7 Study results

There were 344 cases and 34,238 matched control subjects. Three quarters of the subjects were between the ages of 12-18. Cases were more likely than control subjects to have greater risk factors for suicide attempts such as previous suicide attempts and a history of depression (67.2% vs. 5.56%, respectively, $p<0.001$), other mental disorders (50.0% vs. 6.3%, respectively; $p<0.001$), receive psychological counseling, and use medications associated with suicide such as antidepressants, antipsychotics, and anticonvulsants. Cases were more likely to use ≥3 short acting beta-agonist inhalers in the past 6 months (10.5% vs. 3.3%, respectively ($p<0.05$). Cases were similar to control subjects with respect to asthma severity.

Among cases, 5.52% were using LTMAs, primarily montelukast, at the time of the self-harm event as compared to 6.52% control subjects. The adjusted risk of self-harm with LTMA use ever was 0.70 (95% CI, 0.36-1.39), not controlling for other asthma medications. No dose-response relationship was observed. When stratified by age, the risk of self-harm with LTMA use was 5.15 (95% CI = 1.16 - 22.86) in subjects aged 19-24 years. A revised adjusted model which "reassessed the covariates" and accounted for other asthma medications and other drugs associated with suicide within this age-group showed an adjusted OR of 5.64 (95% CI = 0.87-36.66).

3.3.2.2 Ali et al. (2015)[90]

3.3.2.2.1 Study conduct

This study was conducted at the University of Arkansas for Medical Sciences and was approved by the University's IRB. The authors disclosed no conflict of interest.

3.3.2.2.2 Objective

The objective was to examine the association between asthma and neuropsychiatric events (NE as abbreviated by the authors).

3.3.2.2.3 Design, data source, and population

Ali et al. conducted a retrospective cohort study with a matched nested-case control study in subjects age 1-17 in a 10% sample of the LifeLink Health Plan Claims database within the US. Subjects with a primary diagnosis of asthma between 1998 – 2009 were identified. Asthma was defined by at least one ICD-9-CM code (493.xx), and year duration of asthma in outpatient services. Patients with a NE within a year before their asthma diagnosis were excluded. The date of the first claim of the NE was the index date.

3.3.2.2.4 Exposure

Montelukast exposure was described by at least one prescription claim for montelukast within 365 days before the index date. There were four measures of montelukast exposure: any exposure, regency of exposure, treatment duration, and chronic cumulative dose.

3.3.2.2.5 Cases and controls

Cases were defined as subjects with a neuropsychiatric outcome of interest occurring. NEs were classified using four *a priori* defined case definitions ranging from broad to narrow:

1) Neuropsychiatric disturbance (ND) was a primary or secondary diagnosis of mental illnesses, extrapyramidal and abnormal movement disorders, and hallucinations.
2) Psychiatric disorder diagnosis (PDD) was an incident medical claim of a psychiatric disorder. i.e. adjustment disorders, miscellaneous mental disorders, etc.
3) NE diagnosis was a psychiatric disorder mapped to a specific labeled disorder i.e. conduct disorders, anxiety disorders, etc.
4) Psychotropic medication receipt was an incident prescription for a psychotropic medication after index date.

NE diagnoses were based on at least one claim with a primary or secondary diagnosis of a psychiatric disorder (ICD9-CM code) or any psychiatric disorder identified within the CCS (e.g. dementia and depression). Controls without a NE diagnosis were matched 3:1 without replacement to each case based on age, gender and geographic region, and assigned a matching index date within 1 year of the case.

3.3.2.2.6 Statistical analysis

Conditional logistic regression was used to estimate unadjusted and adjusted odds ratio (OR) and 95% CI. After the initial analysis, a second set of models were created for the three age groups (1-5 years, 6-14 years, and 15 years plus) using the appropriate age-based dosing. The study controlled for asthma severity, low socioeconomic status, prognostic factors of psychiatric disorders (allergic rhinitis, CCS, child-abuse, and drug exposures including theophylline, short-acting and long-acting beta agonists, inhaled corticosteroids, anticonvulsants, metoclopramide, zafirlukast and zileuton).

3.3.2.2.7 Study results

There were 1920 cases with ND (100%), 1637 cases with PDD (85.3%), 1007 cases with NE diagnoses (52.5%) and 392 with a psychotropic medication receipt (20.4%). Each case had 3 matched controls. At baseline cases were more likely than controls have a history of a psychiatric disease (7.6% vs. 3.1%, respectively; $p<0.001$) and self-harm (0.5 vs. 0.2%, respectively $p<0.001$). Cases were also more likely than controls to be diagnosed with allergic rhinitis, cancer, or hypothyroidism, were more likely to use ICS or LABAs, and have more severe asthma ($p<0.05$).

The review results will focus on ND and NE diagnosis cases. More than half of the subjects experiencing ND were 6–14 years of age (n=1086; 56.6%). The most frequently recorded neuropsychiatric diagnosis events were adjustment disorders (n=337; 17.6%), attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) (n=323; 16.8%), and aggressive disorders including conduct disorders and oppositional defiant disorders (n=153; 8.0%).

