

FOOD AND DRUG ADMINISTRATION (FDA)

**JOINT MEETING OF THE PEDIATRIC
ADVISORY COMMITTEE (PAC)
& DRUG SAFETY AND RISK MANAGEMENT
ADVISORY COMMITTEE (DSaRM)**

FDA White Oak Campus, Building 31 Conference Center
Great Room (Rm. 1503)
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WELCOME AND INTRODUCTIONS

DR. WADE: Good morning. Thank you for joining us today and thank you to the committee for their presence today. I would first like to remind everyone to please silence your cellphones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Mr. Charlie Kohler. If you are present, please stand. Thank you. I would now like to provide introductions. My name is Kelly Wade. I'm a neonatologist for the Children's Hospital of Philadelphia and the University of Pennsylvania. I am the chair of the Pediatric Advisory Committee. I would now like us to go around the table and introduce ourselves with placing your name and background into the meeting report. We can start here on my left with Dr. Sleeper.

DR. SLEEPER: My name is Lynn Sleeper. I am a biostatistician and clinical trialist at Boston Children's Hospital and Harvard Medical School in the Department of Cardiology.

DR. HOLUBKOV: I'm Rich Holubkov. I'm a biostatistician and also a clinical trialist from the University of Utah School of Medicine in Salt Lake City.

DR. HABEL: I'm Laurie Habel. I'm an epidemiologist at Kaiser Permanente Northern California.

DR. CZAJA: I'm Angela Czaja, Children's Hospital of Colorado Pediatric Clinical Care Medicine and a pediatric pharmacoepidemiologist.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, pharmacoepidemiologist at the Harvard T.H. Chan School of Public Health in Boston.

DR. ORTIZ-AGUAYO: Roberto Ortiz-Aguayo. I'm a pediatrician and child psychiatrist in psychosomatic medicine at Children's Hospital of Philadelphia.

DR. MCGOUGH: James McGough. I'm a child psychiatrist at UCLA.

DR. AMIRSHAHI: Maryann Amirshahi. I am an emergency physician, medical toxicologist, and clinical pharmacologist at MedStar and Georgetown here in Washington, D.C.

DR. MEISEL: Steve Meisel, Director of Medication Safety for M. Health Fairview in Minneapolis, Minnesota.

DR. VOEPEL-LEWIS: Terri Voepel-Lewis. I'm an associate professor of nursing at University of Michigan in Ann Arbor.

DR. LESAR: Timothy Lesar, Patient Care Services Director and Director of Clinical Pharmacy Services at Albany Medical Center in Albany, New York.

DR. HOEHN: Sarah Hoehn, pediatric critical care and pediatric hospice in palliative medicine.

DR. TURER: Christy Turer. I'm an internist and a pediatrician who specializes in obesity care and comorbidity of obesity care at UT Southwestern in Dallas, Texas.

DR. CALLAHAN: David Callahan, pediatric neurologist at Washington University in St. Louis.

DR. SAYEJ: Wael Sayej, pediatric gastroenterologist at Connecticut Children's Medical Center and the University of Connecticut School of Medicine.

DR. HAVENS: Peter Havens, pediatric infectious diseases at the Medical College of Wisconsin and Children's Hospital of Wisconsin in Milwaukee, Wisconsin.

DR. ANNE: Premchand Anne, pediatric cardiology at St. John's Children's Hospital and Wayne State University School of Medicine.

MS. BRILL: I'm Marieann Brill. I'm the designated federal officer for this meeting.

DR. PATRICK: Stephen Patrick, neonatologist at Vanderbilt Children's Hospital in Nashville, Tennessee.

DR. FLICK: Randall Flick, pediatric anesthesia and critical care, Mayo Clinic.

DR. GRIFFIN: Good morning. Marie Griffin, internist and pharmacoepidemiologist, Vanderbilt University.

DR. JONES: Bridgette Jones, pediatric allergy/immunology and clinical pharmacology at Children's Mercy in Kansas City.

DR. WILFOND: Ben Wilfond, pediatric pulmonology and bioethics at Seattle Children's and University of Washington.

DR. KELSO: John Kelso. I'm an allergist at Scipps Clinic in San Diego.

DR. KIM: Edwin Kim, adult and pediatric allergist at the University of North Carolina.

DR. TRACY: Jim Tracy. I'm an associate professor at the University of Nebraska, allergist and from Omaha, Nebraska.

MS. OSTER: Randi Oster, consumer representative, president of Help Me Health.

MS. ROBOTTI: Suzanne Robotti, president of MedShadow and executive director of DES Action USA.

MS. CELENTO: Amy Celento, patient family representative and board member on the Cooley's Anemia Foundation.

DR. PORTMAN: Ron Portman, pediatric nephrologist. I work at Novartis Pharmaceuticals and am the non-voting industry representative to the PAC.

DR. MCCUNE: Susan McCune. I'm the director of the Office of Pediatric Therapeutics in the Office of the Commissioner at the FDA, and I'm a pediatrician and neonatologist.

DR. HAUSMAN: Ethan Hausman. I'm a medical officer in the Division of Pediatric and Maternal Health. I'm a pathologist, a pediatrician, and a transfusion medicine specialist.

DR. SEYMOUR: Good morning. My name is Sally Seymour. I'm the director of the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA, and I'm an adult pulmonologist.

DR. CHIN: My name is Stacy Chin. I'm a clinical team leader in the Division of Pulmonary, Allergy, and Rheumatology Products at FDA. I'm a pediatrician and allergist.

DR. CLARRIDGE: I'm Katherine Clarridge. I'm a medical officer at the FDA in the Division of Pulmonary, Allergy, and Rheumatology Products. I'm in internal medicine and pediatric trained and allergy immunology.

DR. BIEHL: My name is Ann Biehl. I'm a pharmacist safety evaluator in the Division of Pharmacovigilance at the FDA.

DR. SANSING-FOSTER: I'm Veronica Sansing-Foster. I'm an epidemiologist for FDA Division of Epidemiology II.

DR. IBRAHIM: I'm Ibrahim Ibrahim, drug utilization analyst in the Division of Epidemiology, CDER, FDA.

DR. WADE: Welcome, everyone. There are often strongly held opinions regarding the topics being discussed at today's meeting. Our goal is that today's meeting will be a fair and open forum for the discussion of the planned topics, ensuring that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee's Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. Now, I will pass on the microphone to Marieann Brill, our Designated Federal Officer, who will read the conflict of interest statement.

CONFLICT OF INTEREST STATEMENT

MS. BRILL: Good morning. The Food and Drug Administration is convening today's joint meeting of the Pediatric Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act of 2003, the Food and Drug Administration Amendments Act of 2007, the Food and Drug

Administration Safety and Innovation Act of 2012, and the Federal Advisory Committee Act. With the exception of the industry representative, all members and temporary voting members are special government employees, or regular government employees from other agencies, and are subject to federal conflict of interest laws and regulations. The following information on the status of the Advisory Committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208, is being provided to participants at this meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee. Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAS, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda includes pediatric focused safety review of neuropsychiatric events with the use of Singulair (montelukast). Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Portman is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Portman's role at this meeting is to represent industry in general and not any particular company. Dr. Portman is employed by Novartis.

In order to provide the expertise to adequately address the topic covered at today's meeting, Dr. Amirshahi, Ms. Celento, Dr. Czaja, Dr. Holubkov, Dr. Jones, Dr. Kelso, Dr. Kim, Dr. Lesar, Dr. McGough, Dr. Ortiz-Aguayo, Dr. Patrick, Dr. Sleeper, Dr. Tracy, Dr. Voepel-Lewis will be participating as temporary voting members. Dr. Jones is participating in this meeting as a temporary healthcare representative, and that is a non-voting position. Ms. Celento is participating as a patient family representative, which is a voting position.

We would like to remind members and temporary voting members that, if the discussion involves any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement. And their exclusion will be noted

for the record. FDA encourages all other participants to advise the committees of any financial relationship that they may have regarding the topic that could be affected by the committee's discussions. Thank you.

DR. WADE: We will now proceed with the opening remarks from Dr. Suzie McCune, Director of the Office in Pediatric Therapeutics. And from there, we will move into the FDA presentations. We will have all five presentations consecutively before we go into an open question and response. Dr. McCune?

FDA OPENING REMARKS

DR. MCCUNE: Thank you, Dr. Wade. Good morning and welcome everyone to Day 2 of the joint meeting of the Pediatric Advisory Committee, or PAC, and the Drug Safety and Risk Management Advisory Committee, or DSaRM. Yesterday, I have to apologize. I was remiss in not welcoming Dr. Wilfond as our newest member of the PAC. He is the director of the Treuman Katz Center for Pediatric Bioethics at Seattle Children's Hospital and Professor in Chief of the Division of Bioethics, as well as the Professor of Pulmonary and Sleep Medicine in the Department of Pediatrics at the University of Washington School of Medicine, amongst other accolades that are too long to list. But I just wanted to welcome Dr. Wilfond to our committee.

Today, the committee will discuss a pediatric focused safety review of the neuropsychiatric events with the use of Singulair or montelukast. We will be hearing presentations from the Division of Pulmonary, Allergy, and Rheumatology Products, or DPARP, in the Office of Drug Evaluation II and the

Office of New Drugs in CDER and the Office of Surveillance and Epidemiology, or OSE, in CDER. We will then have an open public hearing, which will be followed by committee discussion.

We know that there have been numerous comments to the docket and a number of speakers, who are here in the audience already, are scheduled for the open public hearing. We appreciate all of the patients and parents who have taken the time to come to the meeting today or who have posted information in the docket. We are very interested in hearing the views from the public and the committee on this topic. With that, I will turn the day over to Dr. Wade.

DR. WADE: Thank you. Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages all participants to advise the committee of any financial relationships they may have with the firms at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you at the beginning of your presentation to advise the committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with the presentations from the FDA. The first presentation is by Dr. Katherine Clarridge.

NEUROPSYCHIATRIC EVENTS WITH USE OF MONTELUKAST IN PEDIATRIC PATIENTS

DR. CLARRIDGE: Good morning. Members of the Pediatric and Drug Safety and Risk Management Advisory Committees, guest members, and members of the public, my name is Katherine Clarridge, and I'm an allergist, immunologist, and medical officer with the FDA in the Division of Pulmonary, Allergy, and Rheumatology Products. We are here today to discuss ongoing concerns regarding neuropsychiatric events with montelukast, particularly in pediatric patients. This is not a new safety issue, and you will hear about the regulatory history and background for this topic. In 2017, stakeholders requested FDA reevaluate this safety issue. And in response, FDA embarked on a thorough review of available data. Our briefing package has the details of our review. And today, we will present our findings to the panel and community. We consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision-making processes. So our goal is to obtain your input and recommendations.

Here is a brief outline of the FDA agenda. I will provide a background on the regulatory history, safety labeling, and requests from stakeholders. My presentation will be followed by a brief summary of montelukast utilization in pediatric patients. My colleagues from the Office of Surveillance and Epidemiology will provide a post-marketing, pharmacovigilance review, our review of the observational literature, and the design and summary of a study conducted in Sentinel, a medical claims database. Dr. Chin will then provide a

summary, regulatory considerations, and discussion topics for the panel.

This is the outline of my presentation. The current review requires some historical context. Therefore, after the product information, I will provide a timeline of regulatory actions, labeling changes, and communications related to neuropsychiatric findings that occurred prior to 2017, as well as key events that lead to the current review. Finally, I will briefly mention the regulatory considerations and tools at our disposal, as well as potential topics to discuss after the data are presented today.

Montelukast, brand name Singulair, is a leukotriene receptor antagonist. The mechanism of action is specific cysteinyl leukotriene type-1 antagonism. It has been approved for prophylaxis and chronic treatment of asthma, seasonal or perennial allergic rhinitis, and for the prevention of exercise-induced bronchoconstriction. Generic montelukast has also been marketed under numerous abbreviated new drug applications for all formulations, four, five, and ten milligrams, and oral granules beginning on August 3, 2012.

On the left is a list of the available formulations and corresponding approval dates for montelukast, and on the right is a summary of the approved prescription doses by indication and age. Montelukast is approved down to 12 months in asthma, two years in seasonal allergic rhinitis, six months in perennial allergic rhinitis, and six years in exercise induced bronchoconstriction. To provide context, I will present a timeline of regulatory history related to neuropsychiatric findings with montelukast use. I will focus on the safety reviews and subsequent communications efforts that occurred between 2007 and 2009, followed by a brief

reminder of the topics covered in the two previous advisory committee meetings in which neuropsychiatric events with montelukast use were discussed. Included in this discussion are any other relevant labelling updates that occurred over the course of the last 12 years.

In 2007, Merck submitted labelling supplements to add tremor, depression, and suicidal thinking and behavior to the adverse reactions post-marketing experience section of the montelukast prescribing information. Shortly thereafter, 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. Because of the nature of these events, FDA initiated a safety review of drugs that act via the leukotriene pathway and the potential association of neuropsychiatric events. FDA analyzed the clinical trial databases for montelukast, zafirlukast, and zileuton for neuropsychiatric adverse events, including suicide and suicide related events. FDA posted an early communication outlining the ongoing safety review and ultimately updated the labelling for montelukast, zafirlukast, and zileuton to reflect the findings of the FDA reviews.

As part of the review, FDA also evaluated safety data from literature and FDA post-marketing adverse events reports, or FAERS, and posted updates to the FDA website to inform healthcare professionals and patients of the new safety information and to announce the elevation of neuropsychiatric events to the precaution section of the product label, currently warnings and precautions. Merck issued a “Dear Healthcare Provider” letter to specialists and primary care

physicians and sent communications to pharmacies and professional societies. And AstraZeneca sent a similar “Dear Healthcare Provider” letter shortly thereafter.

On January 30, 2009, during the review of clinical trial data, the Parents United for Pharmaceutical Safety and Accountability submitted a citizen petition requesting FDA to 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 citizen petition request but did not find evidence to support removal of the indication for use in children. On May 2, 2014, FDA convened the Nonprescription Drugs Advisory Committee to discuss the adequacy of the safety and efficacy data submitted by Merck to support the proposal to switch montelukast from prescription only to over-the-counter for the seasonal and perennial allergic rhinitis indications in adults.

At this meeting, FDA raised concerns regarding the risk of neuropsychiatric events and acknowledged the lack of well-designed epidemiologic studies to accurately quantify the suicide risk among patients using montelukast. The Pediatric Advisory Committee convened on September 23, 2014, to review the current montelukast labeling regarding the risk of neuropsychiatric events. After these advisory committee meetings, FDA participated in a Medscape interview in an effort to improve communications and raise awareness amongst healthcare providers of the association of montelukast with neuropsychiatric events. And the American Academy of Pediatrics News published an FDA update entitled

“Neuropsychiatric Events Linked to Asthma Medication.”

The montelukast U.S. prescribing information and patient product information have been periodically updated to communicate post-marketing reports of neuropsychiatric adverse events. These updates have been based upon review of labeling supplements submitted by the sponsor, review of FAERS reports, or in response to outside requests for evaluation such that the current label now includes the following warnings and precautions for neuropsychiatric events. Twenty independent terms are listed with specific language that patients should be instructed to notify their prescriber if these changes occur. There's also information on neuropsychiatric events in the montelukast patient information leaflet that includes a list of potential symptoms, which brings us to our current review.

On November 3, 2017, patient advocacy groups submitted a letter to FDA, noted here in yellow, that has lead to the advisory committee meeting today, shown in purple. The letter stated the incidence of neuropsychiatric side effects with montelukast is more common than suggested by the label and publicly available information and contained an analysis of the FAERS' public dashboard, a collection of post-marketing reports, 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: one, determine the mechanisms for montelukast's neuropsychiatric side effect; determine the risk factors for neuropsychiatric adverse reactions; determine the appropriate way to discontinue montelukast; evaluate withdrawal symptoms and long-term sequelae

of an adverse reaction; reclassify neuropsychiatric side effects of montelukast to be common in children; update labeling to include a warning for the possible delayed onset of side effects including excoriation, hyperkinesia, and obsessive-compulsive disorder; issue a Medication Guide for montelukast due to the life threatening potential of its neuropsychiatric side effects; and consider a boxed warning.

Following receipt of the letter, FDA embarked on a thorough review of available data for montelukast, specifically conducted a focus review of post-marketing FAERS data to evaluate specific concerns raised by the patient advocacy group, reviewed available observational literature, designed and conducted a study in Sentinel, evaluated current montelukast utilization patterns for pediatric patients, reevaluated available nonclinical data, and, finally, explored communication strategies. Throughout the morning, you will hear more about the findings from our review. As you consider the findings from our current review, we wanted to provide some general information on the regulatory tools that may be of interest for the discussion today.

This figure displays some of the regulatory tools that FDA can utilize to address post-marketing safety issues. In the next few slides, I will provide information on some of the labeling options. Dr. Chin will cover the remaining tools in greater detail in her presentation later this morning.

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. We have utilized product labeling for the safety issues and continually update the

labeling with new information. Currently, neuropsychiatric events is listed in the warnings and precautions section of the montelukast label, as previously described. Note that we can modify the existing warning language and also move the warning precaution from the current location to higher in this section of the label to give it more prominence.

One of the requests from the stakeholder group was for a medication guide. The FDA may require a medication guide 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 risks of which patients should be made aware because information concerning the risk 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. Currently, montelukast has a patient information leaflet which is patient labeling that the sponsor voluntarily distributes. The patient information leaflet is reviewed and approved by the FDA, but it is not required labeling.

Another one of the requests from the stakeholder group was to consider a boxed warning. A boxed warning is used to call attention to serious or life-threatening risks with a product. A boxed warning 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 that it is essential that it be considered in assessing the risk and benefits of using the drug. There is a serious adverse reaction that can be prevented or reduced in frequency or severity

by appropriate use of the drug, 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.

To stimulate thoughtful discussion after we have listened to the ensuing presentations, considered the data, and heard from the community, we present a number of potential topics regarding the appropriate response to the concern for neuropsychiatric adverse events with montelukast use and adequate communication methods and outreach strategies. The topics listed here have been drafted for discussion today, including, but not limited to, the neuropsychiatric safety findings with montelukast use that will be presented today; the current label for montelukast, which includes a warnings and precautions, as well as the request for a Medication Guide and boxed warning; and third, your recommendations for successful communication strategies, specifically considering the target audience, target organizations, and modalities of communication that will be most effective. We are also interested in hearing your ideas for implementation for any recommendations that are beyond our control.

As I conclude my presentation on the regulatory background, bear in mind we are here to present data contributing to our knowledge and characterization of risks associated with montelukast use and to weigh the various options available to us going forward. This advisory committee meeting is another point on the timeline in our continual monitoring of existing and emerging safety signals. And we take all reports very seriously. Thank you for your time.

DR. WADE: Thank you. Our next presentation is by Dr. Ibrahim.

PEDIATRIC UTILIZATION PATTERNS MONTELUKAST, 2014-2018

DR. IBRAHIM: Good morning. My name is Ibrahim Ibrahim. I'm a drug utilization analyst from the Division of Epidemiology in the Office of Surveillance and Epidemiology. I'll be presenting data on the pediatric drug utilization patterns for montelukast to provide context for today's discussion.

Here is the outline of my presentation. I will begin with the sales distribution data of montelukast, followed by outpatient retail prescription utilization patterns, our findings on the diagnoses associated with the use of montelukast in pediatric patients, limitations of our analysis, and conclude with a summary of our findings. The settings of care where montelukast was primarily utilized in 2018 was determined based on sales volume for manufacturers using the IQVIA National Sales Perspectives database. Montelukast was distributed primarily to the retail pharmacy setting in 2018. Therefore, we focused our analysis on the outpatient retail pharmacy settings.

To conduct this analysis, we used a variety of proprietary databases available to the Agency. For prescription utilization data, we used a database that measured the dispensing of prescriptions from outpatient retail pharmacies to patients based on transactions from a robust sample of retail pharmacies. Data are projected to provide national estimates of drug utilization.

This graph displays the estimated number of all patients who receive montelukast prescriptions dispensed from U.S. outpatient retail pharmacies from

2014 through 2018. Of note, pediatric patients zero to 16 years old are inclusive of all patients from birth up to the day before their 17th birthday. The number of pediatric patients less than 17 years of age appears to remain relatively steady at an estimated 2.3 to 2.5 million unique patients annually, while adult patients 17 years and older increased during the examined time period.

This graph focuses on the pediatric population utilization. Patients six to 11 years accounted for the largest proportion, followed by 12 to 16 years, two to five years, and zero to one year. This table provides the estimated number of dispensed prescriptions for montelukast stratified by prescriber specialty dispensed to patients of all ages from U.S. outpatient retail pharmacies in 2018. The combined specialties of family practice, general practice, and internal medicine were the top prescribers of montelukast, followed by the combined specialties of nurse practitioners and physician assistants. Pediatrics was the third top specialty.

We obtained diagnosis data associated with the use of montelukast from a database that captures monthly surveys from a sample of 3,200 office-based physicians reporting on patient activity during one day per month. These data are nationally projected and provide an insight into the prescribers' intent. These data may not be necessarily linked to dispensed prescriptions but rather indicate that the drug was mentioned during an office visit.

This slide shows the diagnoses associated with montelukast for pediatric patients less than 17 years old stratified by the different age groups. Cough was the top diagnosis associated with montelukast use in patients less than two years old. The top diagnosis associated with montelukast use in patient age groups two

to 16 years old was asthma. For all pediatric patients, vasomotor and allergic rhinitis was the second most common diagnosis associated with montelukast.

These data have some limitations. Namely, only outpatient utilization was analyzed. Therefore, no inpatient or mail order data were included in the prescription analysis. The diagnosis data are not necessarily linked to dispensed prescriptions, rather that a drug was mentioned in association with the diagnosis during a patient visit to an office-based physician. The diagnoses data were derived from surveys of office-based physicians and may not have captured prescribing patterns of physicians who practice in other clinical settings, such as clinics located within hospitals or urgent care clinics.

In summary, montelukast is mainly utilized in the outpatient retail setting. During the study period, an estimated 2.3 to 2.5 million pediatric patients annually received prescriptions dispense for montelukast. According to the U.S. office-base physician surveys, montelukast was mentioned to be used for the management of asthma, followed by allergic rhinitis and cough in pediatric patients in 2018. Thank you.