Subjects with any exposure to montelukast in the prior year had an adjusted OR of 1.01 (95% CI =0.88 -1.14) for experiencing ND compared to no exposure (**Table 9**). Subjects exposed to moderate cumulative doses of montelukast in the prior year (481–1050 mg) had an adjusted OR=1.27 (95% CI=1.03 - 1.57) compared to no exposure. Exposure to high cumulative doses (>1050 mg) had lower odds (OR=0.64; 95% CI= 0.50 - 0.82) of experiencing ND compared to no exposure. Subjects with a treatment duration greater than 180 days had lower odds of experiencing ND (OR=0.75; 95% CI=0.59 - 0.95) compared to those with a shorter duration of treatment. No association between montelukast and ND was observed when stratified by age groups.

Post hoc analyses among specific NE diagnoses showed that montelukast use was only associated with an increased risk of adjustment disorder diagnoses for moderate cumulative doses (OR=1.80; 95% CI=1.10 - 2.94) compared to no exposure and treatment durations of 31–90 days (OR=1.84; 95% CI=1.16 - 2.92) compared to no treatment.

Table 9. Results from the case-control studies by exposure duration, dosage, and age

Author Covariates	**Adjusted Odds Ratio** **(95% Confidence Interval)**
Schumock	**Suicide attempt**
Any exposure to leukotriene-modifying agents (6 months)	0.74 (0.46 - 1.20)
<=60 leukotriene-modifying agent equivalents (dosage)	0.64 (0.32 - 1.28)
>60 leukotriene-modifying agent equivalents	0.54 (0.23 - 1.30)
5-11 years of age	0.78 (0.03 - 18.09)
12-18 years of age	0.47 (0.20 - 1.09)
19-24 years of age	5.15 (1.16 - 22.86)*
19-24 years adjusting for more medication exposure	5.64 (0.87 – 36.66)
Ali	**Neuropsychiatric Diagnosis**
Any exposure to montelukast vs. no exposure (1 year)	1.01 (0.86 - 1.18)
Low dose	1.14 (0.91 – 1.41)
Modest dose	1.04 (0.84 – 1.29)
Moderate dose	1.27 (1.03 – 1.57) *
High dose	0.64 (0.50 – 0.82) *
<=180 days treatment duration	n.s.
>180 days treatment duration	0.75 (0.59 - 0.82)*
1-5 years of age	0.96 (0.69 - 1.35)
6-14 years of age	1.09 (0.92 - 1.28)
15-18 years of age	0.84 (0.64 - 1.09)
KEY: n.s. – not significant for any of the duration exposure categories <=180 days * P<0.05	

3.3.3 Discussion

The objective of the literature review was to examine if there was an association between montelukast use and neuropsychiatric events including those that occur after montelukast discontinuation. One cohort study (Bénard et al., 2017) et al. showed a >9-fold increased risk, but contained numerous systematic biases which could have resulted in an overestimation of the

risk.[91] The three remaining studies, including one cohort study (Chen et al., 2014) and two case-control studies (Ali et al., 2015 and Schumock et al., 2012), showed a null association. [82,89,90]

The cohort studies by Chen and Bénard were of relatively lower quality and will not be included in the discussion for the reasons discussed below (**Table 10**).

The study by Chen was designed to examine the difference in the risk of self-harm between asthma and non-asthma patients; it was not designed to test an association between montelukast use and neuropsychiatric events. Second, the study examined prevalent users of montelukast, so any montelukast associated neuropsychiatric event which occurred before baseline would not be captured as a study outcome (underestimation of incidence). Finally, the study failed to account for two important confounders - asthma severity and ICS/LABA adjunct therapy. Both confounders are measures of increasing asthma severity (a risk factor for self-harm) which is associated with receiving montelukast or montelukast plus ICS/LABA as 2nd line therapy.

Although Bénard's study was highly publicized for finding a 9- to 12-fold increased risk of neuropsychiatric events with montelukast use, the study had a considerable amount of bias which warrants further discussion.[93] First, the parent interviews were conducted after the 2008 labeling changes and approximately 3 years after drug initiation. The 2008 label informed a prescriber to instruct montelukast users "to be alert for neuropsychiatric events," although ICS users received no such instructions. Thus, parents with children on montelukast compared to ICS might be more likely to report and/or recall a neuropsychiatric event (or normal developmental change), relate it to montelukast use, and cease treatment. Second, the study was unable to validate whether the self-reported outcomes actually occurred, resulting in an overestimation of the risk. Given the 2008 labeling change, parents whose children used montelukast may have been more likely than parents of ICS users to report neuropsychiatric events, even if the events never occurred. Third, although the study was able to detect an increased risk of probable/definite neuropsychiatric ADRs leading to cessation (RR=9.0; 95% CI=1.2 – 69.5), this is based on only 12 events. As a result, the association between montelukast and neuropsychiatric events is imprecise and difficult to interpret as indicated by the very wide confidence intervals. Additionally, the magnitude of the association as indicated by the RR is likely overestimated due to bias.

Table 10. Quality assessment of reviewed studies

Assessments and Criteria	COHORT STUDIES			CASE CONTROL STUDIES	
	Chen	***Bénard***		***Ali***	***Schumock***
Newcastle-Ottawa Quality Assessment					
Selection			**Selection**		
Representativeness of exposed cohort	x	x	Adequacy of Case Definition	x	x
Selection of non-exposed cohort	x	x	Representativeness of Cases	x	x
Ascertainment of exposure	x	x	Selection of Controls	x	x
Study outcome was not present at start of study			Definition of Controls	x	x
Comparability			**Comparability**		
Adjust for other psychiatric or behavioral disorders	x	x	Adjust for other psychiatric or behavioral disorders	x	x
Adjust for asthma severity		x	Adjust for asthma severity	x	x
Outcome			**Exposure**		
Assessment of outcome	x		Ascertainment of exposure	x	x
Was follow-up long enough for outcomes to occur	x	x	Same methods of ascertainment for cases and controls	x	x
Adequacy of follow-up of cohorts			Non-response rate	x	x
Further Considerations of Reviewer					
Control for 2008 labeling changes	x		Control for 2008 labeling changes		x
Authors disclosed no relationship with LTMA manufacturers	x	x	Authors disclosed no relationship with LTMA manufacturers	x	
Powered to test association between montelukast and outcome			Powered to test association between montelukast and outcome		x
Incident use of MON		x	Incident use of MON	x	x
Assess treatment duration			Assess treatment duration	x	x
Adjust for monotherapy or ICS/LABA combination therapy in primary analysis		x	Adjust for monotherapy or ICS/LABA combination therapy in primary analyses		
Quality	Unsatis-factory	Unsatis-factory	**Quality**	Good	Good
Association	None	Positive	**Association**	None	None

KEY: ICS – inhaled corticosteroid, LABA – long acting beta-agonist, LTMA – leukotriene-modifying agent, MON – Montelukast

The nested case-control studies by Ali and Schumock were of high quality and were used to form the basis of the literature review's conclusions. Both studies had adequate sample selection, study group comparability, exposure and outcome assessment, and study power (**Table 10**). Additionally, these studies both examined incident montelukast users and assessed treatment duration. Though the same data source was employed in both studies there were differences in outcomes, study years, and age groups.

Despite the study strengths, both studies were limited by the inability to control for important risk factors for neuropsychiatric events such as alcohol use and family history of behavioral and psychiatric disorders. Since these factors are not known to be associated with montelukast, they are unlikely to confound the results. Also, Ali failed to control for the 2008 labeling changes. However, since the study period was from 1998 to 2009, any possible bias from a change in clinical practice or outcome detection would likely be minimal.

The following sections discuss additional considerations when interpreting the data from Ali et al. and Schumock et al.

3.3.3.1 The studies primary analyses do not control for salmeterol use which carries a labeled warning for neuropsychiatric events

Both studies examined the risk of neuropsychiatric events with montelukast use but failed to account for the risk of neuropsychiatric events due to LABA use, specifically salmeterol. Salmeterol carries a labeled warning regarding reports of "[a]gitation, aggression, depression. Behavioral changes, including hyperactivity and irritability, have been reported very rarely and primarily in children" and "[p]aresthesia, restlessness." It is unknown if the risk of neuropsychiatric events with LABAs, including salmeterol, is equivalent, greater than, or equal to that of montelukast. Thus, failure to control for salmeterol use or exclude those with montelukast combination therapy use could result in an overestimation of the risk of neuropsychiatric events with montelukast use.

3.3.3.2 Ali's study was not powered to detect an association between montelukast and neuropsychiatric events within subgroups

Ali's study was further used to examine risk factors for an adverse reaction to montelukast, but a post hoc sample size analysis of the Ali study revealed there was not adequate power to detect an OR of ≥1.25 (when exposure was 25%). The age-group and post-hoc analyses were only powered to detect an OR of ≥2.0; at most, the study only showed an OR of 1.09 within the 6-14 year age range.

Ali also failed to control for multiple comparisons within the subgroups (e.g., cumulative dose, treatment duration, regency of drug exposure, and specific neuropsychiatric events), thus the likelihood of finding a significant result increased due to random sampling error (Type I error). The study had 80 comparisons between varying exposure and outcome categories, of which seven were significant (four associations would be by chance with an alpha of 0.05). For instance, it was noted that compared to low cumulative doses of montelukast, exposure to moderate doses increased the risk of ND (OR=1.27, 95% CI=1.03 – 1.57) while exposure to high doses had a lower risk of ND (OR= 0.64, 95% CI=0.50 – 0.82). While there may be theories as

to why this information cannot be used to conclude a dose-response relationship, the reviewer cannot rule out that the significance of these values may be due to chance.

3.3.3.3 Schumock's study was partially sponsored by the makers of montelukast and did not fully disclose how a possible risk factor was reassessed

Schumock's study was also used to examine risk factors for adverse reactions to montelukast, but the authors did not fully describe how these risk factors were assessed. T.A. Lee, the last author of the Schumock article, is a consultant for Merck Pharmaceuticals, and Forest Pharmaceuticals (the makers of montelukast) and has received financial support from Novartis. The study's credibility is made questionable when the study reassessed the positive association between montelukast and neuropsychiatric events within the 19-24-year-old population (OR=5.15, 95% CI=1.16 – 22.86) until no further association was seen (OR=5.64, 95% CI=0.87 – 36.66). Specifically, the study "reassessed the covariates included in [the] adjusted model" and added "previous exposure to both other asthma medications and drugs associated with suicide." (Schumock, 2012, pg. 372) The authors do not specifically state what the reassessment of the covariates involved, so this reassessment may not be valid or necessary. It was, however, appropriate to adjust for medications associated with suicide which would result in a reduction of the original estimate. The study did not re-evaluate any findings that had a null association.