DR. WADE: Thank you. Our next presentation is by Dr. Ann Biehl.

NEUROPSYCHIATRIC EVENTS ASSOCIATED WITH MONTELUKAST: POSTMARKETING EXPERIENCE

DR. BIEHL: My name is Ann Biehl. I am a pharmacist safety evaluator with the Division of Pharmacovigilance in the Office of Surveillance and

Epidemiology. And today, I will tell you about the FDA's post-marketing experience with neuropsychiatric events associated with montelukast.

First, we will review the purpose of my presentation. Then, I will give you an overview of post-marketing adverse event reporting trends with montelukast. Next, we will review fatal neuropsychiatric event reports, then select non-fatal neuropsychiatric events with a focus on pediatric patients. We will conclude with a summary of the information presented.

The purpose of this presentation is to analyze adverse event reporting trends associated with montelukast using information from the FDA Adverse Event Reporting System, FAERS, and to characterize cases of select neuropsychiatric events associated with montelukast in the post-marketing setting. Since 2008, the Office of Surveillance and Epidemiology has completed an extensive number of reviews examining post-market reports of neuropsychiatric events with montelukast specifically and leukotriene modifying agents as a class. Most recently, OSE completed a review examining specific neuropsychiatric events reported in the post-marketing database, as well as in the literature, in response to a letter submitted to the office of pediatric therapeutics in 2017 by patient advocacy groups. We will discuss the results of this review in more detail later in my presentation.

The post-marketing database, the FDA Adverse Event Reporting System, is a computerized database of spontaneous adverse event reports for human drug and therapeutic biologic products. Collecting data since 1969, over 18 million reports are currently stored in FAERS, with nearly two million reports submitted in 2018

alone. Reports are submitted from manufacturers or can be directly submitted to the FDA from consumers. Safety evaluators within the Division of Pharmacovigilance review submitted reports routinely and continually evaluate reports for the emergence of safety issues.

FAERS data has limitations. First, there is no certainty that a reported event was actually due to the product. The FDA does not require establishment of a causal relationship prior to submitting a report. Report submission is not required, and events are underreported because of the spontaneous nature of reporting. The quality of submitted reports varies with regard to clinical detail. The FDA requires the presence of only four data elements for reporting. These include an identifiable reporter, patient, adverse event, and a suspect product. Beyond those four elements, the quality and quantity of information depends on what the reporter is willing and able to provide.

Incidence rates cannot be calculated using FAERS data because we do not know the total number of events occurring in the population or the total number of exposures. Reports are influenced by many factors, including the severity of the case, the amount of time the medication has been on the market, media exposure regarding adverse events for the medication in question, and the background rate of the adverse event for the population in question. Despite these limitations, FAERS is a valuable data source.

A majority of FDA's safety related labeling changes come from FAERS reports. FAERS reports contribute to the detection of events not seen in clinical trials or with a rare background rate. FAERS serves a broad population and

allows for the identification of possible risk factors or populations at risk for developing a safety issue. Lastly, FAERS serves as a conduit for the general public to directly communicate safety concerns to the FDA in terms of specific patient experiences. These reports are of the utmost value to the FDA.

Now, I will present a high-level overview of neuropsychiatric adverse events reported to FAERS for montelukast. We queried the FAERS database for all spontaneous post-market reports associated with montelukast from the time of FDA approval to May 31, 2019. Figure 1 depicts the total number of montelukast reports contained in the FAERS database from February 20, 1998, through May 31, 2019, on the Y axis by FDA received year on the X axis. These reports are further broken down into those coded with a MedDRA preferred term in the nervous systems disorders system organ class or psychiatric disorders system organ class. Of the 19,685 total montelukast FAERS reports depicted in Figure 1 by the light blue line, 52 percent, or 10,209, reported at least one adverse event in the nervous system disorder system organ class or psychiatric disorder system organ class, which are represented by the dark blue line.

It appears that both total reports and reports with neuropsychiatric adverse events substantially increased over 1.5-fold from the previous year in 1999, 2008, 2013 and 2018. The peak in reporting in 1999 is an effect we commonly see after new drug approval where adverse event reporting increases over the first two years of time on the market, peaks in year two, and is followed by decline in reporting. 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 specific adverse event mentioned in such an alert due to heightened public awareness. FDA first alerted healthcare professionals and patients about a possible association between the use of leukotriene modifying agents and neuropsychiatric events in 2008, and heightened awareness may explain the sharp increase in reports.

In 2013, there was an influx of reports that were received from a line listing from the previous FDA adverse event reporting database, approximately 857 duplicate reports resulting from a Freedom of Information Act request. In late 2017, the letter from the patient advocacy groups was received by the Office of Pediatric Therapeutics. The peak in 2018 is driven by an influx in total foreign reports, as well as foreign neuropsychiatric reports.

Figure 2 depicts the number of serious neuropsychiatric events on the Y axis reported for adults in the dark blue line versus pediatric patients in the gray line by year on the X axis. The regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, congenital anomalies, or other serious important medical events. We see that 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. According to the most recent utilization review, montelukast use in pediatric patients in the United States for the years 2014 to 2018 has remained relatively stable. And the

increase in reports observed in 2018 is from an influx of reports from foreign countries.

Now, we will review domestic fatal neuropsychiatric events associated with montelukast use. We queried the FAERS database for domestic fatal events containing terms within the nervous system disorders or psychiatric disorders system organ classes from the date of FDA approval to May 31, 2019. We isolated 296 crude reports. After excluding duplicates, multi-substance overdoses reported from Poison Control, causes of death unrelated to neuropsychiatric events, reports containing aggregate data, miscoded reports, transplacental exposures, and illicit drug overdoses, we isolated 82 unique cases of completed suicide.

Of the 82 cases, the majority were reported from 2005 to 2009, most in 2008 to 2009 with an N of 51. Forty-five events were reported in adults. Nineteen events were reported in pediatric patients younger than 17, and 18 events did not report an age in the coded field or narrative. Events occurred mostly in males, both overall and specifically for pediatric patients. Adolescent and young adult patient age groups contained the highest number of events with a total of 35. 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 examining overall suicide rates in adolescents and young adults. This article and others noted a trend of increasing suicide rates, with rates in 2017 for those aged 15 to 19 and 20 to 24 years at their highest point since the year 2000. Increases were especially noted in males and in ages 15 to 19

years.

We evaluated cases for information concerning psychiatric history. Most cases did not provide psychiatric history information. Of the 11 cases confirming a psychiatric history, only two cases contain sufficient information to determine the psychiatric condition preceded montelukast initiation. Four of the 11 cases with psychiatric history occurred in pediatric patients, specifically, depression in all cases, with one case also reporting a history of suicide attempts. Seven pediatric cases reported the absence of any psychiatric history.

In reviewing the individual cases, we noted several key themes. The majority of cases did not contain sufficient information for a robust evaluation of causality. Key pieces of missing information included time to onset of event, concomitant medications at the time of the event that may contribute to self-harm events, and potentially contributory comorbidities, including psychiatric illness, that may increase the risk for self-harm. The remaining cases considered to be well-documented also contained potential contributors, including medications or comorbidities, that may increase the risk of self-harm. Specifically regarding pediatric patients, eight cases were designated as limited information due to lack of information thought to be indicative of an informative case.

We noted the presence of stimulated reporting or reporting alluding to media coverage of the possible association of montelukast with neuropsychiatric events. Specifically regarding pediatric patients, we noted six cases contain information consistent with stimulated reporting. We also noted a lack of reporting of patient counseling. Six cases specifically stated no previous

knowledge of the potential for neuropsychiatric events. However, four of these cases occurred prior to the labeling updates to add suicidality to the product information. Two of these cases, noting a lack of provider counseling, occurred in pediatric patients, both with event dates prior to 2008.

The FDA continues to receive neuropsychiatric adverse event reports for montelukast. However, the frequency of reporting is influenced by multiple factors, including heightened public awareness, duplicate reporting, and reports originating from foreign countries. In light of these factors and the quality of information reported to FAERS, we cannot draw conclusions regarding the frequency of neuropsychiatric events associated with montelukast. In this setting, FAERS data can contribute to the total body of knowledge regarding these labeled events. However, it cannot provide firm conclusions.

I will now present post-marketing reports of select unlabeled neuropsychiatric events outlined in the 2017 patient advocacy group's letter to the Office of Pediatric Therapeutics. As stated, the most recent review previously completed by OSE examined specific neuropsychiatric events, including obsessive-compulsive symptoms, excoriation, hyperkinesia, and withdrawal neuropsychiatric events. The OSE review supported the addition of obsessive-compulsive symptoms to the labeling based upon the information request from the sponsor and a small number of reports, 23, detected in the FAERS database. The review found insufficient evidence to label excoriation, hyperkinesia, and withdrawal neuropsychiatric events at that time. The OSE review also recommended to add the phrase "including but not limited to" as a precursor to

labeling sections regarding neuropsychiatric events to alert clinicians that other unlisted events may occur. These labeling changes were effected December 21, 2018.

The updated review queried the FAERS database from January 17, 2018 to May 31, 2019. The previous review included reports from the time of FDA approval, February 20, 1998, to January 16, 2018. Search terms included events containing the preferred terms: hyperkinesia, skin abrasion, or the high-level term withdrawal and rebound effects. We excluded duplicate or miscoded reports or reports not describing the event of interest.

Here we present the number of cases for each event isolated in the previous review, as well as in our updated search. There were zero cases of excoriation found in either search, therefore precluding the further review for this event. There were three cases of hyperkinesia found in the initial search and none in the update. Of the three cases, one contained limited information for assessment. The other two reported hyperkinesia in the context of other neuropsychiatric events. This review concluded that due to the inconsistency in presentation and the limited number of events the causal relationship between hyperkinesia and montelukast use could not be appropriately established.

There were 15 cases of withdrawal neuropsychiatric events found in the initial search and two in our updated search, which we will discuss in the next few slides. Six of 15 withdrawal events isolated in the previous review reported new onset events following montelukast discontinuation. Nine of 15 developed symptoms during montelukast treatment, which continued or recurred following

montelukast cessation. Anxiety, abnormal behavior, aggression, fear, suicidal ideation, crying, and feeling abnormal were symptoms reported most commonly. Of note, 13 of 15 cases were of unassessable causality. The review concluded that the lack of consistency among FAERS cases reporting neuropsychiatric events following montelukast withdrawal did not justify additional regulatory action at that time. The sponsor also provided an independent review of neuropsychiatric events following montelukast withdrawal and reached similar conclusions.

Our updated review returned two additional cases assessed as possible causality. One case describes a 17-year-old female who developed worsening of pre-existing anxiety and suicidal urges one day after montelukast discontinuation, which improved over the course of several months with inpatient treatment and medications. The second case described a ten-year-old female who developed OCD-like behaviors and anger within two months of montelukast cessation for other neuropsychiatric events, specifically, anxiety and depression with severe mood swings. These symptoms improved over the course of several months under the care of a psychologist.

These 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, including medication and psychotherapy. Both cases were assessed as possible causality due to the timing of the onset of symptoms in relation to drug cessation and improvement with prolonged time off the medication in addition to other medical interventions. 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 assessment of causality.

We noted the following limitation in our search. The reporter must clinically recognize and report the emergent neuropsychiatric events as occurring or persisting upon montelukast withdrawal. If the report is not entered as a withdrawal event, it will remain undetected with the current search strategy. In conclusion, the totality of data regarding withdrawal neuropsychiatric events with montelukast found in the FAERS database remains sparse. The Division of Pharmacovigilance will continue surveillance regarding withdrawal neuropsychiatric events following montelukast cessation.

In summary, we see that the FDA continues to receive reports of post-marketing adverse neuropsychiatric events with montelukast. Many of these events are specifically described in the current labeling, which had language recently adjusted to state “including but not limited to” to indicate to clinicians that other neuropsychiatric events may occur. We do not know the total number of exposures or number of total events because reporting is not mandatory. Therefore, we cannot calculate a rate from FAERS. We greatly value the submission of reports to FAERS and note that the majority, if not all, of the post-marketing safety labeling changes for montelukast thus far have been informed from FAERS data. This concludes my presentation. Thank you.

DR. WADE: Thank you. Our next presentation is by Dr. Veronica Sansing-Foster.

**NEUROPSYCHIATRIC ADVERSE EVENTS AND MONTELUKAST:
OBSERVATIONAL SAFETY ANALYSES**

DR. SANSING-FOSTER: Good morning. I am Dr. Veronica Sansing-Foster, epidemiologist, and I will be presenting the observational literature review and epidemiology safety study for montelukast conducted in the Sentinel Distributed Database. In November 2017, FDA received correspondence from the following patient advocacy groups. These groups stated that the current montelukast label does not adequately capture the scope and magnitude of neuropsychiatric adverse events and that the label has not adequately informed the public of the risk associated with use and withdrawal from montelukast, particularly in children. As evidence, they provided a self-sponsored survey of the Facebook group and survey study by Bénard. In response, the Division of Epidemiology II undertook a two-part investigation regarding the risk of neuropsychiatric adverse events and montelukast exposure, which included a literature review of observational studies and an analysis within the Sentinel Distributed Database.

I will now present a brief overview of the methods and summarize the results for the literature review. In 2017, '18, and '19, the FDA reviewer and FDA librarian searched multiple data sources using the following search string. We

retrieved 71 articles and excluded 67 for the following reasons. We found four articles, including the article by Bénard and a second article by Glockler-Lauf submitted to the FDA for review in 2019. Two well-conducted studies showed no association. A nested case-controlled study by Schumock found no association between LTMA, including montelukast, and suicide attempts, as noted by self-harm ICD-9 e-codes. There was, however, a five-fold odds of being exposed to montelukast in young adults. This study's definition of a suicide attempt only captured the physical symptoms that resulted in medical attention and not the suicidal ideation. An additional case control study by Ali found no association between neuropsychiatric event diagnoses and montelukast in patients under the age of 18. A minor limitation was that the study did not control for multiple comparisons, so some of the positive results may be due to chance.

Bénard conducted a survey study of the parents of pediatric patients exposed to montelukast and inhaled corticosteroids, which I'll refer to as ICS. Although this study had a striking nine-fold increased risk of neuropsychiatric events with montelukast use, the study was vulnerable to recall bias. The risk was probably overestimated since the survey was conducted after montelukast labeling changes and three years after the children initiated the drugs. Thus, parents of montelukast users were more likely to recall any adverse events which happened three years prior. Due to the low number of events, the results were imprecise, as noted by the wide confidence interval.

Glockler-Lauf study found that cases had twice the odds of being exposed to montelukast compared to controls. However, the cases may have included

patients with psychiatric conditions that existed before the asthma medication exposure. The cases were ascertained from hospitalization, same day surgery, and emergency room records but not necessarily in the primary or secondary position. Therefore, the patients may not necessarily have received their initial diagnosis for these events at these particular medical encounters.

In order to further understand some of the answers to the questions raised by the patient advocacy groups, we conducted an analysis within the Sentinel Data System. Using data from the Sentinel Distributed Database, we sought to investigate the association between neuropsychiatric adverse events and montelukast exposure. Specifically, our objectives were to determine if, first, there is an increased risk of depressive disorders, self-harm, and suicides associated with montelukast use compared to inhaled corticosteroids and, second, if the risk of these events were modified by the 2008 montelukast drug safety communications and subsequent labeling changes or were affected by age, sex, or psychiatric history.

Data from January 2000 to September 2015 from 17 health plans contributing to Sentinel were included. Separate study cohorts were created to examine the increased risk associated with montelukast in the five following outcomes: inpatient depressive disorder in the primary position to capture the initial diagnosis; outpatient depressive disorder treated with psychotherapy or antidepressant use within 30 days of the diagnosis, which I'll simply refer to today as outpatient depression; hospitalization due to self-harm; hospitalization due to self-harm including e-codes to increase the sensitivity; and, finally, death by

completed suicide from the six data partners able to contribute this information. Our definition covers both the physical symptoms and suicidal ideation. The death data came from records which were considered to be of excellent quality. Study covariates included comorbidity score, history of psychiatric disorder and psychotropic drug use, substance abuse, allergic rhinitis and other respiratory disorders, the setting of the asthma diagnosis, and asthma medication use, including oral corticosteroids and SABAs.

This is a diagram of the study methods conducted in Sentinel with times shown on the X axis. The date of exposure initiation served as the cohort entry date for the patients, shown as Day Zero. All patients must have a diagnosis of asthma. For inpatient depression, self-harm, and suicide, we allowed medication gaps of 15 days between dispensing of the exposure drug, plus a 15-day episode extension period after the patient's last prescription in order to define continuous drug exposure. For outpatient depression, we used a 30-day gap and 30-day extension period. Patients could only enter the cohort once. In the six months prior to the cohort entry date, we excluded patients with exposure to the following medications listed above, and we excluded patients with more than a 45-day gap in medical and drug coverage and patients who were diagnosed with COPD, chronic obstructive pulmonary disease.

On the cohort entry date, patients had to be age six years and older with no dispensing of the comparator drug or a same day diagnosis of the study outcomes. We assessed the covariates during the six months baseline period. Age, sex, and year of initiation were captured on the cohort entry date, Day Zero. Patients were

followed from the day after the cohort entry until the occurrence of the following censoring criteria: study outcome, other asthma medications, hospitalization for asthma, death, data partner end date, query end date, disenrollment, or end of treatment episode.

Baseline characteristics were described using descriptive statistics and compared between treatment groups using standardized mean differences. We examined the risk estimates for inpatient depression, outpatient depression, self-harm, and suicide separately, adjusting for a potential confounders using propensity score methods. We included all covariates in a logistic regression model to predict the probability of a patient receiving the exposure of interest, either montelukast or inhaled corticosteroids. We used Cox proportional hazards regression to estimate hazard ratios and corresponding 95 percent confidence intervals.

Previous studies may not have captured the initial diagnoses, were limited to select age groups, and did not control for possible channeling or detection bias brought about by the 2008 drug safety communications and labeling changes. Therefore, we conducted subgroup analyses stratified by history of psychiatric disorder or psychiatric drug use, sex, age groups, and the periods before and after the 2008 FDA communications. Furthermore, two sensitivity analyses were conducted using the inpatient depression outcome. We conducted an analysis with a zero-day extension period to examine whether the risk attenuated with exclusion of the post-episode follow up. Now, given the potential for patients to be less adherent to ICS compared to montelukast, we also compared ICS users with a 30-

day gap and a 30-day extension period to montelukast users with a 15-day gap and a 15-day extension period.

I will now present the results from the Sentinel analysis. Before one to one matching between the inhaled corticosteroid and montelukast patients, montelukast users were more likely to have the following: history of psychiatric disorder, allergic rhinitis, other respiratory disorders, outpatient asthma diagnosis, history of psychiatric or psychotropic drugs, a history of oral corticosteroids. ICS users were more likely to have a history of SABA use. One to one matching was successful at balancing the covariates. We included 89 percent of montelukast patients and 34 percent of ICS patients.

This bar graph shows the baseline characteristics of the matched montelukast and ICS patients from the 17 data partners. The majority of patients were exposed to montelukast and ICS during the 2008-2015 time period. The majority of patients were adults, had a history of SABA use, and were female. Only a third of the patients had a history of psychiatric disorders and were under the age of 18. The majority of study outcomes were outpatient depressive disorders requiring treatment. Self-harm was the least frequent. It is noted that the event counts are not mutually exclusive. Most of the events were those with previous psychiatric diagnosis. The average days of follow up was shorter in the ICS patients compared to the montelukast patients.

You're looking at a forest plot for the risk of the study outcomes with montelukast use compared to ICS use. Estimates above one and to the right indicate a possible increase risk with montelukast use. Estimates below one and

the left indicate a possible decrease risk with montelukast use. Statistical significance is indicated when the confidence intervals do not cross one.

Although some of the confidence interval bars may be hard to see in this figure due to the high precision of the estimates, we see that exposure to montelukast was significantly associated with the decrease risk of outpatient depression. This is statistically associated. This decreased risk was observed among patients with a history of psychiatric disorder or psychotropic drug use and in patients aged 12 to 17 years and age 18 years and above, as noted in black. However, in patients with no psych history, the risk estimate is above one, as noted in blue. The magnitude and direction of risk did not change between sex and time strata.

The hazard ratios for inpatient depressive disorder with montelukast compared to ICS was 1.06 but did not reach statistical significance as the confidence interval overlaps one. The upper bound, however, is 1.24. The hazard ratios do not reflect a statistical association when stratified by psychiatric history, sex, age group, and time strata. As shown above, the direction and the magnitude of the hazard ratios for inpatient depression and the sensitivity analyses were similar to the primary analyses. Montelukast was not statistically associated with self-harm or the modified self-harm outcome.

I will provide a simple interpretation of the one-year Kaplan-Meier curve shown above used in our post hoc analyses. As most events occurred before 365 days, we conducted a post hoc analysis with the follow-up time truncated at one year. Time is represented on the X axis and a probability of not experiencing the

event is on the Y axis. The blue line represents proportion of ICS patients at risk over time who did not experience the event of interest, for instance inpatient depression. The red line represents the proportion of montelukast patients at risk over time who did not experience the event of interest.

The one year post hoc results shown here are consistent with the primary analysis. There was no statistical association with montelukast for inpatient depression. There was a statistically decreased risk for outpatient depression with montelukast compared to ICS. Again, no association was noted between montelukast and the rare outcomes of self-harm. As you can see from the Y axis, these events were rather infrequent, with less than one percent of the population at risk for self-harm at any time point.

I will now present the results for suicide. Please note that only six of the data partners within Sentinel were able to provide us with death data. The baseline covariates were well-balanced after matching. Most patients had a history of SABA use and were exposed to asthma medications between 2008 and 2015. More than half of the patients were female and under the age of 18, making this cohort relatively younger compared to the patients within the 17 data partners. Approximately a third of the patients had a psychiatric history.

In the one to one matched patient population, there were two suicides in montelukast patients, both occurring in adult females. This provides a rough estimate of approximately four suicides per 100,000 patients. But with only two events in the numerator, this estimate is not precise. This rate, however, is comparable to the national age adjusted suicide rates for females, which range

between 4.0 to 6.0 deaths per 100,000 patients between 1999 and 2015, approximately the same time period of our study.

For inpatient depression and self-harm, which come to the attention of healthcare providers, the point estimates and our study are consistent with no association. Although, an increased risk of 24 percent as noted by the upper confidence interval cannot be ruled out. An absence of an association for these serious neuropsychiatric events appear to be consistent with the results from the well-conducted observational studies, namely Ali and Schumock. The decreased risk observed with montelukast in treated outpatient depression was unexpected. However, there are plausible explanations for the estimates observed.

First, the majority of our patient population was exposed to montelukast and ICS after the 2008 FDA communications. The subsequent 2009 label informed prescribers to instruct montelukast users to be alert for neuropsychiatric events. Therefore, well-informed montelukast treated patients could have stopped treatment at the onset of depressive symptoms without presenting for outpatient treatment of depression. Second, it is also possible our definition for outpatient depression, which is outpatient diagnosis plus psychotherapy or psychotropic drug prescription within 30 days of the diagnosis -- it's possible this definition may have captured a high proportion of continuing outpatient treatment episodes for pre-existing depression. This would complicate its interpretation as a treatment emergent outcome. This outpatient depression outcome risk estimate was greater than one for the subgroup without a prior psychiatric disorder, which excluded patients receiving treatment for depression. Though, this hazard ratio was not

statistically significant. Most importantly, our findings should be interpreted in the light of the strength and the limitations, which I will discuss next.

We designed our study, so it was not only comparable to the well-conducted observational studies but address some of their limitations. Strengths of our study included a large patient population from 17 different data partners in order to increase our external validity. We had adequate study power for our overall analyses, though we were possibly underpowered for subgroup analyses. We had the ability to study the association before and after the 2008 FDA communications. Our suicide data was extracted from data partners with excellent confidence in their death records, thus ensuring high specificity for this outcome. Our study also captured both the physical and the mental aspects of suicide.

Our study contained limitations germane to observational studies using claims data. First, unlike FAERS data, we could only study outcomes that resulted in actual healthcare claims and not simply discontinuation of the drug. Thus, we studied relatively more severe events. Furthermore, the sensitivity of our algorithms and case definitions are unknown. Depression, self-harm, and suicide are only a few of the long list of neuropsychiatric adverse events that have been reported after exposure to montelukast, both labeled and unlabeled. Inhaled corticosteroid has relatively poor adherence compared to montelukast, creating disparity at risk times. However, our sensitivity analysis that included patients adherent to ICS was comparable to the primary analyses.

We were unable to adjust for socioeconomic status, but we controlled for asthma severity, which was related to socioeconomic status. We found no

evidence that montelukast and ICS are prescribed differently to patients of varying socioeconomic status. While we observe nonproportionality of the hazard ratios for the study outcome over the entire follow up period, our post hoc analysis truncating follow up to one year did not change the study's findings. There is a potential for channeling bias in which patients at lower risk for neuropsychiatric adverse events may have received montelukast due to the 2008 drug safety communications and subsequent labeling changes.

Our study did attempt to control for measured risk factors. We are underpowered to detect risk of less than 25 percent, which is why our confidence interval crosses one. As such, we cannot yet rule out an increased risk of 24 percent. However, there is a final possibility that ICS use may be associated with depressive symptoms since it's hypothesized that a portion of the ICS dose is systemically absorbed. ICS was the best choice of a comparator, as both montelukast and ICS monotherapy are recommended as step two therapy for asthma. Other LTMA's have limited use.

It is very important to consider our study's findings in light of the limitations. We did not find a statistical association between montelukast and inpatient depression, self-harm, and completed suicide that resulted in medical claims. Our study cannot yet rule out a small to modest increased risk. The totality of the observational evidence, including well-conducted observational studies reviewed, is not suggestive of a risk. A decreased risk in treated patient outpatient depression was observed among patients with a psychiatric history. Completed suicide was rare and limited to adult female patients with a psychiatric

history. In conclusion, we recommend discussion from the panel regarding labeling recommendations. Thank you everyone for this effort, and I conclude my presentation today.

DR. WADE: Thank you very much. Our final speaker this morning is Dr. Stacy Chin.

FDA SUMMARY AND DISCUSSION TOPICS

DR. CHIN: Good morning. My name is Stacy Chin. I'm a pediatrician and allergist in the Division of Pulmonary, Allergy, and Rheumatology Products. I will conclude the FDA presentations with a summary of the findings presented today, as well as the regulatory options available to us, and close with the topics we would like the committee to cover in the discussion. As we have heard, the occurrence of neuropsychiatric events with montelukast use is a long-standing issue that has been around for over a decade. The safety signal was not identified in the original clinical trials for asthma and allergic rhinitis but emerged after approval in the post-market setting. FAERS reports are continually monitored by FDA. Multiple reviews of this data have revealed reports for a wide range of neuropsychiatric events with relatively sparse information regarding withdrawal or potential risk factors. As mentioned previously by Dr. Biehl, the reports are taken seriously by FDA but, by their nature, have limitations which hinder our ability to determine frequency or draw causal associations. A review of observational studies in the published literature showed mixed results. Of the studies reviewed

in depth, two showed an association with montelukast use and neuropsychiatric events, while two did not.

Given the limitations in available data, FDA conducted its own observational study in the Sentinel Distributed Database using claims data to examine the risk of neuropsychiatric events and suicide associated with montelukast exposure. As Dr. Sansing-Foster described in her presentation, no statistically significant association was observed between montelukast use and risk of inpatient depression or self-harm in patients six years of age and older when compared to ICS use. Although risk of suicide was evaluated, these events were rare and, in this case, limited to adults with a prior history of psychiatric illness.

While the results from the Sentinel study have not brought much more clarity to the risk of neuropsychiatric events with montelukast, we recognize that this is a real safety issue, and we acknowledge that communication of this risk has been and continues to be a challenge. A major challenge we face is how to generate interest and widely disseminate information about an existing safety issue for which the data are either inconclusive or have limitations. This is an area which we have wrestled with as an agency and will ask the committee to provide your thoughts and recommendations.

Prior to outlining the specific points for discussion, I would like to review the regulatory options and considerations for each. Let's revisit the available options in our regulatory toolbox that Dr. Clarridge touched upon earlier. As mentioned, labeling is our primary tool for communicating essential information about a drug to healthcare providers, prescribers, and patients. Labeling tools

include warnings and precautions, Medication Guides, and boxed warnings.

Montelukast currently carries warnings and precautions for a number of neuropsychiatric events, most of which have been added based upon review of post-marketing reports. Stakeholders have also requested that FDA issue a Medication Guide and boxed warning to the product label, so I will return to discuss these in more detail. But first, let me touch upon some of the other options.

Post-marketing requirements and commitments, or PMRs and PMCs, when we are aware of the limitations of the available data. Under FDAAA, FDA has the authority to require post-marketing safety studies or clinical trials to assess a known serious risk related to use of a drug. FDA has considered requiring additional post-marketing trials or studies to better characterize the risk of neuropsychiatric events with montelukast. However, there are challenges in designing a study to evaluate this safety issue given the wide range of events reported, lower frequency of some events such as suicide, and variability in symptom onset and course. We acknowledge the patient and parent request for further research to evaluate possible mechanisms, how to safely discontinue montelukast when symptoms arise, and the long-term sequelae.

But there are challenges to designing a study that can provide answers to these questions, as well as hurdles in funding. The distribution of montelukast is now primarily generic. So whether Merck, the sponsor of the original NDA product, would conduct additional studies is uncertain. All of these considerations raise feasibility concerns for additional studies with montelukast. However, we

are open to your input on whether additional studies may be informative and feasible.

Risk Evaluation and Mitigation Strategies, or REMS, is a drug safety program that FDA may require for certain medications with serious safety concerns to help ensure the benefits outweigh the risks. Only a few medications actually require a REMS. If labeling is sufficient to ensure that the benefits outweigh the risks, a REMS is not appropriate. As there are additional labeling options to consider for montelukast, a REMS is not under consideration at this time.

Market withdrawal, the Food, Drug, and Cosmetic Act establishes circumstances under which FDA will, after due notice and opportunity for hearing, withdraw an approval. For safety concerns, FDA may withdraw approval of a drug if there is new evidence to show that the drug is not safe for use under the conditions of use upon the basis of which the application was approved or if there is an eminent hazard to public health. This is an extreme regulatory option, and we do not think this is an option to consider for this situation.

Now, I will return to the options we have to maximize labeling, given that this is FDA's primary tool for communication. I should also mention that these options are not mutually exclusive. As you will recall, montelukast carries a warnings and precautions section for neuropsychiatric adverse events that was added following the initial reviews in the 2007 to 2009 time period. Many, but not all, drugs have a warnings and precautions in the product label. However, this section may be used to describe clinically significant adverse reactions or potential

safety hazards.

According to the regulations and FDA guidance, discreet adverse reactions to include should be serious or otherwise clinically significant and have implications for prescribing decisions or patient management. There should be reasonable evidence of a causal association between the drug and the reaction. However, a causal association does not need to be definitively established. Given that the order of warnings and precautions listed in this section should reflect the relative clinical significance, one labeling option is to move the neuropsychiatric adverse event subsection to the top.

Medication Guide is the next labeling option. A Medication Guide is FDA required patient labeling that addresses issues specific to a particular drug and is given each time the medication is dispensed. The target reader is the patient or caregiver. Not all drugs have a Medication Guide, but the FDA may require one if any of the three regulatory criteria are met. One, patient labeling could help prevent serious adverse effects of the drug, or the drug has serious risk 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. Or third, the drug product is important to health, and patient adherence to directions for use is crucial to drug's effectiveness. Stakeholders have requested a Medication Guide for montelukast, and we believe that issuing a Medication Guide may be appropriate, as the second criterion may be applicable in this situation. We ask for your input on whether you think a Medication Guide is appropriate.

A boxed warning represents the final option in our labeling toolbox. One may be issued to call attention to serious or life-threatening risks of a drug. According to regulations, a boxed warning may be appropriate if any of the following criteria apply. There is an adverse reaction so serious in proportion to the potential benefit from the drug 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. Or FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be used safely only if distribution or use is restricted. Whether the existing data support a boxed warning is an open question. However, this is an option available to us, and we are cognizant of stakeholder requests. We also note that feedback from the panel is important for us to consider in making a determination. Therefore, we ask the committee to discuss if a boxed warning for montelukast is warranted and to provide a rationale for your recommendation.

Having reviewed all of the labeling tools available to communicate this risk, I will now shift gears to other methods of communication, such as Drug Safety Communications and “Dear Healthcare Provider” letters. As outlined in our briefing package and Dr. Clarridge’s presentation, FDA has made numerous efforts through the years to communicate this risk with montelukast using a variety of different modalities that are available to us and listed here. That being said, we understand and share the concerns of parents and caregivers that this message is not getting through to all prescribers, and, consequently, the potential nature and

severity of risks are not routinely passed on to patients and parents to allow an informed decision before taking or continuing montelukast.

Within FDA, we have had extensive discussions and brainstorming sessions about other ways to communicate this risk to the public and to have the information stick so that it becomes common knowledge. However, a major challenge is that we have already utilized many communication strategies that are within our purview and control. Therefore, what we would like to hear from the committee today are your recommendations for additional communication strategies. We ask that you please consider the following in your discussion.

One, the target audience, the goal is to ensure that patients and parents are adequately informed of this risk. But what is the best mechanism for this? Dr. Ibrahim presented drug utilization data indicating the montelukast is most often prescribed by primary care physicians, mid-level providers such as physician assistance and nurse practitioners, followed by pediatricians. Should efforts be focused on these prescribers or on other members of the healthcare community, such as pharmacists and school nurses who may come into contact with patients? Are there any others that you would recommend?

Two, target organizations, engaging organizations that can disseminate information to their members may be a strategy to reach a wider audience. This could include professional societies, such as the American Academy of Pediatrics, American Academy of Family Physicians, American Academy of Allergy, Asthma, and Immunology, Nursing Associations, just to name a few. In addition, we also heard that asthma is the most common diagnosis provided for prescribing

montelukast. So engaging with asthma networks is another idea. We welcome your thoughts on others.

Finally, we ask you to discuss and recommend modalities of communication that will be effective for reaching our target audience and organizations. Some potential options include continuing education modules and questions, articles in medical journals, webinars, social media posts, email updates to listserves, and perhaps incorporating this information into treatment guidelines for asthma and allergic rhinitis so that montelukast is not used as first line therapy. The ideas provided on this slide are not intended to limit the scope but hopefully will just serve as a jumping off point for discussion and, rather than a single strategy, a multipronged approach that facilitates engagement and communication among the relevant stakeholders and groups is likely needed to ensure success.

In conclusion, we ask the committee to discuss the following three topics. First, we would like you to discuss your assessment of the neuropsychiatric safety findings with montelukast use that have been presented today. Second, we would like you to discuss the current label for montelukast, which includes warnings and precautions. We would also like to hear your thoughts on the request for a Medication Guide and boxed warning. And third, we would like to hear your recommendations for successful communication strategies. We ask that you specifically consider the target audience, target organizations, and modalities of communication that will be most effective. And please include these in your discussion. We are also interested in hearing your ideas for implementation for any recommendations beyond our control. This concludes my presentation. I

thank you for your time and attention, and we look forward to a thoughtful discussion and welcome your input.

DR. WADE: Thank you very much to all five presenters this morning. That was a thorough overview. We do have an hour and a half session this afternoon after the open public hearing for us to discuss these specific topics and questions laid before us. We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. And we will resume in this room promptly at 10:30 to begin the open public hearing. Thank you.

(BREAK)

OPEN PUBLIC HEARING

DR. WADE: If everyone could please take their seat, I'd like to get started on time. I'd like to remind people once again to please silent their devices. Welcome back. This will be the beginning of the open public hearing session. Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at this open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your oral or written statement to advise the committee of any financial relationships that you may have with the sponsor,

its product, or, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your consideration. Will speaker number one please step up to the podium and introduce yourself? State your name and any organization that you are representing for the record.

MS. ENGLAND: Good morning. My name is Jennifer England, and I do not represent any organization. I have no fancy title by my name. The only people I'm representing are what will always be for me the England Party of Five.

In February of 2017, my oldest son was prescribed Singulair for seasonal allergies. A few days after starting the generic version of Singulair, montelukast, he developed the flu, went back to the doctor, and was prescribed Tamiflu. While

we don't think he took the entire prescription of Tamiflu, we know he took Singulair montelukast for 12 days. And on the 13th day, he did not take the 13th pill. He took his life. No warning, no signs, no reason.

He was given two prescriptions within a week that I now know have neuropsychiatric side effects, and no one blinked an eye about it. And I'm standing here today. I still cannot believe that this is my life. The devastation that we live with everyday is almost unbearable.

Nick did not suffer from any mental health issues, none. He did not have a history of depression. He did not have a history of mental illness. He was just like any other 22-year old college senior, living his best life and making plans for his future. Beyond his allergies, he was perfectly healthy, perfectly healthy.

It took us awhile to connect what happened to his medication change. The local sheriff's department, many of whom are personal friends, went above and beyond to try to piece together what may have happened. And after investigating for several months, they found out -- they told us this. "He was as good as you said he was. Nothing was different in his life but his medication, not one thing." Not only do we believe that he suffered from the side effects of his medication, but the evidence of his life and the evidence surrounding his death support that.

I read in the report you released the other night ahead of this meeting today that the problem you've always had has been how to get the word out about the possibility of the side effects. Ten years ago, you were struggling to figure out how to make the public and the medical community aware of what could happen in worst case scenarios. I'm your worst-case scenario, ten years later.

I don't live here. I live out there in the land of the sea to the shining sea. Settings like this, they're not my circle. I live in a small area. And I can tell you that out there, in small town America, people do not know that montelukast is dangerous. My husband took it for about a year and never one time, not once, did anyone mention to him that it had any kind of adverse side effects. When the investigators stood in my dining room the day that Nick died, they asked me if he'd had any medication change. And I sobbed into their chest, "Just an antihistamine for allergies."

There's a huge disconnect between these FDA walls and the world out there. Medical professionals, pharmacies, nurses, they don't know to talk to their patients about possible adverse side effects. I know because I've talked to them. Handing a fist full of papers with a bunch of fine print to a 22-year-old, that isn't enough. He's just learning to be an adult. Merely signing on the dotted line when you pick up a prescription, that isn't enough. If someone, anyone had been able to talk to Nick for ten seconds and explain that what he was feeling could be a side effect of a medication he was on, it could have saved his life.

I would give anything to have a chance to talk to him again. I know the people who treated Nick would love to be able to go back and talk to him. We don't get that chance, but you do. You have a second chance. Please do what it takes. Put whatever procedures in place you have at your disposal to educate everyone so that someone else isn't standing here ten years from now again, begging for something to be done. Nick's plans after college included a career in medicine, true story. Little kids loved him. I hoped he was going to be a

pediatrician. He wanted to make healthcare better. He can't do that now, but you can. Please do it for him.

DR. WADE: Thank you for sharing that story. Could speaker number two please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. PALAZOLA: Hello, my name is Lisa Palazola, and I'm here representing my family. I'm the proud mother of two adult children, a healthy 31-year-old son and a 27-year-old montelukast affected daughter. My bright, happy, vivacious child was diagnosed with asthma at age three, and at seven years of age she started taking five milligrams of the chewable montelukast on the recommendation of her pediatrician. We asked about side effects and were told there were none to worry about. Her doctor herself said she was on it, and it had worked wonders. We trusted her, so my daughter started taking it nightly.

She seemed to have fewer asthmatic episodes, but she felt sick often. She was put on antibiotics several times a year for various illnesses but mostly respiratory infections. She also complained of headaches, frequent stomachaches, general malaise, aches, pains, and fevers. When she was about 12 years old, her dosage doubled to ten milligrams, which is the recommended adult dosage. My child was small of stature and build, weighing less than 90 pounds. I would like to know why this potent medication is prescribed by age and not weight, particularly when the mechanisms within the brain that cause neuropsychiatric side effects are unknown and yet to be discovered.

She then began to withdraw from friends and activities. She became

agitated often, aggressive, and anxious, seemed to feel ill more frequently, became depressed, was exhausted, and had suicidal ideation. She also had vivid, horrific nightmares of people being gutted, decapitated, and tortured. These, along with the voices that told her to hurt herself, terrified her. She barely slept, afraid of what she'd dream. How does a child who has never seen such atrocities dream about them?

We asked our doctor if these symptoms could be related to montelukast. We were told that she was just a highly emotional teenage girl. Counseling and therapy did not help with her anxiety and depression. She would text me many times while I was at work, begging me to come and get her from school as she was hiding in the girls' bathroom. The light in her eyes had vanished.

Five minutes is far from enough time to share everything she and our family went through, but several years later, after another epic screaming and crying battle with her, I heard a news report of a teenage boy who'd killed himself after taking montelukast for a very short time. I was in shock and began research, which produced many stories of both children and adults who had eerily similar experiences as my daughter. We believe that Cody Miller's tragedy saved my daughter's life because that was her first day not taking montelukast, against medical advice from her doctor. She said she had thought about suicide many times and had even written a goodbye letter.

There were no warnings of these terrible life altering side effects when my daughter took it and no recommendations on how to stop taking it after. A few weeks had passed, and she seemed to be doing better. But about six weeks later,

she experienced withdrawal, which included shaking, crying, loss of appetite, and her anxiety and depression were back as strong as ever. Two days ago marked her 11-year anniversary of stopping montelukast, yet my daughter still suffers from the protracted side effects of anxiety and depression.

I find it very disturbing to have recently learned that protracted side effects were documented in a child taking montelukast in one of the FDA medical reviews. If this had been included in the prescribing information, my daughter may not be suffering now. This drug doesn't just affect people who take it. It ruins relationships, divides families, and destroys parents' dreams of the hope for the future of their children. My daughter and countless others have lost their childhoods, a time when critical years of neurological development takes place. But they are the lucky ones because they are still here with us. It is clear that we need more research, proven solutions and treatment for healing, and action in the form of a black box warning and REMS, along with educating prescribers and other medical professionals. This will give people the critical information they need to make a personal decision in advocating for their own healthcare.

Earlier this year, my 90-year-old father who has dementia was prescribed montelukast for a chronic cough. I spoke with the on-call doctor who was recommending this treatment and said there was no way I would give it to him. He asked why I was so adamant, so I shared my daughter's story. He got online and started reading to verify what I was telling him and said he had no idea. We can't change the past, but we can look forward to hope for change. My daughter shared a quote on social media this week. It said, "You've mastered survival

mode. Now, it's time to live." Thank you.

DR. WADE: Thank you very much for sharing your story. If I could ask speaker three to please step up to the podium and introduce yourself. Please state your name and any organization that you are representing for the record.

MS. MIGRIN: Hello, my name is Kathryn Migrin. I am 14 years old, and this is my story about taking Singulair. Growing up, I had a lot of interests and hobbies that I very much enjoyed. I loved to play piano, and I loved going to school and learning and so much more. I have a great family with some pets, and everyone is very loving and supportive. My education, I've been accelerated with all of it in an ACAT program in elementary school and then the MACAT program in middle school. This is kind of where everything crashed and burned, and things went really badly.

It all started when I was prescribed Singulair in June of 2018 for my asthma. We were not warned of any risks by our doctor. And taking it the end of that summer, by September, I was harming myself, and I was suicidal. In the hospitals that I went to, I was diagnosed with depression, social and generalized anxiety, and OCD. I was put on a lot of medications, but none of them made any progress with my mental health because I still had the montelukast in my system.

I had seven inpatient hospitalizations with five outpatient partial hospitalizations and just too many crisis plans and trips to the emergency room to count. And not a single doctor we saw who knew I was on Singulair told us that these feelings that I have might have been related to taking Singulair. Last year, in total, I spent 75 days in inpatient hospitals. And because of my mental health, I

missed pretty much all but 14 days of my entire eighth grade year. And that was just because of the hospitalizations and how unsafe and unstable this medicine made me.

In January of 2019, six months after I started Singulair, I stopped taking it after my mom found out that how I might be feeling might be related to Singulair. In time after I stopped taking it, I began to feel more like myself, and the suicidal ideation and the thoughts about self-harm started to decline. All of my four attempts at suicide were while I was on Singulair. And since I've been off of it, I haven't made another attempt, and I've been a lot less prone to harming myself.