Like Ali et al., there were too few subjects (8 cases and 32 controls) to provide an accurate estimation of the risk within this age group as indicated by the wide confidence intervals. In sum, there is likely a positive association between montelukast and neuropsychiatric events within the 19-24 age group, but the magnitude of the association cannot be provided by this study. These results have not been replicated in other studies.

3.3.3.4 Both studies' exclusion criteria resulted in an underestimation of suicide

Both studies included only subjects with 12 months of continuous coverage after drug initiation, thereby excluding subjects who committed suicide within a year (immortal time). Thus, the low incidence of this already rare outcome may be further underestimated within these studies. The results from these studies cannot provide accurate risk estimates due to the potential under-capture of this outcome.

3.4 ONLINE SURVEY BY PETITIONER

3.4.1 Methods

The Facebook Montelukast (Singulair) Side Effect Support and Discussion Group co-managers and the Patients United for Pharmaceutical Safety sent an online survey to the Facebook Montelukast (Singulair) Side Effect Support and Discussion Group regarding Montelukast and adverse events. The survey was conducted from January 2017 to March 2017. Further details regarding study conduct were not provided.

3.4.2 Results

A total of 447 persons responded and 390 completed the questionnaire. Two-hundred fifty (250) respondents reported side effect symptoms to a medical physician after making a connection between side effect symptoms and montelukast. Seventy-six respondents reported side effects symptoms before making a connection between the side effects symptoms and montelukast. 76%

of respondents indicated that none of the side effect symptoms existed before starting treatment with Singulair.

The most regularly reported behavior and mood related side effects during use were:

- feeling anxious – n=292
- irritability – n=291
- agitation or aggressive behavior/hostility – n=280
- bad or vivid dreams (night terrors) – n=265
- insomnia (trouble sleeping) – n=238
- attention problems – n=235
- uncharacteristic hyperactivity/restlessness – n=222
- depression – n=217

One hundred twenty-three (123) patients reported suicidal thoughts with 19 suicidal actions and 1 completed suicide. At least 35 patients reported suicidal ideation after cessation of montelukast.

3.4.3 Comments from Reviewers

Results from the survey will not be used towards the discussion due to poor study quality. The DEPI-II reviewer noted that the survey results lacked formal statistical analyses and sampled patients known to have neuropsychiatric events from montelukast (sampling bias). The survey did not receive approval from an Ethics and Review Board (such as an IRB) to collect sensitive and reportable information such as suicidality. DRISK noted that the survey was not well-designed to study the association between montelukast and neuropsychiatric events. The survey was not protocolized, lacked a standardized structure, and provided no evidence that the survey was conducted by persons trained in study methodologies. DRISK further indicated that study results, though descriptive, were not sufficient to inform the association between montelukast and neuropsychiatric events. The lack of internal validity within this survey renders the study of low quality.

4 DISCUSSION

4.1 COMMONALITY OF NEUROPSYCHIATRIC EVENTS

The spontaneous adverse event reporting system, FAERS, cannot calculate the incidence of adverse events, thus cannot be used to describe the frequency of events as "common." The FAERS database continues to receive neuropsychiatric adverse event reports associated with the use of LTMAs in adults and children, of which the majority of reports mention montelukast use. The predominance of montelukast cases is likely due to the relatively higher use of montelukast as compared to the other LTMAs. Over the cumulative time period from March 2012 to September 2013, approximately 40.8 million montelukast prescriptions were dispensed and approximately 8.8 million patients received dispensed prescriptions for montelukast from U.S. outpatient retail pharmacies. Approximately 38% (3.3 million patients) were pediatric patients aged 0-16 years old.[10] The 41 cases identified in our FAERS database case series is relatively low in the setting of high drug usage.

4.2 ADDITION AND RECATERGORIZATION OF NEUROPSYCHIATRIC EVENTS

We support the addition of obsessive-compulsive symptoms or OCD-like behavior to the montelukast product label. The Sponsor of montelukast independently analyzed the association between montelukast and OCD; they concluded that an association between montelukast and obsessive-compulsive symptoms could not be ruled out because of the presence of multiple cases describing positive dechallenge, occurrence with other labeled neuropsychiatric events, and relatively short time to onset. The Sponsor intends to update the montelukast product label with obsessive compulsive symptoms. DPV-I's analysis of the FAERS database identified 23 cases of OCD-like behavior in the FAERS database from February 20, 1998 (U.S. approval of montelukast) to January 16, 2018. While causality is difficult to determine in the FAERS cases identified, the presence of some possible cases in the context of other labeled neuropsychiatric events suggests the addition of OCD symptoms/behavior to the existing warning is reasonable.