It took a whole six months of recovery to get me to the point I'm at now. Things aren't perfect with my anxiety or my depression. But I am so grateful that my mom found that article because I might not have been here if she hadn't have found out it was so bad. My purpose getting up here and speaking today is to get some warnings out that are required and just to help people because what I went through was pretty traumatic. I don't want anyone else ever to have to go through this. I strongly encourage you to put a warning on all montelukast products. That's the end, I think.

MS. S. MIGRIN: I just wanted to bump in, and I don't think Katy knows this. So cover your ears, honey. But it was \$186,000 in medical bills between September of 2018 and January of 2019 for our family. Thank you.

DR. WADE: Thank you to both of you and to Katy for sharing your story yourself. I will now ask speaker number four to step up to the podium and introduce yourself. Please state your name and any organization you are

representing for the record.

MS. ANDERSON: Good morning. My name is Charmayne Anderson. I'm the Director of Advocacy for Allergy and Asthma Network. We're a national non-profit dedicated to ending the needless death and suffering due to asthma, allergies, and related conditions for the 60 plus million Americans living with these conditions. We have no financial disclosures to report. I appreciate the opportunity to share concerns reported with neuropsychiatric adverse events involving montelukast. These concerns were raised by thousands of patients within our community, and here are a couple stories I want to share of families who will forever be changed as a result of this product.

First, there's Izaiah Fiedler (phonetic) who was a born leader, gifted musician, loved running cross country, and was a senior class high school president. He lived on a Cherokee reservation in Tahlequah, Oklahoma. He had dreamed of becoming a medical missionary, but unfortunately, his life was cut short due to suicide in 2016. His family is still haunted by their lack of knowledge regarding the risks of montelukast for which they attribute his death.

Next, there is the Marotta family, who you will also hear from later. Mom Laura wrote to share her son's experience, describing him as a happy, healthy boy, who changed seemingly overnight when starting this treatment. She was frustrated and afraid because, unfortunately, his symptoms did not resolve after discontinuing the medication. Constant night terrors, angry outbursts, and uncontrolled crying became the norm in their home. Ultimately, they were referred to Boston Children's Hospital where they were tested and learned of their

son's variations on two of the three genes directly involved in the metabolism of montelukast. This may have increased his susceptibility to these adverse events.

Because genetic variance related to the transport and metabolism of montelukast had been previously suggested to increase the susceptibility to neuropsychiatric events, it is imperative that a large-scale study evaluate the data and potentially establish a formal screening process before prescribing. Over the past several years, Laura has assembled a team of health professionals and advocates, as well as affected patients and caregivers, to learn how an asthma and allergy medication acting on the respiratory system can have such severe potentially irreversible effects on the brain. This harrowing journey led to one conclusion. The focus of the current safety evaluation must shift from simply quantifying risk to examining the actual biologic mechanism for the neuropsychiatric adverse events.

For almost two decades, parents have watched their healthy children suffer from depression, anxiety, hallucinations, paranoia, panic attacks, and so many things more both during and after treatment with montelukast only to be dismissed because there was no proof. But at the same time, there are studies being conducted across the globe showing montelukast has biologic effects on the brain, both structural and functional, which can be either positive or negative depending on psychological conditions. The focus of the pre-meeting report focused on prevalence rate for the neuropsychiatric events. The report acknowledged a distribution across the blood brain barrier, the negative impact on the hippocampus, and the inhibition of this GPR17. Much of the information

presented is considered new scientific information that has emerged since the original market release of the drug.

This new information actually served as a foundation for the clinical trials currently being conducted in humans for use of montelukast in treating Alzheimer's disease. As such, the focus should be on the evaluation of biologic effects to the brain. Clearly, the American public and medical community has the right to know that a medication they are giving their child and/or patient to treat their respiratory system is also acting on their developing brain. In addition to the new scientific information, FDA admits to knowing the amount in the brain exceeded that in plasma during the pre-clinical trials, and the subsequent clinical trials in humans were not designed to measure those effects to the brain. And they have no plan to conduct further studies. This is unacceptable.

It is now up to members of this committee to address the research with the understanding that there has never been a clinical trial to measure the effects on a child's developing brain. It is essential the asthma community be fully aware of all research, as well as the potential biomarkers, in order to make necessary treatment decisions without harming patients. We implore the committee to consider the Fiedler and Marotta families, as well as the millions of others impacted by these diseases and potentially harmed by this product. And I will also add let us be one of your communication channels. Thank you.

DR. WADE: Thank you very much for that presentation. I would now like to ask speaker number five to please step up to the podium and introduce yourself. State your name and any organization that you may be representing for

the record.

MS. MAROTTA: Hi. My name is Laura Marotta. I do not represent an organization. You are about to hear the true horror inflicted by montelukast directly from the mouth of a child that lived it, my son Nicholas. His story is representative of those that experienced the new or worsening symptoms after the medication is stopped, and it's an important story to be told here since our adverse event report was not filed during the limited timeframe of the FDA FAERS review, where they only identified two cases of withdrawal.

For 120 days after discontinuation, we helplessly watched as our son was tormented by his own mind, left paranoid, terrified, and unable to sleep or function. The experience was strikingly similar to withdrawal syndrome we see when people abruptly stop taking medications that are essentially acting like an antidepressant. But the professionals completely repudiated the possibility that an asthma drug could be associated with a discontinuation syndrome, under the premise that montelukast only acts on the respiratory system, not the central nervous system.

Their belief is rooted in Merck's pre-clinical data that claimed only trace amounts of montelukast were detected in the rat brain and in Merck's prescribing information that indicates there is only minimal distribution across the blood brain barrier and that it only inhibits the airway leukotriene receptors. Their denial prompted me to embark on a journey to learn how an asthma drug just acting on the respiratory system could have such severe, potentially irreversible affects on the brain. Together with a team of doctors, researchers, drug safety advocates, and

caregivers, I evaluated the new scientific information about this drug and its pathway that has emerged since its market release back in '98.

The findings have allowed me to stand before you and confidently state the FDA's investigation completely missed the mark. Their entire focus, from the FAERS review to the observational literature review, Sentinel study, was all aimed at quantifying a prevalence rate for an unintended side effect in the central nervous system. But yet, the FDA acknowledges that montelukast directly acts on the central nervous system. Page 14 of the FDA briefing document, that was completely excluded from their oral presentation today, summarizes the studies being conducted across the globe showing that montelukast does, in fact, have biological effects on the brain, which can be either positive or negative, depending on underlying conditions.

The FDA acknowledged that montelukast negatively affected the neuroproliferation in the hippocampus of an intact juvenile rat brain, a part of the brain that plays a key role in learning, in memory, with alterations being linked to a variety of cognitive pathologies, such as anxiety and depression. The FDA acknowledges that montelukast does not just inhibit the leukotriene receptors but also the GPR17, the function of which was completely unknown 20 years ago but is now recognized as a regulator of cells linked to several major mental illnesses and disruptive mood regulation. And keep in mind the studies that the FDA acknowledged served as the foundation for the current clinical trials in humans for use of montelukast in treating Alzheimer's disease, a brain disorder.

The FDA's investigation did not include a single study showing the

association between genetic variance and efficacy, nor did they address the strong recommendation from leading experts for a pharmacogenomic study. Understand the significance of this meeting transcends the neuropsychiatric events relating to an asthma drug. This meeting is a portal for the American public to see how the FDA responds when new scientific information emerges after the drug has been released to the market. Today, we discovered the FDA does not recognize the need to update the prescribing information with this new scientific information. The FDA does not recognize the need to alert the medical community to this new data. Distressingly, without this information, the community will continue to deny the possibility of a discontinuation syndrome and not understand that side effects could have a delayed onset and be potentially irreversible.

Please, I implore the committee members, before you vote today, fully evaluate the list of recommendations in my written submission. I provided copies at the registration desk. This inclusive list is the only way to ignite real change. Thank you.

DR. WADE: Excuse me. Thank you very much for that presentation. Will speaker number six please step up to the podium and introduce yourself? State your name and any organization you are representing for the record.

MR. MAROTTA: My name is Nicholas Marotta. I just turned 13 last Friday. I thought a lot about how I could try to describe what happened to me after I stopped taking montelukast, but I realized a bunch of words could never really make you understand what I went through and how scared I was. I thought maybe if you saw it with your own eyes, it would help you understand a little

better. So I made a video that I want to show you. But before you watch it, I want to ask you one thing to keep in mind. When your brain gets tormented by thoughts that no one should think of or pried apart by so many nightmares that you don't know which ones are real or knocked out by emotions of depression, anxiety, and anger, no one will ever see the torture chamber inside you. No one can see that.

When I was going through this, everyone was trying to help find the problem they couldn't see. They looked at me to explain what was happening, but, at first, I didn't know what to tell them. I didn't know. It was easier for me to agree to their ideas, like maybe I was homesick from Boy Scout camp or maybe I was nervous about starting middle school. But deep down, I knew that wasn't it, and I felt trapped, scared, alone, and hopeless.

I'll never forget the night my mom told me that she met another mom on the internet whose son was going through the same thing after he stopped taking the medicine. I'll never forget that moment . I felt relief. I felt like I wasn't alone. I felt hopeful that if we found the problem we could find a way to fix it. And that's why I am here.

I want to ask you to give other families that are scared and alone, just like mine was, that moment. Help them make the connection from their symptoms back to the medicine. I know there's nothing you can do to stop other kids from having these side effects, but you can help them by making it easier to figure out what's really going on inside their skin. I'm depending on you.

(Video.) My name is Nicholas Marotta. I'm 11 years old, and up until

recently, I lived a basic life. I lived with my mom, dad, twin brother, little sister, and my dog, Lola. I'm a brownbelt in karate. I work hard, and I'm dedicated. I just started learning how to play guitar. I love school, and I have great friends. But one day, all this changed.

I started feeling sad all the time for no reason. Turns out the medicine I was taking for my asthma, called montelukast, which is a generic for Singulair, was known to make some people feel sad. The plan was to stop taking this medicine and go back to being just a happy kid again.

But once I stopped the medicine, everything got worse, a lot worse. I became so depressed I couldn't get out of bed. I didn't want to eat or talk or go to school any more. I would cry for hours. I couldn't stop myself, even though I wanted to. I could only stop when I was too exhausted to continue.

I'd fall asleep but would have such scary nightmares. Then, I started hearing voices. I was so confused. I felt like everything was fake. I started seeing images that weren't really there. I was scared. The worst part was my parents were scared, too. Parents always know how to make everything better. So when I saw them scared, I knew something was seriously wrong.

They started taking me to doctor after doctor after doctor after doctor, but no one had any answers. My mom made me promise not to give up, and she promised me she would find out what had happened to me. She started researching every hour of every day and night. After 14 long weeks, she found a pharmacogenomic team in Boston that thinks all my problems are because of the montelukast got stuck in my body because I have a variation on a very important

gene.

We found an amazing doctor that helped me. Slowly, my body is healing. I know I can't go back and change the beginning of my story, but I can change the ending. My story will end with me helping as many people as I can. I wrote a song to remind people to never give up. It's called "Hope is Hidden." I also encouraged my parents to share my story on Facebook to spread awareness. After we received thousands of comments, we realized that these side effects are not extremely rare like we first thought but simply unreported. If the people that are there to help us and protect us don't even know how bad the side effects can be, nothing will change. Please, help us make sure this never happens to another kid ever again. Together let's change the ending of our story.

DR. WADE: Thank you, Nicholas. I would now like to ask speaker number seven to step up to the podium and introduce yourself. State your name and any organization that you are representing for the record.

MS. HAMMER: Good morning. My name is Stephanie Hammer, and I am here not representing any organization. I'm here to represent what happened to my son. I come here to address you today because in 2014 my 11-year-old son suffered severe neuropsychiatric side effects from Singulair. There is no doubt in my mind that what my child experienced was caused by this medication. My three-sport athlete, high-achieving student, loving boy with no history of mental illness, living in a stable home with loving parents, experienced absolute horror because of this poison.

After a dosage increase from five milligrams to ten milligrams, my son

suddenly became deathly afraid of the dark, began having night terrors of being murdered or his family being murdered, began crying over every little thing, and would hold his head saying the bad thoughts just wouldn't leave his mind. His self-esteem plummeted, and he started to believe he was a bad kid with bad thoughts and not worthy of this life. He was scared and could not understand what was going on. As his mother and a registered nurse, I also could not understand what was happening, and I was afraid. Was he being bullied at school? Was this some strange pre-teen developmental phase, or could he suddenly be mentally ill?

Initially, we tried to handle this alone at home to avoid judgement and the harsh stigma mental health issues bring. However, we were losing ground fast. Our family was stressed. Our marriage was strained, and our other children were afraid and sad. Everyone and everything was broken.

For eight months, we struggled to handle this at home. We did not share with the pulmonary or the pediatric physician. But we did seek the assistance of a counselor. One sleepless night, we did a Google search only to find carbon copy stories of what was happening to our son happening to other children. The common thread, all these children were on Singulair, montelukast.

We stopped the medication immediately and informed the counselor. The counselor doubted it was the medication, but we felt confident that if we stopped this he would get better. Nothing else could explain this sudden and drastic decline in mental health. Unfortunately, things intensified after abruptly stopping Singulair, and our son became withdrawn and started having suicidal thoughts.

In complete despair, we had him admitted to a psychiatric facility. It was

one of the hardest things I have ever done, and the memory of all of us crying and waving through the window as we left will haunt me forever. And this trauma has left a deep scar on the psyche of my son. We visited him daily and devised a counseling plan with the professionals. And we argued with doctors that we did not want our child placed on any psychotropic medications, as they began throwing around possible major diagnoses, such as OCD and major depressive disorder. I knew in my heart this was not my son. Singulair had done something to his brain, and I refused to allow them to label him.

It took three months after the cessation of Singulair before these severe neuropsychiatric symptoms subsided and I got my son back. The trauma of this time has left a painful scar on my son and my family. The anger and guilt I hold for allowing this to happen has driven me to advocate for change where I feel there has been great failure. This medication was prescribed to my son without any patient counseling by the prescriber or the pharmacy.

I wish I knew then what I know now. I wish I knew then that the data from the original drug application for this drug's approval depicts a table in which the concentration of ten milligrams of Singulair, 24 hours post-dose, is 971 percent greater in the brain than that of the plasma, 971 percent. Despite this, the FDA granted approval of this drug without requiring the drug company to perform appropriately designed clinical studies to assess the effects on the brain or determine the actual biological mechanism. I wish I knew then that the new scientific evidence has confirmed this medication crosses the blood brain barrier in substantial quantities and not only acts on leukotriene receptors but also GPR17,

which is linked to mental illness.

I wish I knew then that pediatric advisory committee sat here in 2008 to review this very issue and required a “dear doctor” letter that they thought would help with awareness. I wish my son’s doctor would have conveyed that information to me. I wish I knew that any benefit of this drug would never outweigh the unimaginable life altering and life destroying risks.

For 20 years, Singulair, misleadingly marketed as safe and effective, has been prescribed to babies and children with vulnerable developing brains. How many other children have been prescribed this without any patient counseling to watch for neuropsychiatric adverse reactions? How many other children and families are suffering right now and have yet to put it together but are blaming it on developmental behavior issues? How many babies are being tortured but can’t verbalize what they’re going through? How many more lives need to be destroyed before we stop and practice responsible medicine?

When I graduated nursing school, like many medical professionals, I took an oath. The underlying ethical message behind that oath was to do no harm. This drug is greatly harming people, and the governing powers are allowing it to continue. Instead of admitting a mistake was made, instead of admitting scientific evidence to conclude what is happening in the brain is lacking, instead of admitting that adequate clinical trials to assess mood and behavior while on this drug are non-existent, the governing powers and makers of this drug are scrambling for evidence to say it’s okay that it gets into the brain and that it has no effect.

You can pull incomplete data from medical claims databases, come up with excuses of other reasons why these patients suffer neuropsychiatric adverse events, and you can attempt to discredit any study that shows what you do not want to acknowledge. But facts are facts. The scientific evidence is not there for you to look me in the eye and tell me how it gets in the brain, what it does in the brain, and the effect it will have on mental health. This is irresponsible practice of medicine.

I ask that you imagine this horror happening to your own child, that you acknowledge the failures that have occurred along the way by the physicians, the drug developer, the manufacturers, and the FDA, that you take the opportunity to use the power given to you today to recommend the necessary actions and changes to protect other patients and their families. At a minimum, your recommended interventions should include a black box warning and a required medication guide. It is clear what has been done to date is not enough. If you choose not to listen and weigh heavily the real-life evidence speaking to you today, then you will perpetuate the problem and become a part in continuing to harm.

DR. WADE: Thank you. I'd now like to ask speaker number eight to step up to the podium and introduce yourself. Please state your name and any organization you are representing for the record. I would just like to pay attention to our time constraints because we'd like to make sure that all 14 speakers have an opportunity to speak to us today. Thank you.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-

Rawlings. I am a neuroscientist trained at Case Western and Children's National Medical Center. National Center for Health Research analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

The reports on neuropsychiatric adverse events during and after the use of montelukast deserve our complete and thorough attention. We need better data to identify how likely patients are to experience these side effects. The studies conducted by the FDA and sponsors tried to address these concerns, but there are major limitations to the sources of the data used in these studies that makes the results inconclusive. FAERS reports are voluntary and lack a lot of basic information about the patient and the adverse event. Moreover, many clinicians don't report side effects that are already listed on the label. We know that these reports are only available for a fraction of actual occurrences, but we don't know what percentage of events they represent nor are they necessarily characteristic of all events.

The Sentinel database provides information on claims data, so patients' adverse events that are only identified if they are treated in a medical facility with properly coded claims data. Someone who, for example, becomes aggressive or suicidal but does not seek medical treatment would not be identified in the Sentinel database as having an adverse event. The sponsor's clinical trial data includes a large number of patients in randomized double-blind controlled clinical trials, which seems like a good source for comparative data. However, many of

these trials were short term, and they were not designed to capture information on these kinds of adverse events. Thus, it is likely that many patients who experience these symptoms did not have them reported or recorded in these studies.

It may be difficult to determine the subset of patients who have an increased risk for harm, but it is important to do so. Studies have identified that some genes that affect the efficacy of montelukast. It is likely the genetics or other inherited characteristics also affect its safety. In addition, we know that this drug can affect the brain. We encourage the FDA to require more definitive research on this topic as soon as possible.

In the meantime, patients, parents, and clinicians need to be aware of the risk for neuropsychiatric events so that they can weigh the benefits and the risks for each patient, especially if the drug is prescribed for mild symptoms. Many patients and parents are not sufficiently informed about these risks, so they cannot make an informed choice. What can the FDA do to help patients, parents, and prescribers make an informed decision on whether to use the drug? Require that a brief, easy to understand medication guide and check list are provided by the prescriber prior to writing the prescription. FDA has required checklists on other medical products which patients or parents must sign to show that they understand the risks. The purpose is to improve informed consent and help patients recognize and appropriately respond to neuropsychiatric side effects.

In summary, we need much better data to determine the likely benefit and risk of harm for patients. FDA has an important role to play in encouraging this research. In the meantime, patients, parents, and clinicians must know about the

risks so that they can make an informed decision about whether or not to use it.

Thank you.

DR. WADE: Thank you very much. I'd now like to ask speaker number nine to step up to the podium and introduce yourself. Please state your name and any organization that you are representing for the record.

MS. PANY: My name is Kammy. I've traveled from Arizona and stand before you as a parent representing the 7,300 members of the Montelukast Singulair Side Effect Support and Discussion Group. This group has more than doubled since our 2017 letter referenced in today's meeting.

Several years ago, I found myself in a desperate search for answers. Our then seven-year-old changed. He became angry, depressed, hyperactive, and developed suspected Tourette's. He went from top of the class to special education. One day, he even attempted to leap out of our car in anger. Doctors provided no valid explanation for this horrific change, which came on gradually and insidiously 18 months after starting montelukast. Our son worsened after discontinuation and suffered an intense withdrawal period lasting months. MRI showed his brain was inflamed. He couldn't leave the house and developed heightened sensitivities to artificial additives. After two years, countless medical bills, and a harrowing journey to find doctors that could assist, his teachers noticed significant improvement. Sadly, to stay stable, his life must now be regimented with a restricted diet and regular therapy.

Our story isn't unique but rather a blueprint for what we've seen reported over and over within our group. Our administrators have communicated with

thousands of families, and we continue to regularly hear about the delayed onset of side effects, withdrawal, and the protracted long-term effects caused by an adverse reaction. We are not medical professionals, but we have become a valuable support system for families devastated by these debilitating and possibly irreversible adverse effects. We ask you at what point did suicide, suicidal thoughts, and depression become an acceptable side effect for an asthma medication considered safe with no intended psychotropic effect?

It is not acceptable to prescribe this medication without informed consent. Doctors must inform parents that they will be consenting to the possibility of suicide or mental health injury, particularly when symptoms can be controlled by other safer medications. What is dangerous about this drug is that it gives you a false sense of security. If it works for you, it can relieve your allergies and asthma well to a point where you don't notice you were feeling off mentally. The side effects can appear subtle at first or all of a sudden dramatically after stopping and restarting and after dosage increases.

This medication is a ticking time bomb for some. Many members report that, when that time bomb goes off, their children become a shell of themselves. Parents report school refusal, suicidal thoughts and actions, uncontrollable crying, uncharacteristic hostility, hallucinations, vivid and horrific nightmares, thoughts of death and dying, and the list goes on. Why doesn't montelukast have a black box warning, a medication guide, and a risk evaluation and mitigation strategy? How many need to die before this drug gets a black box for suicide? Are the deaths of montelukast induced suicide of Cody Miller, Sarah Hozen, Izaiah Fiedler,

Nicholas England, James Burke, Terry Burry, and Basil Yarba not enough?

Currently, there is no medical guidance on how to recover from the aftermath of an adverse reaction. The most well-intended physician may struggle to provide support, especially when encountering a child who suffers from this unrecognized withdrawal. Parents or doctors may not report withdrawal if reporting an adverse reaction immediately.

We are telling you that withdrawal is not such a rare phenomenon but lives in the tail of a bell-shaped curve. Our Facebook group has allowed us to connect the people who exist in this long tail of the normal distribution that dominates the results of most scientific studies. The existence of these common experiences can no longer be denied. We have almost 480 individuals that suffered protracted side effects, of which 411 are children. We have over 326 individuals that suffered withdrawal, of which 267 are children. Our members have filed MedWatch reports, made public statements for this docket, and some are standing here in this room today. We can assure you that there is no recall bias in the reports of our members. I say this because the majority of interactions amongst our group are real time desperate requests for help while these events are unfolding in front of their very eyes.

The FDA acknowledges montelukast affects the brain, but do we know exactly how? Published Alzheimer's research shows that montelukast works differently in the brains of young and old rats. However, details of those difference have not be published. It's frightening that montelukast decreases the proliferation of neurons in the hippocampal region of young and healthy mice.

The risks to the growing brain are too significant to allow doctors to continue to prescribe this medication to children for mild coughs and allergies.

Why isn't the FDA demanding that drug manufacturers or other researchers identify the mechanisms that cause neuropsychiatric side effects? What epigenetic changes, what damage has occurred in the brains of our children? If using montelukast can cause irreversible damage, then it must be communicated. At what point is the absence of action on this dangerous medication considered negligence?

On my flight here, the mother next to me connected her son's recent behaviors to montelukast from this very speech just glancing over and seeing it. As stated in our group's written public statement, which we hope you have had a chance to read, we ask you to make brave decisions today, to minimize the risks and save lives because, for our families, the benefits do not outweigh the risks. Thank you.

DR. WADE: Thank you. I'd now like to ask speaker number ten to step up to the podium and introduce yourself. Oh, thank you.

MS. WITCZAK: My name is Kim Witzak, and I'm coming to you from Minneapolis, Minnesota. I have no financial conflicts of interest in the matters being discussed today. I just wanted to offer my perspective on this very important safety discussion of montelukast.

I like to call myself the accidental advocate. I never set out to be a drug safety advocate 16 years ago. However, I was thrown into this world and not by choice. In 2003, my husband Woody was given an antidepressant for insomnia,

and five weeks later, he took his own life without any history of depression or any other mental illness. At the time, there were no black box warnings on antidepressants. Shortly after his death, I established Woody Matters, a drug safety organization representing the voice of families across the country who live every day with the consequences of a flawed drug safety system.

I see many similarities between the safety discussions you are having today on montelukast and the ones we had on antidepressants back in 2004 and 2006. Many of the serious harms that were not initially seen in the original clinical trials are now coming to light after being on the market for years and taken by millions of people. The real-world reports of parents watching their children suffer from depression, anxiety, hallucination, paranoia, aggression, panic attacks are being dismissed by the medical community because there's no scientific proof. They say the risk of serious adverse psychiatric events is rare. But if this small risk happens to you or your family, it's your 100 percent.

There's a growing body of new scientific evidence, literature, and ongoing global studies that has emerged since the drug came on the market showing serious neuropsychiatric side effects and issues with discontinuing the drug. Yet there is yet to be a pediatric study looking at the impact of the drug on a growing child's brain. But we're testing the drug on Alzheimer treatment?

There's a general perception that this medication is safe; yet there's a lack of understanding by the medical community of the mechanism which is causing the potential harm in some people. The need for black box warnings is real. The current warnings for montelukast found under precautions and prescribing

information do not go far enough.

Learn from the antidepressants. It took the FDA 13 years after they first held the hearings in 1991 to finally add black box warnings to these drugs. How many lives were lost in between that time? Of course, there's always the fear of not wanting to scare parents or patients. But asthma is a huge market. According to the CDC, one in 13 people have asthma. There's over 25 million Americans. There's a lot of money at stake.

But at the end of the day, to us as patients, it's about having information. A black box warning should be added when there is a reasonable evidence of an association of a serious hazard with a drug. This would send a strong signal to the medical community, including pharmacists, psychiatrists, the psychiatrist, and the public about the potential for serious neuropsychiatric harms. At minimum, a med guide should be required. However, if a parent is unaware or even knows what a med guide is, it will not do any good. These med guides need to be available at the doctor's office and given to parents at the time the drug is being prescribed so that a conversation can happen.

Maybe we could do some trainings of physicians, including the psychiatric community, as well as a public awareness and media campaign aimed at patient groups. Maybe we could require informed consent forms that a patient and the family signs, acknowledging the potential for these harms. But at the end of the day, what if this was your child? Wouldn't you want to know, if they started to experience things like hallucinations, increased agitation, thoughts of suicide, that it could be their asthma medication? Trust me. I know I would. Thank you and I

appreciate your careful consideration of my comments as you deliberate the need for additional warnings.

DR. WADE: Thank you. I would now like to ask speaker number 11 to step up to the podium and introduce yourself. State your name and any organization you are representing for the record.

DR. ALADDIN: Good morning. My name is Meena Aladdin. I am a health researcher at Public Citizen. I have no financial conflicts of interest. So this is a second advisory committee meeting convened to discuss the labeling of montelukast and the risk of neuropsychiatric events. On September 23, 2014, PAC unanimously recommended to format the labeling to highlight the potential for adverse events and improve communication with healthcare providers so that they become informed about label changes to better counsel their patients. The FDA corresponded with the sponsor to consider communication options, but it was felt that these options were not warranted. The FDA did, in fact, collaborate with Medscape to communicate the effects of leukotriene modifiers to healthcare providers, but this effort was insufficient as there was evidence to suggest that caregivers were not adequately communicating the risks associated with this drug.

We strongly urge the committees to recommend that the FDA strengthen warnings on product labeling and improve caregiver communication to mitigate the potential risks of neuropsychiatric events associated with montelukast use. There is an ongoing risk communication problem, as noted in the FDA briefing material. Despite FDA's communication efforts and information in product labels, stakeholders have raised concerns that many physicians and patients are not aware

of the risks for neuropsychiatric events nor what to do if symptoms occur. Interestingly, despite the majority of cases reported by family members and consumers, we noted that no cases confirmed receiving patient counseling regarding possible neuropsychiatric effects of montelukast.

Compounding the issue of a lack of effective care provider communication is the widespread use of montelukast, particularly among pediatric patients. It is estimated that at least 2.3 million pediatric patients age zero to 16 were dispensed montelukast in 2018. There is a biological plausible mechanism by which montelukast does have a potential off-target effects. It binds to the cysteinyl leukotriene receptor-1 to prevent its interaction with inflammatory mediators, leukotrienes.

Now, expression of this receptor is not limited to the lung, and there's a growing body of evidence to show that it is expressed in different cells in the body, including microvascular endothelial cells, components of the blood brain barrier. Animal studies have amply demonstrated that montelukast administered orally can be found in the brain. As the FDA itself noticed, the biological mechanisms underlying the neuropsychiatric events associated with montelukast treatments are currently not well understood. However, evidence from animal studies suggest that montelukast could act directly on cells in the brain. Orally administered montelukast was detectable in the brain tissue and cerebral spinal fluid, providing evidence for its ability to cross the blood brain barrier.

There are other facts to support stronger warnings. The precautionary principle, so in accordance with gaps in knowledge, it is always safer to err on the

side of caution and take necessary steps to protect patients. Enhanced warnings, such as boxed warnings, do not require an establishment of causal relationship between a drug and adverse event. Furthermore, there were confirmed cases of positive de-challenge and re-challenge and reemergence of neuropsychiatric symptoms in patients.

In conclusion, we hereby make the following recommendations to the committee. We urge that the committee recommend the addition of a black box warning to the product labeling for montelukast for the potential of neuropsychiatric adverse events. Furthermore, we also ask that the committee recommend distribution of letters to healthcare providers and prescribers to better counsel them on montelukast use, the risk of neuropsychiatric events, and the importance of counseling to monitor patients. And lastly, we urge them to recommend that an FDA approved medication guide containing prominent warnings about neuropsychiatric events that is provided to patients or their caregivers when montelukast is dispensed. Given the lack of communication between prescribers and patients and the gaps in knowledge regarding montelukast effects in the brain, we strongly urge the committee to recommend to the FDA to take action and strengthen the warnings associated with montelukast use. Thank you.

DR. WADE: Thank you for that presentation. Will speaker number 12 please step up to the podium and introduce yourself, stating your name and any organization you are representing for the record?

MS. HICKLIN: Hello. My name is Elizabeth Hicklin, and I am

representing myself. I have traveled here with my loving mother from Orlando, Florida by my own expense. I'm a proud wife and mother of three and five-year-old boys. First, I want to thank you for being here to hear my story. As you see, I am not a child that has suffered from this drug. I am an adult. However, I felt it was necessary to speak today to clearly articulate the effects of montelukast in my life.

I took my last pill of montelukast on June 10 of this year. I had been on the medication for over 20 years, since 1998 while a sophomore college student when I was around 20 years old. I never had issues with depression prior to using this drug. Throughout these 20 years, I have dealt with severe depression, anxiety, sleep issues, and daily suicidal thoughts. I've been through years of psychological therapy since at least 2005 and recently went to a psychiatrist. He was the first doctor to question the use of montelukast in its relation to my condition, even after the added patient education information in 2008.

My main reason for speaking today is to talk about the effects of weaning and coming off of this medication. With the support of my primary care physician, PCP, and my psychiatrist, I decided to wean off the medication. On October 21 of 2018, I reduced my dose from ten milligrams to 7.5 milligrams. The first day, Monday, I felt fine. The second day, I started to feel anxious and more depressed than normal. By October 24, day three, I was in what I would now compare to detoxing off of a drug. I was shaking, sweating, and nauseous. My body ached all over, and I had extreme anxiety and depression and could not sleep, even with the use of my prescription sleep medication. I was ready to admit

myself to the hospital psychiatric ward.

But fortunately, my very supportive family helped me through this detox nightmare. I called my psychiatrist immediately, who advised me to go back to the ten milligrams and come see her again. This experience made me realize how much this drug had impacted my life and brain. I consulted with my psychiatrist and PCP, but neither of them knew how to wean off of montelukast. My asthma doctor, who had prescribed the drug originally in 1998, passed away a few years ago. And since montelukast was controlling my asthma, I did not seek out a new asthma allergy/asthma specialist.

However, when the debacle with weaning off the drug occurred, I called three allergists in the Orlando area to attempt to make an appointment but specifically about weaning off montelukast. Every doctor I spoke to said there was no reason to wean off the drug, that it would be fine to stop cold turkey. After consulting my physician, psychiatrist, and psychologist, I went back to the ten-milligram dosage until after the new year and then slowly started weaning off the medication.

There is no documentation. This was a shot in the dark. We decided to wean one milligram per month. Once I got down to six milligrams, I started decreasing every two weeks. I am now off of montelukast and in maintenance using an inhaled corticosteroid inhaler. My weaning process was slow and scary. There were times I thought my symptoms of depression were getting worse, but I pushed through. Presently, I do not have daily thoughts of suicide. My anxiety is less, and I am less emotional in general. And my confidence is being regained.

However, I have not been able to eliminate my depression, anxiety, and sleep medications. Hopefully in time, my body will heal, and I can get off those drugs, too.

Montelukast has had an enormous impact on my life. I honestly didn't believe my psychiatrist when she first related these psychiatric issues with montelukast. Who would think a drug that is supposed to treat a respiratory ailment could have such severe neuropsychiatric side effects? I hope you can seriously consider a black box warning and medication guide to this drug. I know many PCPs who prescribe montelukast and have no clue that there are neuropsychiatric side effects.

Just three months ago, my husband, at 48 years old, went to his PCP, and he wanted to put him on it for a cough. When my husband said he preferred another drug because his wife has had severe depression and anxiety from the drug, the doctor told him "Those side effects are not proven." Too many health providers do not know the serious effects that are associated with this drug and continue to prescribe it without hesitation.

I ask you to take my story into consideration and add a black box warning and medication guide to this prescription drug. It is important to other children, parents, adults, pharmacists, and doctors become more educated and made aware of the potentially dangerous side effects of montelukast. Even though my life was affected for more than 20 years, at least I am still here. I am one of the lucky ones who is still here to tell her story. However, montelukast has robbed me and cheated me out of the life, especially the joy of raising my precious boys. In my

case, when using this drug, the benefits did not outweigh the risks. I ask you to please take action and prevent others from suffering from the consequences of this drug. Thank you so much for your time and consideration.

DR. WADE: Thank you. We'll now have speaker number 13 step up to the podium and introduce yourself. Please state your name and any organization that you are representing for the record.

MS. MILLER: My name is Kate Miller, and I'm one of the founding members of Parents United for Pharmaceutical Safety and Accountability. And I have no financial conflict. My son's name was Cody. He was our only child, and he died from suicide in 2007 while taking the drug Singulair. I stand here once again and plead my case why this drug should be relabeled or taken from the market for pediatric use.

Cody was on the medication for 17 days, days in which his behavior changed dramatically, days which I had no time to understand he was having an adverse reaction to his allergy medication. Why? Because we were unaware it was even a possibility. I read all the material that was given to me with the prescription. Nothing there to worry about. His pediatrician was certain it was safe and effective. I asked because that is what I do. It did me no good. The fact that depression had been added to the label four months prior to Cody being prescribed this drug, the doctor knew nothing about it, had no words of warning, and the patient medication information sheet had no warnings either.

It's infuriating that I'm back here 12 years later. I can tell you as a mother of that child I would never have given him a drug with side effects of that nature

for a seasonal allergy. And at the very least, I should have had all the information about the possible risks in my hand so I could make an informed decision. I'm an intelligent person. That did not happen. I felt ill informed. What has been done about this situation happening over and over again? Nothing of any significance. This shows you.

The strongest warnings are needed. It will hold the hands of the physicians to the fire. It will make them take notice. They will give the information to these people. Our grass roots campaign began after our loss. I have had private meetings with key members of the FDA, my representative, Kiersten Gellibrand, in 2008 after the announcement of the risk communication safety review of Singulair. I spoke at the risk advisory meeting in 2011 about the changes in labeling and dissemination of emerging side effects and preventing the lag that cost our child his life. It has not helped. Children are still dying and being harmed mentally. This drug needs a strong warning because this is a consumer safety issue. People, especially parents, need to know what they are dispensing and all the possible dangers and risk.

We submitted a public comment with our recommendations for the safe use of montelukast. I hope you've read it. The FDA is quick in acting on things like the vaping thing going on and monumental recalls for romaine lettuce. Yes, they're important. But why not this drug? I ask you: why wasn't the media notified that the Pediatric Advisory Committee was reviewing this once again? Why not a post-marketing safety trial? Look at the drug thoroughly. Find the science. These outcries warrant a serious label.

I ask once again why is this taking so long? So many have died and are so sick from this drug. Children are suffering daily from the lack of this proper warning. This drug has a distinct neuropsychiatric effect on a population of people, and it cannot be denied. For some, like my family, my small family, it was catastrophic.

My child died from a drug that I thought would help him through allergy season so he could play football. He didn't even make it to allergy season. He didn't make it to his 16th birthday. My son would be 28 years old next week. I've been in this fight since 2007, and it's astounding that I find myself here once again because it takes courage for these people to come forward. I look around the room, and I see all the parents who are here because they've witnessed these terrible side effects. And they, again, had no idea what they were up against. I call them the mother warriors because they are doing a better job at an awareness campaign than the FDA.

A dear friend said to me, "Kate Miller, you were the shot that was heard around the world." These mothers are a strong voice forming awareness groups, offering support and all the information they can safely provide. But sadly, it should have been the FDA. It's time to do your jobs. The advisory panel needs to be our voice, not an echo, but a strong voice. Let it be known this drug has a capability to damage children's brains. There's no worse feeling in the world than knowing and trying to ease your child's suffering. You unknowingly poisoned him and were destroying his mind. No child, no parent needs to suffer like this because, when your child suffers, your entire family suffers. And you cannot get

back that loss of time.

I will close in saying that the children who lost their life to these ongoing side effects from Singulair didn't give up the fight, as it was a fight they weren't aware they were in. Jacob, A.J., L'Angie, Andrew, Sarah, those were the names that were given to me the minute I reported, and it went out onto the media. People are unaware until sometimes they see it up on the TV screen. It is not this setting. It is a private setting. It is hell for these parents, and they need to have the warning. And I'm sorry if I ran over because I just -- this needs to be done. Thank you very much.

DR. WADE: Thank you. If we can now have speaker number 14 step up to the podium and introduce yourself, stating your name and any organization you represent for the record.

MS. OKUN: Good morning. Thank you for having this opportunity for us to speak. My name is Sally Okun. I'm from a company called Patients Like Me. We are an online patient-powered research network. I have one conflict to disclose, and that was that we would have worked with Merck as a company that we would have had some research projects with, however not in the context of this particular drug that we're discussing today. I also want to acknowledge that Patients Like Me had the privilege of working with the FDA closely on a research collaboration agreement from 2015 to 2018 through the Office of Surveillance and Epidemiology, helping them understand a novel data source.

The reason I'm here today is I had the opportunity to meet Laura Marotta just for the first time today, but I heard her story a year ago. Laura reached out to

Patients Like Me after having been recommended to us by the FDA specifically. Three staff members had mentioned it might be worthwhile trying to see if maybe they could gather some more data. My comments today are going to be specifically around four of the seven requests that actually came out of the November 2017 letter.

Number one and number two, specifically, determine the mechanisms for montelukast neuropsychiatric side effects and determine the risk factors. So the data sources used for the review are not suitable for making these determinations that were requested and would require further studies focused on the biological impact of this drug. FDA, in their report, has kept their focus on quantifying these neuropsychiatric events from traditional data sources that really wouldn't be able to provide the kind of information you would need to make an informed decision on these issues. Unfortunately, the report is silent on the underlying mechanisms of neuropsychiatric events or what makes one child more at risk of experiencing these events than another. The report doesn't offer any consideration of possible pathways to further the study to better understand the findings from the animal studies that have been cited in Section 1.4.4 despite the fact that FDA acknowledges the data from animal studies suggests the drug could impact brain cells and that there is evidence that the drug crosses the blood brain barrier.

On number five request that was made in the November letter of 2017, to reclassify the events of montelukast to be common in children, it seemed FDA does not feel that this is warranted since the events are represented on the label already, and prescribers are expected to discuss what to look for with their patients

and parents. However, given the number and seriousness of the potential events that could occur, it does seem that the current system is not working very well to ensure that prescribers are aware, and if they are aware, they take the time to alert parents and patients.

On number seven, issuing a medication guide for the drug due to the life-threatening potential of its effects and considering a boxed warning, the medication guide I would definitely recommend, but I would definitely recommend that you create and develop this with parents and patients. Past communication strategies have targeted healthcare providers. Given the number and seriousness of these events that occur, a more effective approach could be a “dear doctor mom” letter, based on the people we’ve been listening to today.

In closure, let me say that knowing why these 20 neuropsychiatric events occur and in whom they are most likely to occur are lingering questions that, without further biological focused studies, will remain unanswered. For any patient or parent who has had the misfortune to experience one or more of these neuropsychiatric events, the stories we heard today, just knowing they are known about and have the potential to occur isn’t enough. These are frightening and intolerable side effects that no child or parent or any patient should have to endure. Thank you.

DR. WADE: Thank you for that. I would like to thank all the speakers for the courage of coming here today and also for sticking to the timeline so that we could allow all 14 of you to speak. We’d also like to acknowledge all the people who submitted to the public docket for further comments -- that those have been

reviewed as well. In the four minutes remaining in the open public forum, I would simply ask if there are any more speakers in the audience? Please step up to the podium and introduce yourself, stating your name and any organization you are representing for the record.

MR. ROSENBERG: Good morning. My name is Stuart Rosenberg. I'm not representing any organization except my family, and I wasn't actually planning on speaking here today. We did suffer. My wife has been involved for the last ten years with one of the Facebook groups and has been helpful in pulling together all the people you've heard from today. And there's a few things from the comments that just seem self-evident to me that I'd like to highlight.

I'm not a doctor. I'm not a physician. I'm not a healthcare professional. But I am a relatively intelligent adult who has seen the effects as this happens on their otherwise normal and healthy child. And when I sit here today, I understand the traditional science only allowed us to observe and make conclusions based on the data that we have. But when the presentation, the major key theme that's highlighted in the slide, says "We can't make any conclusions because there's missing information," think about that.

We're not going to make any decisions because there's missing information in the database? Do you think the first thing that happens when my son started having troubles and we go to the allergist and he says there's absolutely no way this drug is causing this problem -- do you think the first thing we do, even though we're relatively self-aware adults, is run to the FDA database to make a claim, to log it? And if we do log it, and I don't use the correct key words, you're doing a

simple key word search, right? Is my claim going to show up? We submitted a letter. I have no idea if we used the key words that the gentlemen on the team used to find that out.

I'm not criticizing the approach. The approach is the best that the team can do based on the information available. But I can tell you that our son, when he went to the providers, they didn't classify him as depression because they didn't know. They were the allergists. He had potentially runny nose, seasonal allergies, and they decided, "Oh, we'll give him montelukast." Okay. Well, that will help. They didn't say, "Listen. There's some risks here and we should try some other things first because, you know what, one out of 10,000 people might have suicidal thoughts or tendencies."

You have no idea when your son is five or six years old and they start acting a little bit odd and a little bit temperamental. You think, "He's five or six years old. He didn't get to watch Thomas the Tank Engine. He's upset." So you don't know. You don't go run and file a -- go to the psychologist. And they don't file a claim for the office visit and diagnose them as depression or whichever one of those codes that would have made it show up in the first database. Right?

That's why you're not seeing it. These parents, these mothers, all these folks, for years, they're just trying to deal with it. They're trying to help their kids have a normal happy life. And yes, for a lot of people, this drug is effective and it's useful. But it doesn't show up in the traditional studies. It doesn't show up. But now, you have access to people here. You want to know how to make an impact, do something different? Take advantage of the channels of

communication here. Has anybody from the FDA thought to reach out and ask, “Can we come to this group? Can we have an online chat with the 4,000 members and talk about it and understand?”