We cannot conclude that a causal relationship exists between montelukast and excoriation or hyperkinesia based on the current FAERS data and does not support addition to the product label. DPV-I identified zero cases of excoriation in the FAERS database. The Sponsor concluded that there were a low number (n=9) of excoriation cases reported from both the clinical trial and postmarketing data and the cases contained limited information or identified other risk factors for neuropsychiatric events. The factors which provided a likely alternative explanation for the excoriation included sun sensitivity leading to excoriation on hands and face while on vacation, "strong smelling urine causing excoriation" in an infant, excoriation accompanied by a rash and hives, excoriation in the setting of a pruritic rash, and perianal and vaginal excoriation which may have developed since the use of a different toilet paper in the setting of diarrhea. Lastly, the letter to OPT cited a single study by Haarman et al., which identified at least one serious report of excoriation in the Netherlands Pharmacovigilance Centre Lareb database, however no addition information was provided.[23] FAERS cases of hyperkinesia were limited in number (n=3) and lacked sufficient clinical detail to discern if the quality of the symptoms suggested any organic pathological condition. Furthermore, the cases of hyperkinesia did not provide sufficient information to rule out the behavior as normal in the context of the patient's developmental stage. The Sponsor's IR noted that there are several adverse events listed in the labeling consistent with hyperkinesia: psychomotor hyperactivity (including irritability, restlessness, and tremor), and tic. The cases of hyperkinesia reported from clinical trials and the postmarketing database do not describe any new aspects of increased muscle activity that are not covered by the terms already included as adverse events. The Sponsor concluded no new safety concern has been identified for montelukast as this event is adequately described in the current labeling.

Within the observational study by Ali, there were no reports of excoriation, hyperkinesia, OCD, or any additional unlabeled psychiatric events. Among 1007 cases of subjects with neuropsychiatric events, the most commonly reported events were disturbance in attention/ADD (24%) and restless/hyperactivity (17%). Concurrently, these two labeled events compose the trademark symptoms of hyperkinesia. Hyperkinesia is also marked by a greater magnitude of impairment and less impulse-control. However, Ali did not capture if the disturbance in attention and restlessness occurred together, nor the magnitude of these conditions. Thus, there is no observational evidence that these conditions should be reclassified as hyperkinesia.

4.3 DELAYED TIME TO ONSET OF NEUROPSYCHIATRIC EVENTS

There is insufficient information to update the label with a warning for possible delayed onset of side effects based on the FAERS analysis, observational data analysis, and Sponsor's analysis. The Bénard study, which was cited within the petition as observational evidence of delayed symptom onset within years of treatment, provides an inaccurate estimate of time to onset. The parents within this study were interviewed approximately 3 years after their children first used montelukast and ICSs. The average parent is not likely to accurately remember the exact timing of onset of the symptoms. Events which parents claimed to begin years after montelukast initiation may be attributable to other risk factors, life events, or developmental changes. Furthermore, the study authors never reviewed the pediatric subjects' medical records to confirm when and if the reported neuropsychiatric events actually occurred. These limitations, among others, seriously hinder the internal validity and lower the quality of evidence from the Bénard study to support delayed onset. The theory of delayed onset years after montelukast initiation cannot be supported by additional observational studies by Ali et al. and Schumock et al. since both studies examined psychiatric outcomes within one year of initiation.

4.4 RISK FACTORS FOR NEUROPSYCHIATRIC EVENTS

The FAERS data and observational studies were not appropriate for studying the risk factors for an adverse reaction with montelukast use. The FAERS case series (n=41) of hyperkinesia (n=3), OCD-like symptoms (n=23), and neuropsychiatric events following withdrawal of montelukast therapy (n=15) contained limited information and did not present an observable pattern to adequately characterize factors that would increase the risk for these adverse events.

The risk factors for adverse reactions with montelukast use are not well-studied in observational data. A 2012 study by Schumock et al. provided non-conclusive evidence that being between the ages of 19-24 posed a greater than 5-fold increased risk of suicide attempts with LTMAs use, primarily montelukast, compared to non-use OR=5.15 (95% CI = 1.16 - 22.86). However, there were too few subjects of this age group to provide an accurate estimate. No other well-designed observational studies have confirmed this association. The association between montelukast and the risk of suicides within this age group require further stringent investigation.

4.5 WITHDRAWAL FROM MONTELUKAST

Montelukast withdrawal effects were not systematically evaluated in clinical trials. The FAERS database cases are not a suitable data source to evaluate the appropriate way to discontinue montelukast. There is a lack of consistency among the FAERS cases of neuropsychiatric events after montelukast withdrawal. The analyses of the FAERS cases together with the Sponsor's database analysis in response to the IR do not provide the strength of evidence needed to support regulatory action. We identified 15 cases of neuropsychiatric symptoms after withdrawal of montelukast. The majority of cases (9/15) reported patients whose neuropsychiatric symptoms developed during montelukast therapy and continued after drug discontinuation; the remaining cases (6/15) reported new-onset neuropsychiatric symptom development after drug discontinuation. The most common neuropsychiatric symptoms associated with montelukast

discontinuation are listed in the WARNINGS AND PRECAUTIONS section of the montelukast product label, but the labeling does not specify the time of onset for neuropsychiatric events relative to montelukast therapy. Overall, there was a lack of consistency among the FAERS cases of neuropsychiatric events after montelukast withdrawal. The analyses of the FAERS cases together with the Sponsor's database analysis in response to the IR do not provide the strength of evidence needed to support regulatory action.