Why do you throw out data points of non-U.S. personnel? Sure, they’re not paying the bills here. But is the drug going to interact differently because someone is living in the UK than here in the United States of America? And yet that data was discontinued and was discredited, if I understood the commentary, from the study, from the conclusions. It was not included to influence the conclusions. And I only had 48 hours to look at this stuff, 120 pages. And that’s the problem.

I know you all are doing the best you can. You’re trained to be scientists, to look at the data, to understand. But we now have access to additional information. You have people here who’ve spent their hard-earned money. Instead of taking their kids to Disneyland, they’re flying here to White Oak. I’m up in Olney. I love this place. But let me tell you. There’s other places you’d like to be. They’re flying here to tell you this is not a statistical phenomenon.

Yes, traditional scientific methods didn’t allow you to see it. Twenty years ago you didn’t know. But now you know. Nobody’s saying take it off the market, but make sure people can make informed consent. Let them know the risks. Let them try other things first. And then, if absolutely they need to take it, let them take it. But it is not worth the risk for a lot of people, particularly if they’re making that decision without information.

And all of these doctors, I speak English. I’m fortunate I can go to great

doctors. I can go to multiple doctors. None of them said this was a potential problem. None of them. And when we go and show up in a semi-intelligent manner, having a semi-intelligent conversation with the confidence to go question the doctor, do you all understand how long and hard you study to become a doctor, how intimidating it can be for the average person in that conversation to go and question the doctor?

I understand it's frustrating that everyone wants to be a Google doctor. I googled it. I understand. I can only imagine how frustrating it is after you spend years and years and years studying medicine. But you have to understand that there are -- there is data. There are people who live in the tails, and now you have access to them. You have direct access to them. So if you want to make a difference, you want to do something different, try. These people are there. You don't need a FAERS database. You need to connect and access the people that are here. Thank you.

CLARIFYING QUESTIONS

DR. WADE: Thank you. And again, thank you to everyone. This will now close the open public hearing portion of the meeting and we will no longer take comments from the audience. We do thank you for your participation and for bringing these stories directly to us today. We will now have an opportunity to take clarifying questions from the committee to the presenters. Remember to state your name for the record before you speak and direct questions to a specific presenter. We will then proceed with the panel discussion of the questions laid

before us. Remember, once again, if you would like to make a comment to place vertical your nametag so that I can call on you directly. I will be keeping a list so that we can go around the room. We'll start with Dr. Ortiz-Aguayo.

DR. ORTIZ-AGUAYO: Thank you. Roberto Ortiz-Aguayo, Children's Hospital of Philadelphia. My question is to Dr. Chin. Hi. I would like a clarifying question with regards to the slides around the instructions for medication guide and the boxed warning, particularly if there is a specific threshold that separates the phrase on the medication guide around serious risk relative to benefits versus the first line on the boxed warning of adverse reaction so serious in proportion to benefit that it is essential to consider assessing risk and benefits of using the drug.

DR. CHIN: Hi. Could you pull up slide 16, please?

DR. SEYMOUR: My interpretation of those -- this is Dr. Seymour -- is that they're very similar, and they're for different types of labeling. And often, you will see products that have a boxed warning also have a medication guide because of the similarities in some of the criteria.

DR. ORTIZ-AGUAYO: I'm just trying to identify if there's a differentiating factor as we prepare our recommendations.

DR. SEYMOUR: Not necessarily. I think you have to look at each of the criteria and make a determination if you think that the situation warrants a medication guide and for what reason is provided for in our regulations. I think that's the type of input we want from the committee today.

DR. ORTIZ-AGUAYO: I ask of the chair if I can ask a follow up

question?

DR. WADE: Yes.

DR. ORTIZ-AGUAYO: My follow up question would be to Dr. Sansing or if any other allergy and pulmonology colleagues here want to weigh in. Considering the incredible burden of disease that asthma places on the individuals in the population, high costs, decreased quality of life, perhaps decreased life span, do we have any data that shows that the effectiveness of montelukast, even as a drug itself or as a monotherapy and, therefore, hopefully improving adherence versus the risk ratio or the ratio of adverse side effects?

DR. SANSING-FOSTER: Hello I'm Dr. Sansing-Foster. I'll defer to my clinical colleagues in regard to the efficacy of montelukast versus inhaled corticosteroids.

DR. CLARRIDGE: Hi this is Dr. Clarridge. Can you hear me now?

DR. ORTIZ-AGUAYO: Yes, thank you.

DR. CLARRIDGE: You might get different answers depending on which allergist you ask and at what point in time during the approval history of this drug. And it also, obviously, depends on the patient and their symptoms. As time has gone on, since the approval of this drug, there are other medications, too, that have come out that are very effective for allergies and the indications that montelukast is approved for. So again, it has changed over time, and it has changed by the patient and the diagnoses.

DR. ORTIZ-AGUAYO: Thank you.

DR. CHIN: This is Dr. Chin. I'll just add that I think the general

perception is that it is no more effective than any other medication that is available. So I think the risk-benefit is certainly something we'd like you to take into consideration.

DR. ORTIZ-AGUAYO: Thank you.

DR. WADE: Before we ask our allergy colleagues to comment, as you referred, I just want to ask Dr. Hernandez-Diaz, if your question was a clarifying question of the data that was presented or rather more in the general sphere of the conversation?

DR. HERNANDEZ-DIAZ: It's a clarifying question with connection to the discussion.

DR. WADE: Great. Go ahead then.

DR. HERNANDEZ-DIAZ: Okay. The clarifying question was for Dr. Ibrahim regarding the trends that you presented for the utilization in slide number five. You went back to 2014 to 2018, and it was a flat trend with no clear reduction of utilization in the pediatric population, not an increase but not a reduction. And I was wondering if you had any information of any change in the years between 2007 and 2014? And the connection with the discussion is that there were some changes in the label, some additions of warnings. However, we don't see any impact in the utilization. So if the trend is flat, going back to 2007, my interpretation would be that the changes in the label are not having a great impact in utilization, and, therefore, that will inform the discussion around that.

DR. IBRAHIM: So we did look at utilization from all the way back, but we don't have the results here with us. For this PAC discussion, we only looked at

these five years. Maybe after the break we can share the results if we have it, but we don't have it with us right now.

DR. HERNANDEZ-DIAZ: Okay. It would be just to know if there was a reduction -- a clear decrease after the labeling change. And another clarifying question with connection is, in your table on the top prescribing specialists, you have a footnote that says all ages. Do you refer to all ages under 18 or everybody? It's slide number seven.

DR. IBRAHIM: Everyone. This is the total number of prescriptions that were dispensed of the drug to all populations in U.S. retail pharmacies.

DR. HERNANDEZ-DIAZ: And the connection I wanted to make with the discussion, if we decided one of the communications is with the healthcare providers, if these are everybody and around 25 percent of the population using the drug is pediatric and pediatricians are not prescribing the others, then in the pediatric population, the pediatricians are going to represent a much larger proportion, like probably 50 percent or more. Would you agree with that interpretation, since the pediatricians are only prescribing to infants, to under 18? And this is everybody. They would be a much larger proportion of the prescribers among the age that we are discussing today, correct?

DR. IBRAHIM: That might be true, but it's not something that we were able to explore based on the limitations of the databases that's available to us as the Agency. So because of that, it's the reason why we looked at all prescriptions to look at the top prescribers. So because of the limitations, if you look at my limitations slide, it clearly states that these databases have some limitations. And

because of that we were only able to explore the data in certain ways.

DR. HERNANDEZ-DIAZ: Thank you.

DR. WADE: Among those of you with your cards up, is there anyone who has a specific data clarifying question before we move into the general discussion? Okay. We'll start with Dr. Meisel.

DR. MEISEL: Steve Meisel, Fairview Minneapolis. I have a question for Dr. Biehl, if you could put up slide number ten of her presentation, please. As I look at this graphic, I know there's some bouncing around for reasons you described. But it looks as though in the last ten years or so we have between 800 and 1,000 case reports annually of a neuropsychiatric effect, give or take. Do you have an estimate for what percent of population effects are actually reported into FAERS? Most events, as we've heard from the public comments, don't get into FAERS. Is it one percent, 0.1 percent, ten percent? Because if it's one percent, then that 1,000 a year is really 10,000, which is a whole different order of magnitude.

DR. BIEHL: Yes. Thank you for your question. So the amount of under reporting, I believe that's what you're referring to, varies specifically by drug and event. So there was a recent publication, McAdams et al., that looked at statins in rhabdomyolysis. And what we saw was that it varied significantly within this statin how much underreporting was suspected. And then we also saw that following a drug communication the amount of reporting then increased with one of the suspect statins that had previously been on the lower end. So again, it really does vary by event, by interest group, by specific medication. But I hope that

helps.

DR. MEISEL: But can you be a little bit more specific about -- should we multiply this by ten? Should we multiply these numbers by 100? Should we multiply them by 1,000? Should we take them at face value?

DR. BIEHL: So unfortunately, there's no magic formula. I can't tell you to multiply them by a specific figure. What I can say is that we are aware of phenomena such as heightened public awareness. We're also aware that physicians who are aware of events that are labeled often decrease reporting. So we just have to put this information in that context and also accounting for our duplicate reporting and foreign reports.

DR. WADE: I'd like to remind the committee that it's 12:15. So at 12:30, I would like to open the conversation to the specific questions addressed for us and spend the next 15 minutes limited to questions specifically about data that can be truncated as short as possible. That will then leave us at 12:30 to put the three questions before the committee for more general discussion. So leave your cards up if you're falling in that domain of the next 15 minutes so we can just clarify the data at hand. Let's start here with Dr. Flick.

DR. FLICK: Thank you. This question is for Dr. Sansing-Foster. First of all, I want to congratulate you on the conduct of the study, the Sentinel analysis. I think it's a well-conducted study, and you're appropriately cautious in your conclusions. The study, I think it's important to recognize the study is a comparison of the endpoints between montelukast and inhaled corticosteroids, as you appropriately point out. What we don't see is some better sense of the

frequency of adverse neuropsychiatric events occurring in patients who are taking inhaled corticosteroids. You mention that, but you don't quantify that. The fundamental question here is not the comparison between the two drugs. It's the frequency of events related to montelukast. Does that make sense, and can you give us a better sense of the background that you did on the frequency of events associated with inhaled corticosteroids so we can put this in some sort of context?

DR. SANSING-FOSTER: Hi, I'm Dr. Veronica Sansing-Foster. You mentioned in regard to the frequency. Our study and our backup information and within the manuscript itself has more information regarding the incidence rate for the neuropsychiatric adverse events and inhaled corticosteroids. If you don't mind, I can pull up that information right now. I do not have it in the backup slides, but it is within the background information.

DR. FLICK: I'll leave it to the chair to decide whether she thinks that's important for the committee. But I think it's probably important from the standpoint of the study, the Sentinel study is a comparison of frequency in two populations, rather than a comparison in the population, if that makes sense.

DR. SANSING-FOSTER: Dr. Sansing-Foster speaking again. In order to get the quantification as opposed to the risk estimate and stating that montelukast patients have an increased risk or decreased risk as compared to ICS but to get the raw frequency rates.

DR. WADE: Yes. So perhaps for the sake of time, Dr. Sansing-Foster, if you could be so kind as to work on pulling that information forward, and we will continue to hear these very specific clarifying questions about the data while you

do that. And perhaps you can just let me know when you have the data ready.

Let's move forward with our allergist, Dr. Kelso.

DR. KELSO: John Kelso. Mention has been made a couple of times about the medication guide. I've never prescribed a medication that requires a medication guide. So probably for Dr. Chin, just how that works practically? I'm sort of picturing that this is a piece of paper with some information on it, and the patient signs the paper. And it's done at the time that the medication is prescribed. But I don't know if that's really how it works or who keeps track of that or monitors whether it's being done.

DR. CHIN: So the medication guide is usually within the drug when it's dispensed. It does not necessarily require an informed consent from the prescriber at the time the prescription is being written.

DR. KELSO: So it's given out by the pharmacist?

DR. CHIN: Exactly.

DR. KELSO: And it's just handed to the -- it's a requirement that it be handed to the patient at the time -- in the pharmacy when they're being given the medication? Okay. Thank you.

DR. CHIN: That is correct.

DR. SEYMOUR: The only thing I was going to add is that it's required patient information from the FDA. Currently, what they have is a patient package insert, which is a voluntary information they provide for patients. And we do review it and approve that. But this would be required information. And some of the medication guides that are out there are actually targeted towards highlighting

a specific adverse event, as well. But there's no informed consent. There's no signature. It's dispensed. It's given when the prescription is dispensed to the patient.

DR. KELSO: And is it monitored in some way? How do you know that they're actually being given out?

DR. SEYMOUR: That's a good question. I don't know if there are patient labeling groups here. There we are in the back. Let's see if we can get an answer for you there.

MS. FULLER: Good afternoon. I'm Barbara Fuller with the Office of Medical Policy. I'm the patient team leader. Can you hear me now? Good afternoon. I'm Barbara Fuller. I'm a team leader with patient labeling in the Office of Medical Policy. Could you please repeat your question?

DR. KELSO: Is there any monitoring done to make sure that medication guides are actually given out?

MS. FULLER: Unfortunately, no. We don't monitor to see if they are being dispensed as they are required from patient labeling.

DR. WADE: Thank you. Dr. Kim?

DR. KIM: Hi Edwin Kim, Pediatric Allergist, University of North Carolina. Just a quick clarifying question regarding the trends for Dr. Biehl on slide 10. There was just a quick description that the third peak was because of foreign reporting. And I was just wondering if there was any understanding of any event that might have triggered that, or whether some sort of new approval or safety information?

DR. BIEHL: So to be specific, the 2013 peak is actually due to a recycling of reports from a FOIA request. So a sponsor requested FAERS reports, and we supplied them. And then they resubmitted them to us as part of their expedited reporting. The spike in 2018 is the one that reflects a large proportion of foreign reports. In further analysis, these reports were mostly attributed to Canada and Great Britain.

Recently, as of September of 2019, Great Britain elevated their neuropsychiatric labeling from their adverse reactions section of the label to their warnings and precautions. So I suspect that the Great Britain reports have a significant interplay with that change. As for Canada, further analysis shows that a significant number of those reports were actually associated with another medication that is commonly prescribed in asthma. And it does not appear that montelukast or adverse events associated with montelukast were the focus of those reports.

DR. WADE: If I could just clarify, as you referenced the changes in the UK and you say they elevated it from adverse effects to the warnings, is that now equal to where it is in our current FDA label?

DR. BIEHL: Based on my knowledge of the UK labeling, it appears to be analogous to where we currently are.

DR. WADE: And were there any other changes brought forth?

DR. BIEHL: Not to my knowledge.

DR. WADE: Thank you. Dr. Tracy?

DR. TRACY: You can go ahead and keep that slide up. So you may have

actually kind of already answered this. So when you compare your slide ten with Figure 3 in the executive summary, in that figure you have the same three peaks, but you also compare it against, basically, these peaks, which are domestic adverse reports and that's compared against foreign reports. And it's pretty flat all the way along until we get to that 2017. So is this really an issue of -- which I wasn't clear about -- whether this was just reporting? Was it in incidence difference versus just the awareness that we kind of have already touched upon? This is for Dr. Biehl again.

DR. BIEHL: Yes, of course. This is Dr. Biehl. So can we just go to Figure 3 in the executive summary so I can see it. Can we pull that up? I just want to make sure that I'm referencing the correct figure that he's referencing. Can you give me a page on the executive summary and I'll just search it?

DR. TRACY: Page 45. I guess it's actually in the briefing packet. There's a lot of goofy page numbers here.

DR. BIEHL: And to restate your question, just so I'm clear, you're asking about the differences in the foreign trends versus the domestic reports and just that the foreign trends had slowly trended up over time, whereas we have distinct peaks in our U.S. reports?

DR. TRACY: Well, if you look at, again, Figure 3, so the figure that we had up on the screen was actually Figure 2. So it's really just the one right after that. But in Figure 3, the reporting is pretty much flat from '98 all the way to 2017. And then that's when it kind of bumps up a little bit. So all the peaks that we saw on the domestic appear to be pretty limited to what we have. So the

question becomes is this a difference in reporting versus a different population between the domestic and foreign versus, again, just the awareness issue we've kind of talked about?

DR. BIEHL: So I suspect that it is a combination of multiple factors. Again, I can't speak as much to what's going on for foreign reporting other than to state that we did examine the peaks in 2018 and noted that, at least for the contribution of the Canadian reports, it was more attributed to another medication and also just to restate the labeling changes in the UK.

DR. WADE: Ms. Oster?

MS. OSTER: Randi Oster. This is for Dr. Sansing-Foster. I just wanted to understand, when you did your article search, what information, if any, was used with articles about the blood brain barrier and how that kind of information might have enhanced or maybe hasn't been looked at in terms of coming to the conclusions for the analysis.

DR. SANSING-FOSTER: Dr. Sansing-Foster speaking. If you can turn to slide 4. You mentioned articles about the blood brain barrier, and I'm glad that you did. Our study focused on observational literature review. These are reviews that exclude in vitro studies and only basically capture observational studies, those done post-market and within a true patient population. So therefore, our studies did not include -- our review did not include this. You can see that Section 1.4.4 is actually divided into two sections: animal studies and observational data.

DR. CHIN: This is Stacy Chin. I believe we may be able to address your question, so I'm going to have my colleague who's a pharmacologist/toxicologist,

Dr. Matthew Whittaker, come up. If you could pull up my background slides starting at slide 29?

DR. WHITTAKER: Can you please go to the next slide, please? Yeah. So there's really two sources of information regarding the ability of montelukast to cross the blood brain barrier. There was the work that Merck had done during the development of their product where they looked at the presence of radio labeled montelukast in the brain of rats after they were given a single dose. And they measured -- excuse me. Okay. Yeah. So they measured radio labeled montelukast in the brain of rats after given a single dose. And then, there was a publication in 2015 in which the investigators dosed rats for seven days and then measured the amount of montelukast in the brain using mass spectrometry techniques. So both sources of information came to the same conclusion that, in rats, orally administered montelukast is detectable in brain tissue.

DR. WADE: Excuse me, Kelly Wade. On this slide, is there any brain data in adult human? It looks like there's -- that box code is not present.

DR. WHITTAKER: Correct. So if you look to the two bars to the far right in this publication, they looked at I believe it was a single adult human patient. They measured montelukast in a patient that was taking oral montelukast in the cerebral spinal fluid and in the serum. So they were able to measure montelukast in the CSF. I think it's important, though, to distinguish the reality that measuring a drug in the cerebral spinal fluid is not the same as measuring it in the brain parenchyma, which, of course, is very difficult to do in humans.

DR. WADE: I think Dr. Havens has a question for the toxicology.

DR. HAVENS: Just a follow up to this. So there are data to suggest that absorption of montelukast is associated with 2B transporters. And we know there's genetic variation in those transporters. We also know that those similar transporters exist in the brain. And there would, therefore, be potential for genetic variation in those. Are there data that specifically look at, perhaps, either CSF levels or, more importantly, cellular levels in the brain by transporter type?

DR. WHITTAKER: Are you talking about in humans or in animals?

DR. HAVENS: Well, this would have to be in animals, not humans presumably.

DR. WHITTAKER: I don't believe that that's actually been investigated at this point. But I agree. There is evidence that the 2B-1 -- that is the one that montelukast is transported from the GI tract into the blood. Those same transporters are expressed on endothelial cells in the brain vasculature. But beyond that, I don't believe there's been any more detailed investigation of genetic variation in that specific transporter and its effects on the ability of montelukast to cross the blood brain barrier in animals.

DR. HAVENS: Thank you. That's very helpful.

DR. WADE: Dr. Meisel, was there something specific for the toxicologist?

DR. MEISEL: Right, about this. The package insert -- the only comment in the package insert about this is that crossing into the blood brain barrier is minimal, yet that's contrary to everything we've just been talking about. So I'm trying to understand that disconnect.

DR. WHITTAKER: Yes. If we could go back to that slide in Dr. Chin's backup. I believe it was the first one that you showed. There's a table of montelukast levels across tissues in the rat.

DR. CHIN: It's slide 29.

DR. WHITTAKER: Okay. So if you look at this table, again, this is an experiment where the -- this was done by Merck where they gave rats a single dose, oral dose, of montelukast. The montelukast was labeled with the radioactive label C14. They measured the amount of radioactive signal at 1, 6, and 24 hours after dosing. If you look at the bottom row, the levels in the brain are shown. So again, on an absolute level, if you're looking at 0.12 micrograms per gram at one hour, 0.84 micrograms per gram at six hours, 0.68 micrograms per gram at 24 hours, I think at the time of the original review of this experiment in 1997 the conclusion may have been made that, in an absolute way, the amounts of montelukast detectable in the brain were characterized as minimal at that time.

DR. WADE: Thank you. Terri Voepel-Lewis?

DR. VOEPEL-LEWIS: Yes, thank you. Terri Voepel-Lewis, I'm a nurse from University of Michigan. If you leave Dr. Chin's slides up, I have a couple of questions for you and maybe anybody else on the FDA panel who could help me understand this hierarchy of communication. On slide -- I guess we could just go to slide 5, which starts that image of warnings/precautions to medication guide to boxed warnings. Can you help me understand why we have boxed warnings for other medications where there's anecdotal data on deaths, like for instance codeine and tramadol where there might not be statistical differences in deaths in those

kids versus deaths and neuropsychiatric events in this group of people taking montelukast -- why we would have boxed warnings for some anecdotal data for some drugs and not for others? Also, just sort of in line with this, when we're communicating with parents, why do we have I believe it's an FDA requirement for informed consent for a drug like Accutane for children but not these other potentially harmful drugs?

DR. SEYMOUR: This is Dr. Seymour. I think we have to approach each product on a case by case basis. The differences you're talking about, for instance, the informed consent, I think probably has to do with a REMS associated with Accutane. And I believe that kind of decision was also the subject of an advisory committee where they talked about the risks versus benefits and how to mitigate those risks. Those are all options that we have outlined here. I've also been a part of the codeine safety issue as well. We've been to multiple advisory committees seeking input, like we are here today, on each individual case to present the data that we have so that we can get feedback and input whether you think any of these are warranted. I think we can't necessarily compare each one. We have to look at each individual case. And that's the reason we're here: for your input whether you think any of these are warranted or not.