There is no well-designed observational study that examined the long-term safety of montelukast after discontinuation or described the process of withdrawal. The observational case-control studies within this review primarily examined the onset of neuropsychiatric events after the initiation of montelukast. Aside from completed suicide which is permanent, no reviewed study examined the long-term implications of the neuropsychiatric side effects.

4.6 MECHANISMS FOR MONTELUKAST'S NEUROPSYCHIATRIC SIDE EFFECTS

The FAERS database cases and the observational data cannot contribute to the understanding of the biological mechanisms behind the possible side effects. The FAERS cases do not contain sufficient information to add to the medical perspective on the biological mechanism for neuropsychiatric effects. Observational studies primarily examine the pharmaceutical safety with real world data and do not examine the biological mechanisms for adverse events.

5 CONCLUSION

OSE agrees with the Sponsor of Singulair to update the montelukast labeling to include obsessive-compulsive symptoms. The analysis of the FAERS database, case reports, and the observational data did not find sufficient data to support the addition of excoriation, hyperkinesia, or withdrawal neuropsychiatric events to the product label.

The observational studies do not provide conclusive evidence regarding the association between neuropsychiatric events and montelukast exposure in pediatric subjects. The data from the Schumock study is suggestive of an increased risk of self-harm in subjects aged 19-24 years; however, these results have not been duplicated in other studies. There is no observational evidence for montelukast regarding the safety of withdrawal, the duration of the neuropsychiatric events, and the sequelae from the neuropsychiatric events (e.g., suicidal ideation arising from depression).

6 RECOMMENDATIONS

OSE agrees with the Sponsor of Singulair to update the montelukast labeling to include obsessive-compulsive symptoms. Due to the constellation of neuropsychiatric symptoms with montelukast use, we furthermore recommended adding the phrase "including, but not limited to" as a precursor to sections of the label which describe neuropsychiatric adverse events.

Sentinel can serve as an observational data source to address existing knowledge gaps regarding montelukast and neuropsychiatric events. Specifically, DEPI is conducting an analysis in Sentinel (expected completion late 2018) to examine the clinically relevant determinants that may increase the risk of neuropsychiatric events in montelukast users.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (Mudra) 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 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.

8.2 APPENDIX B. DSM-V CRITERIA FOR OCD DIAGNOSIS

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):

1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):

1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

8.3 APPENDIX C. FAERS LINE LISTING OF OCD AND HYPERKINESIA CASE SERIES

OCD Case Series									
	Initial FDA Received Date	**FAERS Case #**	**Version #**	**Manufacturer Control #**	**Case Type**	**Age (years)**	**Sex**	**Country Derived**	**Serious Outcome(s)***
1	2003-11-18	7888585	1	2003040953	EXPEDITED	9	Male	USA	LT, OT
2	2001-03-26	3654488	1	WAES 01010487	NON-EXPEDITED	11	Male	USA	
3	2012-10-12	8838614	2	US-009507513-1210USA004771	EXPEDITED	9	Male	USA	DS
4	2013-01-12	9008977	1	US-009507513-0901USA02249	EXPEDITED	12	Male	USA	OT
5	2008-04-04	6614372	1		DIRECT	17	Male	USA	HO, LT
6	2008-03-31	6608062	1		DIRECT	10	Male	USA	OT
7	2008-04-21	6619508	1	US-MERCK-0804USA03105	EXPEDITED	5	Female	USA	OT
8	2008-04-04	6614100	1		DIRECT	7	Female	USA	LT, OT
9	2008-04-02	6612022	1		DIRECT	11	Male	USA	OT
10	2008-10-01	6776332	2	PR-MERCK-0809USA04519	EXPEDITED	13	Female	PRI	
11	2008-06-24	6692134	1		DIRECT	6	Male	USA	OT
12	2008-08-15	6740902	1		DIRECT	9	Male	USA	OT
13	2008-10-14	6792428	1		DIRECT	7	Female	USA	OT
14	2011-05-24	7979991	1		DIRECT	4	Male	USA	HO, RI
15	2009-06-01	7013757	1		DIRECT	25	Female	USA	OT
16	2009-07-14	7055988	1		DIRECT	61	Male	USA	DS
17	2012-03-20	8467820	1		DIRECT	3	Male	USA	OT
18	2012-09-26	8811533	1		DIRECT	8	Female	USA	OT
19	2015-01-02	10690494	1		DIRECT	4	Male	USA	OT
20	2010-05-28	7404176	1	US-MERCK-1005USA04087	EXPEDITED	9	Male	USA	OT
21	2009-04-14	6974054	1		DIRECT	10	Male	USA	OT
22	2012-05-17	8575068	1		DIRECT		Male	USA	OT
23	2008-05-13	6649140	1		DIRECT		Not Reported	USA	

Hyperkinesia Case Series

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	2009-08-17	7093416	1		DIRECT	3	Female	USA	OT
2	2012-08-07	8710423	2	US-009507513-1206USA03370	NON-EXPEDITED	2	Male	USA	
3	2004-04-27	4130975	1	ES-MERCK-0401ESP00023	EXPEDITED	3	Male	ESP	OT

Withdrawal Case Series

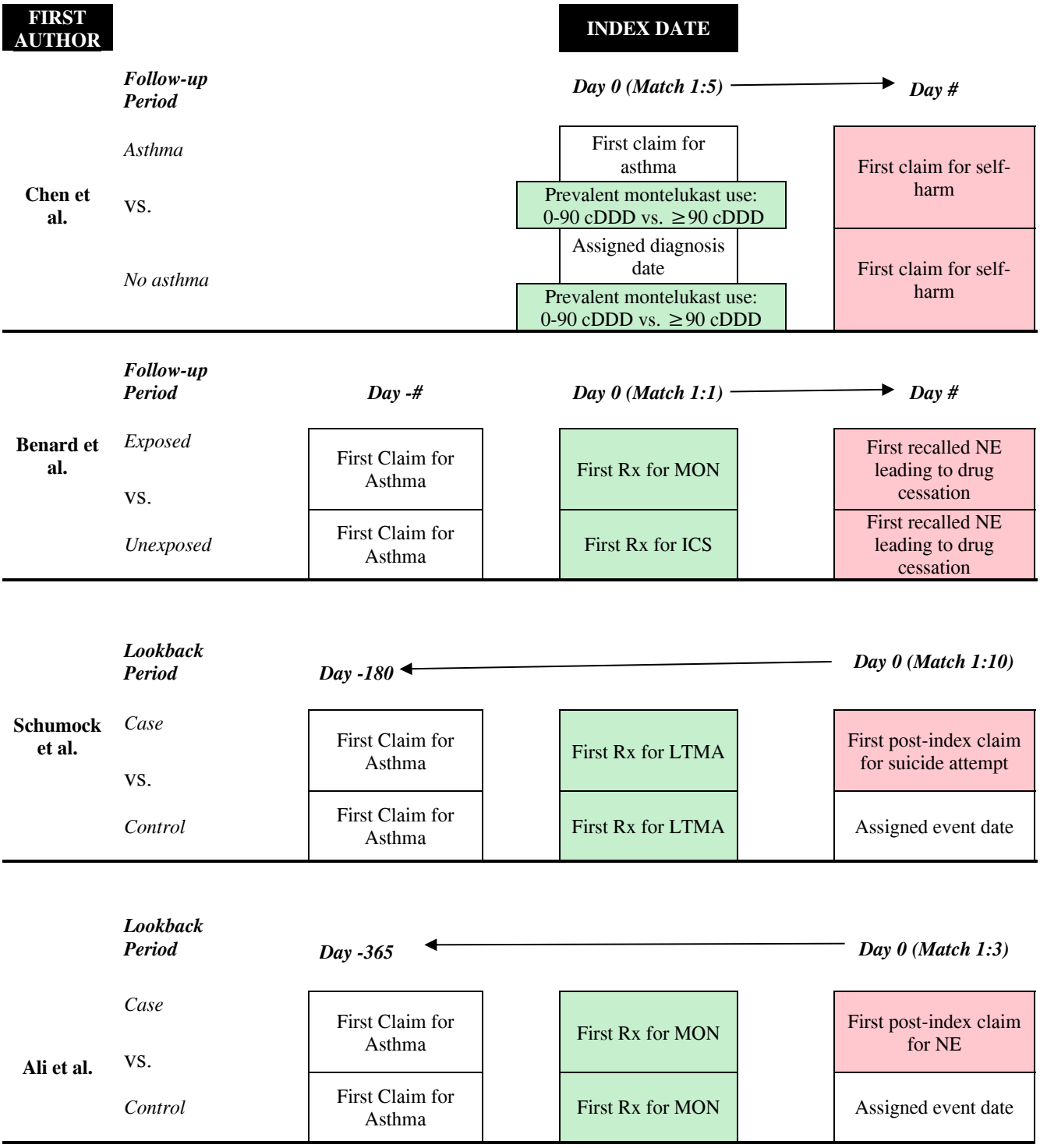
	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	2008-07-25	6710858	1	US-MERCK-0804USA03804	Expedited	12	Male	USA	OT
2	2009-04-30	6991197	1		Direct	11.94	Male	USA	
3	2009-05-29	7006890	1	GB-MERCK-0704GBR00253	Expedited	9	Male	GBR	OT
4	2010-04-08	7355325	1		Direct	3.27	Female	USA	OT
5	2010-06-30	7455392	1		Direct	44	Female	USA	
6	2011-06-20	8012263	1		Direct	7	Male	USA	OT
7	2012-04-19	8522762	1		Direct	5	Male	USA	OT
8	2012-05-29	8599830	1		Direct	4	Male	USA	
9	2013-01-10	9009932	1	US-009507513-1004USA01806	Expedited	33	Male	USA	LT,OT
10	2013-01-22	9025166	1	US-009507513-1301USA004456	Non- Expedited	5	Male	USA	
11	2015-01-06	10696218	1		Direct	56	Female	USA	OT
12	2015-06-30	11227304	1	US-009507513-1506USA012163	Non- Expedited	22	Female	USA	
13	2015-11-12	11737392	1		Direct	49	Female	USA	OT
14	2017-08-16	13887829	1		Direct	9	Female	USA	OT
15	2017-11-18	14204846	1		Direct	41	Female	USA	DS