DR. WADE: Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi, Georgetown. So my question is for Dr. Chin, as well. So some of the regulatory measures that you had suggested was moving the warnings and precautions on the label up. So my question is, number one, as a toxicologist, I know that overdose is always Section 10. So what

would that label look like if you moved it? And secondarily, have we done this before, and is there any data to suggest that it has a meaningful impact compared to a boxed warning?

DR. CHIN: It is one of the options available to us. We could certainly move it up, along with other recommendations that we hear from the committee. Labeling changes, I don't think we have any consistent data that shows that one labeling change versus another always has a particular impact. The precedent for moving up the warnings and precautions, I'm sure, has happened for other products. I don't have any of the top of my head.

DR. SEYMOUR: This is Dr. Seymour. Just to clarify, it would be moved up within Section 5 to 5.1. It wouldn't be moved up to Section 1. We can make those changes if we think looking at the risks it belongs in a higher position based upon the available data and considering what the other risks are in the label. But I don't think that kind of move we have a lot of information about how useful that would be.

DR. WADE: Dr. Czaja?

DR. CZAJA: Angela Czaja. I had two clarifying questions for Dr. Chin. So kind of extending a little bit on the last two questions, for the black box warning, I think I have a good understanding for the potential benefits of it. And I was wondering if you could just share to the committee what we should be considering as potential downsides of adding on a black box warning for this medication? That's my first question.

DR. CHIN: That's a good question. Is it on? One, I think we would like

to hear from you if you feel like there are any downsides to elevating it to a boxed warning, given the data that we have and given that -- okay. Let me start over. So I think we would like to hear from you, as well, to hear if you think there are any downsides to elevating it to a boxed warning. Do you feel like it rises to that level, one? And also, do you feel that, given the data that we have, the fact that a lot of the data is imperfect, unfortunately, and that we may not have new information to provide guidance about risk factors or tapering down the dose or withdrawal, et cetera, that it would still be informative as a boxed warning?

DR. SEYMOUR: I'll just add I think the biggest concern that is often raised with a boxed warning is that we've heard that sometimes patients are scared about taking a medication with a boxed warning or it may deter them from using it. But that's the only real downside that I've ever heard from groups or practitioners or, I would say, professional society's requesting removal of a boxed warning.

DR. CZAJA: Thank you. And then just the second question I think might be for you as well -- is looking at potential future studies, can you just help us understand the FDA's authority for mandating subsequent types of studies versus requesting subsequent studies, both on a basic mechanistic side of things, as well as post-marketing observational or clinical trials?

DR. SEYMOUR: So as Dr. Chin mentioned, we do have authority under FDAAA for, in this case, a known serious safety risk, that we can require studies from the manufacturer. In this case, it would be Merck. And I think any of the studies that we think might be informative to address that safety concern could be

requested. So it can be animal studies. It could be observational studies. It could be a controlled clinical trial. I think we have to be realistic here about the situation. I honestly don't know how Merck -- if they would conduct a study or not. It's a generic product. The branded product has very little market distribution. So I think while recommendations for studies that they should conduct we definitely want to hear about, but I don't know if we went to them and said, "You need to do these studies," if they would actually happen.

DR. CZAJA: I guess just as a quick follow up; then what would be the consequence to them if you asked for those studies and they refused to perform them?

DR. SEYMOUR: I'm just giving you my opinion here. I have no inside knowledge about what they would do. But you could imagine a company who no longer makes a lot of money off of this product, looking at a very expensive trial to do, may make a business decision that we no longer want to have an NDA for this product. We'll just let it be all generic. So they could remove their NDA. And then I don't think we would be able to require a study. We can't require studies from generic sponsors. And this is all sort of hypothetical. But I think it's something to keep in mind that requesting a large trial from the sponsor -- if that's the recommendation, we do want to hear it. I'm not confident that we can actually see that happen.

DR. WADE: I think there's been some data that's available to show us from the FDA. And when that is completed, I'd like to ask that the questions posed to the committee be put before us so we can discuss those.

MS. GILL: Hi, this is Rajdeep. I'm the drug use team lead in the Office of Surveillance and Epidemiology. We would like to share the data that was presented at the 2014 Pediatric Advisory Committee meeting. There we go. So those are the numbers. Please pay attention to the red line, which shows zero to 16 years of age. So they have peaked around 3.1 million, I would say, in 2007 and kind of dropped down to two and a half million patients. And the trend sort of continues, the one we showed you earlier. In Ibrahim's presentation, it kind of holds steady around 2.3, 2.4 million patients annually. Does that answer your question?

DR. HERNANDEZ-DIAZ: Yes. Thank you so much.

DR. SANSING-FOSTER: Hello, this is Dr. Sansing-Foster.

DR. WADE: Please

DR. SANSING-FOSTER: I wanted to follow up with the question from Dr. Flick. Catherine, if you could present our information on the screen, we have the adjusted incidence rates for the study outcomes by montelukast and inhaled corticosteroid use. While this is being brought to the screen, I can briefly give you the numbers, if that would be okay. For montelukast inpatient depression, 3.73 per 1,000 persons per year. While for inhaled corticosteroids, it's 3.93. Outpatient depression for montelukast was approximately 43 versus 39 for inhaled corticosteroids.

DR. FLICK: You don't have to keep reading. So I just want to make sure that we're on the same page here. This is the risk ratio, the risk of one versus the other, the treatment versus the comparator. So for the committee and for the

public, if the risk of psychiatric events in the inhaled corticosteroid is high and the rate in the montelukast is equally high, then your study will show no difference. But yet, montelukast has an association with psychiatric event. We know very well that corticosteroids, not necessarily inhaled corticosteroids, have very high rates of psychiatric events associated with high dose oral or intravenous steroids.

The question is, and it's a very important question, I think, is what do we know about inhaled corticosteroids and the rate of neuropsychiatric events in that setting? Another way to think about this would be to say what is the rate of these events in the population at large? Are they excessive relative to the population at large? If they're not, then we can feel comfortable that montelukast is not really -- is not likely to be the culprit, so to speak, in these events. Does that make sense?

DR. SANSING-FOSTER: That makes complete sense. Andy Mosholder? One of our limitations that we studied is the potential systemic absorption of ICS, which may carry a risk for neuropsychiatric adverse events. Andy, if you could speak to that?

DR. MOSHOLDER: Andy Mosholder, Division of Epidemiology I. Yes. The nature of this study was comparing the risk. We were trying to model a clinician's choice between the two treatments. For neither one do we measure the absolute risk versus no treatment. You'd have to look at something like placebo-controlled data for that. We do have this incidence rates that you see on the screen, and you're asking how do they compare to the general population. One thing we found was that there was very high psychiatric comorbidity in our samples. About one-third of the patients had a previous psychiatric history. So

that's one point. These rates, when I looked at them versus the population rates, they're kind of in the ballpark, but it's very hard to make precise comparisons to population epidemiologic data. But they're kind of in the ballpark. Does that answer your question?

DR. WADE: Dr. Flick?

DR. FLICK: Randall Flick, Mayo Clinic. This is the best study, at least as far as I can tell, that examines it. And please, I am not in the least bit criticizing the study. It's very well-done, and these are very difficult studies to do. In order to appropriately interpret that data and put it in the context of the questions that the committee has been asked, we really should have a sense of where these rates fall within the population so that there's a sense on my part and the part of the rest of the committee that this isn't just simply a phenomena of two drugs that are both associated with neuropsychiatric events. And we're comparing them without having a clear context in which to place that comparison.

DR. HOEHN: Can I clarify? Because I thought somebody presented the CDC had a rate of four to six per 1,000, which would be a comparison we could make to this. I can't find the slide right now, but somebody presented a CDC population data which would be comparison to this with no meds.

DR. SANSING-FOSTER: Hello, Dr. Sansing-Foster. I think you might be referring to the suicide outcome. That's on slide 28 of my presentation in which we examined extremely crude incidence rates based on a numerator of two. And it was 4.0 compared to the CDC rates of 4.0 to 6.0.

DR.HOEHN: Thank you.

DR. WADE: So if I could ask someone to work on putting the questions before the committee before us, and I will allow others to put cards up. I suspect there are several people around the table who would like to make comments. I would like to start with Dr. Sleeper, followed by Dr. Jones, who have been waiting patiently.

DR. SLEEPER: Thank you. This is also a question for Dr. Sansing-Foster about the Sentinel study. It's a really nicely executed study, and I just had a few statistical questions. One was I was wondering whether you had also used a composite outcome of all the outcomes that you have presented separately and then performed the interaction analysis to see if there's any differential risk in any of these subgroups. And related to that, since I noticed that there's censoring at deaths for the time to event analysis, death would be a competing risk, and wouldn't it be important to perhaps have those also included?

And lastly, I was just curious about your thoughts about having done that really nice propensity score matching but then have chosen an unconditional analysis instead of a conditional analysis, which may or may not make a difference. But I thought slide 25, that's the one that has Kaplan-Myer, has sort of an overall for one outcome, but maybe some of these forest plots with the composite outcome -- maybe we could see some other signals in certain subgroups. So look at all those incidence rates overall may or may not be helpful if it's really certain subgroups that we're going to pick a signal up in. Thank you.

DR. SANSING-FOSTER: Okay. I hope I can answer. I think I heard four questions, and I would like to address them. This is Dr. Sansing-Foster. First

to touch on the composite endpoints. As you can see, the majority of the outcomes were basically outpatient depression, approximately 97 percent. So the hazard ratios with the estimates would basically go in the direction of anything that outpatient depression produced. So you'd possibly see a possible decreased risk for a composite endpoint. So therefore, when we did our final analysis in terms of actually doing an inferential analysis, we decided not to utilize the composite outcome. For the second question in regard to death, you said it was a competing risk question, if I'm not mistaken. All right. I have my backup slide number 54.

This shows the reasons patients were censored between inhaled corticosteroids and montelukast. Evidence of death comprised very little. It comprised actually zero percent as a competing risk within the patients' follow up time. The third question you mentioned was propensity score matching in which we examined unconditional as opposed to conditional. We actually did conditional as well. The follow up time for the conditional matching, of course, differed. However, we saw no differences in terms of the final endpoint, in terms of no difference in terms of the magnitude and the direction of the risk. Do help me answer your fourth question. I didn't quite capture it.

DR. SLEEPER: I'm not sure I recall what the fourth one was. But one final clarifying question was just that I notice your time axis tend to go out to a year. There was a lot of methodology, and I'm still a little unclear as to the time axis. Time zero is the time of initial prescription? But it seems that a lot of these adverse outcomes occur possibly many months or many years after someone starts

taking the drug. So I didn't quite understand how that works in terms of counting the events.

DR. SANSING-FOSTER: That's actually one of the additional limitations. So should the censoring criteria occur before an outcome, we cannot capture that outcome. So for instance, even though you see that cessation of the drug was one of the main reasons, the end of exposure episode was one of the main reasons, like we heard from the patient population, sometimes it occurs after. We have the 30 day follow up period after the patients last prescription, but after that, we're unable to capture that because it introduces competing risk. For instance, we don't know if life circumstances may have occurred. So we're basically doing this on treatment analysis. Like I said, we can't expand it any further because we do not want to introduce other competing risks that are unmeasured.

DR. SLEEPER: Thank you.

DR. WADE: Dr. Jones?

DR. JONES: Dr. Bridgette Jones. I had a question for FDA. So in 2014, the FDA recommended to the sponsor that they develop a physician letter regarding the risks. So I was just wondering -- so for the med guide, the FDA does have the authority to require a medication guide, correct? And in that med guide, what type of authority does FDA require to specific language, and is there a difference between the authority for the language in the med guide versus a black box warning?

DR. SEYMOUR: This is Dr. Seymour. We review the medication guide

and the boxed warning, and, often, the language in the boxed warning is for healthcare providers, primarily. But it's translated, that information, to more patient friendly language in the medication guide. So we have to, ultimately, approve that and agree to the language in both. So we certainly have a lot of leverage and say so over the content of both of those pieces of labeling. Does that answer your question?

QUESTIONS TO THE COMMITTEE/COMMITTEE DISCUSSION

DR. WADE: So the three questions posed to the committee today are shown on the screen. For the sake of time, I'm not going to read them. But we will now open up committee discussion to specifically provide comments related to these questions. I'd like to start here with Amy Celento.

MS. CELENTO: So first of all, I want to thank the parents, the family members, the advocates who came here today to share their stories. And I know some of them are horrific. When you listen to what they have to say and you look at the over 200 comments submitted online, which one after the other tells a horrifying story, experiences for children as well as adults in taking montelukast, and then you look at the safety findings, which are very well -- I'm going to say processed because you're pulling data that's available on FAERS. But it's very clear to me that if you have 4,000 parents in an advocacy group talking about their terrible experience -- or 4,000 members, parents, adults, et cetera -- and you have such a limited number of adverse events documented in a database that is designed to help the FDA and, I'm going to say, industry present safe medications to the United States of America, the citizens, there's a huge gap.

I don't know if I'm speaking out of turn, but you can see that the information that's being evaluated is really not instructive to us today. So it's incredibly disconcerting. This has been a continuing ongoing problem. I've been a representative for 12 years now, and I've seen it again and again. And I've commented on it in the past. But at this point, we are in our 20th year of the 21st century. If we can't figure out a way to capture these incidences and to really use the information to determine safety signals, then we're just all spending a lot of time coming here, not really having anything that we can really make a clear decision with. So I do want to say that, and I appreciate your time hearing me out on this.

So I do want to just add that this whole angle of pharmacogenomic data -- in 2005, the FDA was applauded for issuing guidance on pharmacogenomic data submission. And the idea was to develop safer and more effective medications. So we're 14 years later. It doesn't seem like pharmacogenomic data is required now in testing. If I'm wrong, please somebody let me know that it is. I can tell you that right here there's an app for Merck. It's their consumer -- it's their consumer version of the Merck manual. There's actually an app, and they talk about pharmacogenomic data, and they do reference some medications that prescribing varies based on your genetic makeup.

And then I just want to reference that there was an article -- there was a publication of August 28th of this year. It's actually the pharmacogenomic testing marketing forecast and growth, looking at 2018 to 2028. So the financial markets are starting to look at the importance of pharmacogenomic data. They're actually

making forecasts about how that data will be used. And I just think that, at some point, we have to close the gap here. So thank you for hearing me out.

DR. WADE: Thank you. I'm going to jump around the room and hopefully have time for everyone to make forth their comments. So I'll bounce around the room. On the left, Dr. McGough.

DR. MCGOUGH: So I'm going to actually give my feedback on all three things just to be efficient. And I'm speaking as a child psychiatrist researcher and clinician and actually someone who's had NIH funding for pharmacogenetics. I was also on the committee that reviewed the SSRI suicide stuff 18 or however many years ago. So let me kind of try to synthesize all this. It's too bad today -- well, in 1998, the FDA did not require prospective assessment of suicidality, for example, in its clinical studies. We really only began to do that using the Columbia rating scale, et cetera, which is now fairly standard with the SSRI issue.

So we don't have the best data as to whether there truly are differences in suicidal events between placebo and treated groups, which is too bad. What we then have, of course, is the observational data. And unfortunately, the age of onset for many of these symptoms and disorders parallels exactly the age of use of these drugs. So the peak age of onset of OCD is age ten, and we have the very tragic story of a girl who's ten years old developing OCD symptoms. Maybe the medicine gave rise to it or maybe not. I don't know any way to disentangle this.

Again, with all respect to our families, I learned a long time ago kids don't read the books, and anything can happen. And when a family tells me that they're experiencing something due to a med, no matter what I know or believe, I believe

them. And I think physicians have to take people at their word and be open to things that don't really follow what we know. But that being said. The evidence here that there really is a signal is virtually non-existent. We have some very painful anecdotal experiences, but we can't find a signal that really says that at least this is major concern. So we have to make sense of how can we then respond to this, take care of our citizens, but still be respectful of the science.

So I think that one issue is go down below. With the SSRIs, in our initial hearing, we concluded it by saying it really seems a clinician should be mindful that these things can happen, particularly when you initiate or change doses. And this should be discussed with people. And I think that is a message that we want to get out. I think physicians who prescribe these drugs -- I deal with psychotropics. I'm always aware. I always counsel my families, if anything weird happens, if they start acting strangely, call me. I think that message is important, and we should think about how to do that.

But at our second meeting on the SSRIs, a split committee voted in favor of a boxed warning. This has proved to be a disaster. I don't know anybody in the field of psychiatry who thinks now it was a good idea. It led to a serious decrease in the prescribing of these drugs. The study cited several times yesterday and today adolescent suicide has increased. Whether this is due to the fact that fewer SSRIs are prescribed or not, we can't say. But there's a clear association between declining antidepressant use and increased suicide among youth. The black box was overkill. The proper message was to counsel about the possibility of changes in mental status, get back to me, et cetera. But the black box warning was really

more harmful than beneficial. And I don't see that you would gain much here.

In terms of the last comments raised, there are some disorders, there are some drugs where a single gene makes a difference. But I have publications in *Lancet*, in the *New England Journal*. In psychiatry with mental illness, response for both the conditions and the med responses are way multidetermined. Dozens of genes with small effects and varied environments contribute to responses. You are never going to get genetic testing to solve this, at least not this decade.

Similarly, we know almost nothing. You can accept Alzheimer's and other things like that. But for the most part, we don't know any mechanisms that give rise to mental illness. NIH, it's all they want to fund these days -- is figure out the mechanisms. We have no idea what they are. We will not ever, again, I think in the next decade with current technologies, figure out how this medication is affecting the brain and giving rise to this whole variety of symptoms. So I don't think more study there is going to yield much.

If FDA wants to spend any money, if you have any to spend, the one issue that does trouble me is this whole discontinuation question. We've heard mixed things. Some people start the drug. They have problems right away. Other people are on the drug for years, and then they start having problems. Some people stop the drug and they get better. Other people stop the drug, and ten days later, horrible things are happening. A placebo-controlled discontinuation trial would make, I think, really good sense. Have a group of people who've been on it for a while and then blindly discontinue some of the group. You can figure out how to do this best. I think that's a way you could fairly easily get information as

to whether this is a true occurrence or not, at least scientifically. And if you can document that, then you really have a challenge. Are we going to get these people off this medicine? We've only now been grasping this with SSRI discontinuation, which is a real problem.

But I think, if there's any -- it could be a limited study. It certainly would be fundable and designable where you could really assess what is the true pattern of discontinuation withdrawal symptoms. Figure that out, and then I think there'd be something to build on. Other than that for now, I think we should get some word out. Physicians, clinicians really need to be aware that this stuff can happen. And we need to, I think, raise it. I wouldn't scare people away, but we need to tell them, "If you're noticing things that are strange, you call me back and let's figure it out." That's probably the sum of my comments. Thank you.

DR. WADE: Thank you. Dr. Kim?

DR. KIM: Edwin Kim, pediatric allergist, University of North Carolina. I'm going to echo a lot of what was just said. So the safety findings that I've seen or heard about today -- again, it sounds like there's limitations and it's hard to make conclusive findings. But I think by virtue of already being on the label, there's an acceptance that there's a possibility. And there's no data that I've seen today that would remove that, at the very least. As far as the number two, the labeling, I do think it's important that we all think of the idea of uncontrolled asthma as well. So if there is a concern that has come up with the black box warning that somehow it would scare folks away from using this medication, understanding that inhaled corticosteroids may have lower compliance, I think that

has to be considered at the same time as any labeling considerations may be made here. And it is a real concern of mine.

But I really do think the focus is on number three, just like was just brought up. I think the communication strategies are important. And one clarifying question, maybe, or at least a point I'll make is the number of pediatric patients that were getting prescribed this was stable. But I wonder if there's any way to capture who's prescribing and whether their prescribing pattern has changed to make sure that the communication is targeted to the right people. Because if it's not the pediatricians, perhaps the pediatricians have gotten the message but, say, family practice has not. And we're speaking to the wrong people. So any way we can capture that better to target the information I think is going to be important.

The other consideration that I had, too, is all of us -- I think the bane of all of us in medicine is the electronic health medical record. But I wonder if that's another way that we can capture who is actually prescribing and in what settings and, again, maybe be able to target some of the communication towards that as well.

DR. WADE: Dr. Patrick?

DR. PATRICK: Stephen Patrick from Vanderbilt. So echoing kind of what has been said, we clearly have communication gaps with both patients and providers. And one of the questions are what are the mechanisms. So the med guide seems to be a good potential mechanism for patients but not for providers. And I think my question is about the potential black box warning, what evidence is that that we would do a better job of communicating with providers versus the --

I think SSRIs may be a little bit different in terms of alternatives but maybe not in terms of efficacy for asthma. So those trade offs should be considered.

I'm thinking about novel ways to engage providers, too, not just like AAP, but also the American Board of Pediatrics, including education around maintenance and certification, CME, things like that that could be novel ways to garner things. And I also wonder, when changes like this are made, how FDA generally promotes it. I'm assuming through a press release, but if novel strategies like infographics, social media, including engaging the national press, perhaps even partnering with a patient organization to do editorials. There may be ways to get the word out in just a broader way. And I think that's about all I have.

DR. WADE: Dr. Hoehn.

DR. HOEHN: Sarah Hoehn, University of Chicago, Pediatric ICU and Palliative Care. I have just a couple comments, and then I'm going to put my recommendations for the questions. In full disclosure, my children, together, have been on Singulair for over ten years with no problems whatsoever, so we're clearly lucky. It's been prescribed by a variety of people. No one has ever spoken to us about it, nor have I, as a physician, ever actually read the label. So if you say do I think we currently are getting the word out, no, I don't. So do I think people are appropriately aware? I don't at all. Do I think that we need to change what we're doing? Yes, I do.

I understand the science and the data that it doesn't make sense what it is. But I think it's hard to know where everything fits in and how you factor this in. Had my nine-year-old started having symptoms, I wouldn't have thought to

attribute it to that. So I think there has to be something that changes, that connects people to it to sort of reconnect the dots. You don't want to be the lucky one. I'll just be the first to say we take it for the least, least indication. So my kids are on it because they have a runny nose and they cough less.