*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, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant

8.4 APPENDIX D. TABLE 11 – DESIGN SUMMARY TABLE FOR REVIEWED STUDIES

Cohort Studies					
First Author (Year) Conflicts of Interest	**Exposure (type)**	**Outcome**	**Exposed (N) Unexposed (N)**	**Risk Estimates + Confidence Intervals**	**Comment**
Chen (2014) No disclosed conflicts of interest	<90 cDDD of montelukast vs. ≥90cDDD of montelukast (no true unexposed group)	Self-harm	726 on <90 cDDD 165,960 on ≥90 cDDD	Adj. HR = 0.92 (0.29-2.91)	This study was unsatisfactory and not included in the discussion: ▪ Underpowered to test association between montelukast and self-harm ▪ Did not adjust for asthma severity, and LABA combination therapy. ▪ Examined prevalent use of montelukast according to dosage
Bénard (2017) No disclosed conflicts of interest	MON	NE	84 on montelukast and 84 on ICS	Adj. HR = 12.0 (1.6-90.2) Adj. HR of probable/definite events = 9.0 (1.2-69.5)	This study was unsatisfactory and not included in the discussion: ▪ Underpowered to test association between montelukast and NE (very wide confidence intervals) ▪ Entire study conducted after 2008 labeling changes ▪ MON users instructed to be vigilant of NE and to consider drug cessation ▪ Interviews by proxy conducted 3 years after drug initiation ▪ The occurrence of study outcomes were unvalidated
Nested Case-Control Studies					
First Author (Year) Conflicts of Interest	**Exposure**	**Outcome**	**Case (N) Control (N)**	**Risk Estimates (95% Confidence Intervals)**	**Comment**
Schumock (2012) Merck, Forest Pharmaceuticals	LTMAs	Suicide Attempts	344 cases and 3438 matched controls	Adj. OR = 0.70 (0.36-1.39)	▪ The last author received funding from Merck, so results may be biased in favor of MON. ▪ Study failed to control for combination therapy with LABAs.
Ali (2015) No disclosed conflicts of interest	MON	NE	1920 cases and 5760 match controls	Adj. OR = 1.01 (0.88 – 1.14)	▪ Underpowered to test association between montelukast and NE. ▪ Study failed to control for combination therapy with LABAs.

KEY: adj. – adjusted, cDDD – cumulative daily dosage, ICS – inhaled corticosteroid, LABA – long acting beta antagonist, LTMA - leukotriene receptor-modifying agents, MON – Montelukast, NE – neuropsychiatric events, OR – odds ratio



8.5 APPENDIX E. FIGURE 1. SCHEMATIC DESIGNS OF REVIEWED STUDIES

KEY: Neuropsychiatric outcome, Drug exposure, cDDD – cumulative defined daily dose, MON – Montelukast, NE – neuropsychiatric event, ICS – inhaled corticosteroids, LTMA - leukotriene receptor-modifying agents, Rx - prescription

8.6 APPENDIX F. TABLE 12. INCIDENCE OF NE IN STUDIES WHICH EXAMINED MULTIPLE LABELED OUTCOMES (BÉNARD AND ALI)[90,91]

Adverse Event	Bénard et al. – Probably/Possibly Related NE	Ali et al. - NE diagnosis
	N=106	N=1007
Labeled	*% among montelukast exposed population*	*% among cases*
Agitation	4.7%	NR
Aggressive behavior or hostility	6.6%	7.97%
Anxiousness	0.0%	13.12%
Depression	0.9%	10.31%
Disturbance in attention	0.0%	24.27%
Dream abnormalities	1.9%	NR
Hallucinations	0.0%	0.21%
Insomnia	0.9%	1.72%
Irritability	7.5%	NR
Memory impairment	0.0%	0.57%
Restlessness (hyperactivity)	0.0%	16.82%
Somnambulism	0.0%	NR
Suicidality/self-harm	0.0%	0.52%*
Suicide	0.0%	
Tic	0.0%	1.51%
Tremor	0.0%	2.50%
Sleep disturbance	5.7%	1.72%
Headaches	4.7%	NR
Not labeled		
Drowsiness	1.9%	0.00%
Behavior problems	3.8%	0.00%
Mood swings	2.8%	0.00%
Stomachaches	3.8%	0.00%
Excoriation (dermatillomania)	0.0%	0.00%
Obsessive compulsive behaviors	0.0%	0.00%
Hyperkinesia	0.0%	0.00%

KEY: NE – neuropsychiatric event, NR – not reported
*Suicidality and self–harm were grouped together.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VERONICA V SANSING FOSTER
09/18/2018

IVONE E KIM
09/18/2018

DIPTI KALRA
09/19/2018

EFE EWORUKE
09/19/2018

LOCKWOOD G TAYLOR
09/19/2018

LISA M HARINSTEIN
09/20/2018

MONICA MUNOZ
09/20/2018