As an ICU doctor, I'm very aware -- Chicago has the highest death rate of asthma. Asthma is a huge problem. So you don't want to do something that's going to make kids not get their medicine for asthma. But should every child who has a little bit of a cough in pre-school go on Singulair for ten years? Probably not. So from a recommendation perspective, I have two things to say. One is I think maybe we should think about changing it and removing rhinitis. Do you really need to take it for a runny nose? Sorry. Just me.

And then the second thing is I do think there should be some part of a black box warning or something to notify providers. And as I was reading all of this, this isn't something that people see. It's not something pharmacists talk about. And I don't think that AAP and the ABP are the way to go because they're not the majority of the people prescribing it. The majority of the people prescribing it are family practice, advanced practice nurses, and physician assistants. So we have to be mindful of all the people that are giving this out like water and how you can get to those people because it's not going to be, I don't think, the board-certified pediatricians. I think it's a really, really diverse population giving this to everybody because maybe their kids cough a little bit at night.

DR. WADE: I do want to make sure we have time to hear from our allergy experts and also our psychiatrist. But I want people to be also mindful of the time

yet the importance of the conversation. Dr. Tracy?

DR. TRACY: Jim Tracy, University of Nebraska. I've kind of actually -- well, first of all, I would be very cautious about a black box warning. It creates definite obstacles to care. And as I listened to all the other stuff that's happened, I'm reminded the FAERS data really is just to alert us to safety signals. And one of the safety signals that I was quite frankly unaware of until today was the withdrawal effect. So if you just imagine right now we have X number of people out there who have this potentially, but now they all of a sudden get terrified. And they, without supervision, they just stop their drug. Are we not creating a problem with that? And that doesn't even get to the worsening of asthma symptoms in these kids. I just think we need to be very cautious.

As a physician, we're continuously balancing risk benefits of these drugs. I can tell you for a fact, on any given day, I may prescribe this drug at least ten times, at least ten times. Now, not always to kids. But as I teach my residents and fellows, close follow up covers up for a multitude of sins. So one of the, to your point, ten years is a long time to be on a drug. So if you're going to do it, and legitimately you could, as we've seen in the data. Cough is the number three use. So maybe you use cough for a month, and then you stop it. But ten years is a bit of an overkill.

The last thing, I remember a lot of these conversations came up in 2014. I was on the committee for the over the counter switch. And these issues were not all well-defined back then. Now, we're kind of revisiting those in a little more formal fashion. I can tell you for a fact after coming here today that I'm glad I

voted no for that switch. Can you imagine this drug going OTC? It frightens me, even though I don't think it deserves a black box. It definitely doesn't deserve OTC. Thank you.

DR. WADE: Thank you. Dr. Ortiz-Aguayo?

DR. ORTIZ-AGUAYO: Thank you. I have a couple of comments. I'm going to try to follow the same. I think that the data is faulty, but the data is what it is. I guess I had a question I'm mulling with is that we've had similar drugs for non-psychiatric reasons that have been noted to have an association with neuropsychiatric side effects, such as Accutane or some of the anti-malarials. Particularly for Accutane, a black box warning went in place. There's a REMS on it as well. And I think that the data, with regards to the hazard ratios, was also inconclusive.

So I'm wondering what's the role of precedent in making the decision of the degree of the labeling level that we should be encouraging. With regards to part two, and in part based on that same thought, there was something on the slides that showed that the patients -- the outpatients had some decrease in the depressive rates, outpatient depressive rates. And a similar association has been seen with Accutane, decreased rates of depression and suicide. It's probably -- there's just an association, no causation. But it's probably because people are asking the questions and people have been educated on how they have to ask these questions and how often to monitor, et cetera. So in that end, I think that while I'm less convinced that we need to go the way of a REMS, I do think that the minimum standard here should be a boxed warning.

In terms of recommendations on communication strategies, it has to be multiprong. I do think that the professional societies are a place to start. We have to engage consumer groups to at least ensure that “Hey, doctors, you are supposed to read this. And we know that it’s there.” And I would also encourage that whatever label language is used is comprehensible enough to the lay public so that they can have serious discussions with their physicians in terms of making the determination. As a pediatrician, I struggle a lot with the burden of asthma in the overall population and the quality of life of the kids and the families. So I would hate to see a similar effect to what happened with the SSRIs. But I think that if this side effect or side effect profile is possible, the discussions need to be a little bit more thorough than perhaps they’re occurring presently.

DR. WADE: Thank you. Dr. Griffin?

DR. GRIFFIN: Yeah. Thank you. Marie Griffin. I think we do need better communication strategies. But I would hate to see we focus just on that without moving the science forward. I think we really don’t know enough about neuropsychiatric effects. They’re reported with a number of drugs. Like people have said, people are now taking these for years and years. And there’s concern about persistent effects. If this was something like cancer, I think there would be long-term studies. Somehow because it’s mental illness, I think it doesn’t get the types of studies that it should. So this is just a plea for the communication is not going to be enough. I think we need studies because, right now, the science really doesn’t support strong effects. But the stories are very compelling. So for me, there’s a disconnect. And I think we need to move the science forward.

DR. WADE: Dr. Kelso?

DR. KELSO: So we've been talking about how to get the word out, and I'm wondering what the word is. What is it we're trying to communicate? We've heard that the data suggests that there is not an increased risk for these events, and perhaps even a decrease. But I absolutely agree that there's a disconnect because, although you can consider it multiple anecdote, there's not a group of 4,000 people reporting something -- there's something there that probably is not being captured. But given where we are now with the data we have now, what is it we're supposed to communicate?

I can't tell people -- if you tell people there's a risk that your child will develop depression or suicidal ideation and the parent says, "Well, what is the chance of that?" Is it one in 100? Is it one in 1,000? I don't have any idea because I'm not really sure how to quantify that or really all we have is kind of gut feeling that there's a risk there at all. So I don't know what it is we're trying to communicate.

I agree that we should consider the potential downsides of warning about something and having people stop taking the medicine because, clearly, the vast majority of patients who take this medication do not have this side effect, if, in fact, it is a side effect. So I think what we're left with of what we're trying to communicate would be to somehow have providers be reminded or be more aware that this has been reported. Because that's all we're telling people. We can't say quantify the risk. We don't know if it's a real risk. What we're telling people is this has been reported. It continues to be reported, and it may, in fact, be

a side effect of this medication. So somehow, we need to make providers aware of that again and also make patients aware of the idea that, once they're prescribed a medication, that if they start to notice various things, that they would be aware that that might be related to the medication and get that back to their provider.

So I'm not sure exactly how we get that message out, but I do think, given what we're left with in terms of data, that what we're trying to communicate is to just have providers be aware -- more aware that this has been reported and for patients and parents to be more aware that it has been reported so that they can report back to their providers if they notice concerning signs in their children.

DR. WADE: Ms. Robotti?

MS. ROBOTTI: Hi Suzanne Robotti. Significant questions have been raised, and they could be addressed through a study or studies by the makers of Singulair. If the company, as was suggested by the FDA, decides to drop their status as a sponsoring company, how can we assure the public that this product is safe? There seems to be a significant disconnect between the data we've been given, studies coming from Europe, and significant levels of online community groups and anecdotes. There's a problem going on here. Yet, we do need to address the care of asthma. So perhaps the threat of a black box warning would push the company off the dime. Is it Merck? Whoever is the manufacturer. But if there's a refusal to do this continuing research, I don't see how we keep this product on the market without a black box warning. If new research is being done, then we can wait. We can assess it. But if there will be no new research done on this, there are just too many questions.

I totally support Dr. Hoehn's suggestion of taking rhinitis off the label to narrow the label to only what it's most effective at and most needed for. And all those spikes that came out after news reports, I think that that's an indicator that people and doctors have no concept that there's a linkage between the drug. And med guides should be a given. There shouldn't be any discussion that we need it. We have to get that out because it's the public that needs to know this. We need to be reaching out -- the FDA should be reaching out to online community groups, health information sites, and do public Twitter chats. There's a lot of ways to get information out here in the 21st century. Let's use it.

DR. WADE: In the remaining time, I'm going to start by calling on people who have not yet had an opportunity to speak. So Dr. Premchand?

DR. ANNE: Premchand Anne. What was communicated today was the lack of information among the physicians itself. And some of the panel members have mentioned that also. I was recently involved in prescribing a medication that had REMS. They forced us to know what the effects are of prescribing this medication and how to monitor this. And actually, when you look at the FDA website, it says one of the purposes is to inform the healthcare stakeholders. I think this is a potential option that FDA should consider in terms of educating the providers that there is this possibility of neuropsychiatric symptoms, which can be pretty detrimental not only to the patient, but to the family as well. So I'll stop there.

DR. WADE: You sure?

DR. ANNE: Yes.

DR. WADE: Okay. We'll start here. Dr. Amirshahi.

DR. AMIRSHAHI: Maryann Amirshahi. I'd like to echo that I think there is a big disconnect between the data presented and the stories of the individuals who spoke to us. And there's even more online groups. I am a little hesitant to move ahead with a black box warning. I do work part-time in our Children's National Medical Center, and I can't tell you how many hospitalizations we have every shift for poorly controlled asthma. And I don't think the data necessarily backs up doing a black box warning.

However, I don't think that we should ignore these signals either. So I was hoping that, perhaps, in the current warnings and precautions, I know we talked about maybe moving it up a little bit in the section. And maybe, I was reading over in preparation for this just the language -- so maybe we could change the language to report not just neuropsychiatric events but perhaps severe neuropsychiatric events and maybe go into a little bit more depth because that might catch the prescriber as well. And then, I'm also not opposed to having a medication guide for patients because it sounds like the individuals who shared their stories with us really had to go and search for that information. And I think that, if we're going to do medication guides just in general, we need to find a way to vet them.

I was a retail pharmacist for 13 years prior to my medical career. And when I worked at CVS, we would have these long print outs that you basically -- were thrown out by the patient and not necessarily read. And it was not a balanced discussion of the risk and benefits. So I think a medication guide would

be great, but I think that we need to have a careful risk benefit discussion in those so it's just not a list of side effects. But that being said, I think that it's important to get the word out there so we can start a dialogue between patients and providers so they can make the most informed decision for them. Thank you.

DR. WADE: Dr. Jones?

DR. JONES: Bridgette Jones, Allergy, Immunology and Clinical Pharmacology. I think we've been talking about this issue for over a decade now. So when I was a fellow -- I'm just going to give a little anecdote. When I was a fellow in 2005, it was one of my first times being on call. One of the calls I got was a mother who had just started her child on montelukast, and she reported that her child was acting weird and was bumping into walls and was just acting strange. And the child was two. I talked to my attending, and he said, "Well, the child is two." And I'm like, "Yeah. The kid is two. Two-year olds fall down." But it was just a very strange call. So we told the mom to stop the medication. And then in follow up, she reported that the symptoms had stopped.

So it's been a long time, and we're continuing to have these anecdotes come out. I think the data presented today is inconclusive, in my mind. I don't think we can say for sure that there's not an association there or there is an association there. But I think that the stories that were told today were impactful. And the thing that was most impactful for me was the fact that no one knew these potential risks was out there. So the families didn't know. The physicians didn't know, and I don't think we're doing a good job at all in putting out there what even a potential risk could be.

I'm not sure if placing a black box warning on this medication can be compared to SSRIs where there aren't great alternative medications. We do have alternative medications for asthma. In my opinion, montelukast is not a great drug for treatment of asthma. I rarely prescribe it. When I have prescribed it, I cannot recall seeing significant improvements in asthma. It does bother me to see that it's being used frequently in really young children, so babies six months old for things like cough. So that does trouble me. So I do feel like we need to do a better job in sending a strong message to at least have these conversations occur in the office.

So a few years ago, we had a black box warning on long acting beta-agonist, which we used for asthma. Some patients, when I wanted to place them on it, they didn't want to go on the drug. But we had a conversation about the potential risks, and they made an informed decision whether to start the drug or not. And I think that's what needs to happen with this medication. There needs to be discussions with parents about the potential risks, the fact that the data is not very strong in either direction and allow parents and families to make those decisions.

DR. WADE: In light of the time, I just want to acknowledge that I know that some people have flights to catch that are not moveable. It's okay with me, if it's okay with the members of the FDA, if we extend another ten or 15 minutes to make sure everyone has the possibility to have their comments made. But I surely want to allow those members in the room who have transportation that they need to get to to be able to leave and that we will respect that. Ms. Oster?

MS. OSTER: I'm going to talk about what we know and then how we can

solve the problem. We know that there are 4,000 members that we've been told -- oh, 7,000. And we also know there are 2.3 million people using this particular drug. What do we know? That's statistically significant. That is something we have to look at, and that is something that we have to do research on. At a minimum, the discontinual withdrawal study that has been recommended is something that we should do. We need to also understand that there are new scientific evidence and that that is something that we have to include. But now how? How do we get out there?

It's not 1995, and I think we need to be thinking with what we have available to us. And the how that I believe we can get there fast is the pharmacist. Every single person who has to pick up that drug, we designed it so that the doctors don't have the time to read. We're hearing it right here. They're not reading. It's not because they're bad people. They don't have the time. But that pharmacist is there, and here's how we do this. It is in the business interest for the CVSs, for the Walmarts, for them to add a value add of education. What I would challenge is that we at the FDA build that relationship so that we go in there and say, "You know what? When they're picking up that drug, here's what you can do."

And here's the second thing that we could propose is the modality that you talked about -- how do you do this? Well, it turns out you can do a two- or three-minute video. They only cost like 300 bucks, the little whiteboard videos. And guess what? It doesn't even cost anything to put it up on a YouTube channel. So here's what you want to do. You don't know what you need to say? There's

enough information -- we have the information. We have the distribution channel, and we have the need to acknowledge that I don't want to be here in ten years saying we knew that this was a problem. Those babies, those children can't protect themselves, and we have to move quickly and do something. So I challenge us to require a minimum discontinual withdrawal study, that we also find a new method and advocate for the pharmacist to require that information come out. It's in their best interest, as well.

DR. WADE: Dr. Flick?

DR. FLICK: I want to just make a couple of comments. As committee members, I think we are bound or should be compelled to make our decisions based on the best available data. In this situation, Dr. Kelso's comments I think were right on target. The best available data showed no evidence that there is a risk associated with this drug in neuropsychiatric events. So we have to be very careful about -- and I'll confine this to black box warning because the black box warning needs to have an impact with prescribers. The use of the black box warning in situations where those who prescribe don't have confidence that it represents a true reflection of data dilutes the impact of black box warnings for all other drugs that is potentially used for.

The study that was done here, these are very difficult studies. It was done very well. A study like this, for some of us who are a little older, remember the Reye's syndrome. Reye's syndrome was associated with aspirin use in children. The hazard ratio in that study -- in those studies was in the 20s. The hazard ratios of around one or 1.2 or 1.3 are almost always associated with confounding within

a study. This study is negative. It's negative in essentially all of its outcomes, and it's a well-done study. So I just really think that there are no data to support a suggestion that there are neuropsychiatric effects that flow from the use of this medication. Certainly, observational studies have weaknesses, but I think that is the best available data. So I would strongly urge against the use of a black box warning.

DR. WADE: Dr. Havens?

DR. HAVENS: Thank you very much. To answer the specific issues, I think it's reasonable for a medication guide to be developed. I agree that it's not ready for a black box warning. The NIH and the National Heart, Lung, and Blood Institute have not updated their asthma guidelines since 2007. It's my understanding that they're doing that now. That would be an important target audience for the communication strategy to have the new national asthma guidelines include something about montelukast and this potential complication in their guidelines. And finally, the NIH pharmacogenomics research network would be a place to further explore the potential of pharmacogenomics evaluation in this context. So when you're talking about target organizations, it would be the NIH asthma guidelines writing committee and the NIH pharmacogenomics research network, which does include montelukast on their website already.

DR. WADE: Dr. Voepel-Lewis.

DR. VOEPEL-LEWIS: Terry Voepel-Lewis. I'm going to have to respectfully disagree with the suggestion that we don't do a black box warning. I understand that it was said earlier that it has been said that people become afraid to

take the drug if it's got a black box warning. We don't have a lot of evidence for that. Yes, prescribing rates may go down. Codeine, when the black box warning came out, the FDA made a strong statement about it. We've seen the codeine prescribing rates go down, but they haven't gone to zero. Nor I don't think they should.

When codeine deaths related to pharmacogenetic hypermetabolism occurred, there were probably no statistical differences in those deaths compared to other drugs. And in fact, since the prescribing rates have gone down, we've seen oxycodone prescribing go up. And I know of three overdose deaths related to therapeutic use of oxycodone in the Midwest that were in the media and one that was in our institution. So just because we -- we need to understand these risks and benefits.

So I do research in parental understanding of risks and benefits. Parents want the information about the risks. That doesn't mean they're going to decline a drug that's going to be helpful to them. We tell them that their kid could die under anesthesia, and they still say yes to anesthesia. We consent them for sedation. They still undergo sedation, even though there's a risk of death with sedation. Parents will make the decision based on the best risk and benefit information that they have. But they need that information to make an informed decision. And they also need to know what to look for. So I do think that a medication guide is warranted. I would suggest its warranted for every single drug on the market. I don't know why we don't have them, simple one-page medication guides, but at least for drugs with serious adverse effects.

And a boxed warning would help with maybe getting rid of the prescribing for rhinitis and using it more judiciously. And I just want to say with a caveat. I've taken Singulair for a decade. When I started taking Singulair, I was able to wean off of all albuterol. So for me, I didn't have any bad effect of taking Singulair, and I'm going to continue taking it because, when I stop taking it or miss a dose, about 36 hours later I start getting tight and a little bit wheezy. So I do think we need to understand weaning drugs. I think your body probably needs to keep taking those. I think Singulair is a great drug when it's warranted and for people that don't have a pharmacogenetic response. And it probably is pharmacogenetics. We'll never know unless we do those studies.

DR. WADE: Dr. Meisel.

DR. MEISEL: Steve Meisel, Fairview Minneapolis. First, I want to applaud and thank the brave people who came to speak to us today and those who posted online. Very impactful, very remarkable. 35 million prescriptions written a year, 80 percent of them by family practice, internal medicine, PAs, nurse practitioners, pediatricians, osteopathic medicine, 50 percent for rhinitis cough. That tells me that this drug is being prescribed in a cavalier manner, without regard to and in understanding of the risks that are involved. The FAERS data shows that between six and 800 neuropsychiatric events have been reported every year. I believe that less than one percent of what actually happens out there gets reported. I think if you extrapolate this out conservatively it's 100,000 of those events a year. That's a lot of numbers. 7,300 people in this Facebook group. That tells you that this is real. We may not be able to predict and understand the

science behind it, but this is real.

So I believe that we do need a black box warning, and I would hope that that black box warning does result in a reduction in its prescribing. And it should result in a reduction in its prescribing to those people for whom alternative therapies for conditions such as asthma are ineffective or have their own set of side effects. For cough, rhinitis, allergies, those sorts of things, there are plenty of alternatives. And if it reduces the exposure of this product in the community, so be it. That's a good thing. That reduces the risks to people that don't otherwise need to be exposed to that particular medication for.

I don't believe that "dear doctor letters," professional groups, communications to the media have any long-term impact. What has a long-term impact are things such as REMS programs, black box warnings, and those sorts of regulatory actions that are out there and continually in everybody's face, I guess, for lack of a better way of looking at it. If there's a black box warning, there'll be third-party payers that may impose some prior authorization with some special diagnostic codes that go along with that and will have a further impact on reducing its use in the community. So I think any notion that we could impact the number of adverse effects that we're seeing by communication, by soft communication, is frankly naïve.

I think we've got to do it in a stronger manner. A REMS program would probably be even stronger than a black box warning, but I'm willing to start at the black box warning level. And I think we need to be changing the package insert approval to reflect that it should be used only in patients with asthma for whom

alternative therapies are ineffective or have their own set of side effects. And finally, this is a minor point. I would modify the package insert to reflect what we know today about crossing into the blood brain barrier as opposed to what is currently reflected about minimal penetration. Thank you.

DR. WADE: Our last comment before we adjourn, Dr. Turer.

DR. TURER: Christy Turer. I work in primary care, and I think that the findings, though they are not convincing, I have to agree. I think that the data are inconclusive. I don't think that we have all the data that we need. And so, especially, what I did not see in the presentations were data regarding children less than six. We know that using this in infants -- that's a time of great neurodevelopment. Many of those kids can be colicky. And sometimes it's hard to discern the behavioral changes. I recently started a child on a different medication, and the parents noticed a change in behavior. But that doesn't always happen, especially for our less educated families, many of whom I care for. So I worry about the great neurodevelopment and the use of this drug and the widespread use of it for very minimal, minimal indications.

I also think we need data by race/ethnicity. If we look at the numbers of who is dying from asthma, it's African Americans. I did not see among the people who spoke today African Americans. I'd really like to know, by race/ethnicity, who is being affected by these things so that we can really understand risks and benefits. In terms of the labeling, I think we do need to send the message to primary care providers. I don't think that there is great awareness of these things. I think that we should remove the labeling for allergic rhinitis. I don't think that

we should be using for that. I think a black box warning does send a clear message. I think in this case, in contrast to antidepressants, antidepressants are treating a disease that causes death.

I think for asthma, I'm not convinced -- I've been looking up data on the impact of montelukast on morbidity and mortality. It doesn't appear to reduce hospitalizations nor death. Inhaled corticosteroids do. So in thinking about risk benefit, I think the black box would send a message and would decrease prescribing.

We as a country, our physicians, our prescribers, we over-prescribe. We under de-escalate therapies, even to ask the question of is this still needed. If I lower the dose, is the patient -- am I going to wheeze? Am I going to have significant effects? I'm hoping perhaps a black box warning would at least get us to use this drug less and to consider, perhaps, de-escalating it, for which we would need data on if there is any impact of de-escalation and, if so, some information on how to do that. We use this a ton in primary care. So thank you.

DR. WADE: So I will try to very briefly summarize in the essence of time. I think this has been a really wonderful and productive insightful conversation. We'd like to thank all the working groups at the FDA and all the family representatives and organizations who are present and also submitted information to the docket for this meeting today. Clearly, the stories that are told are very impactful. And their description and the type of symptoms that were described seemed consistent with what is already existing in the warnings of the label. Yet there is this disconnect in what providers, be it all levels of providers,

our physicians, pharmacists, and nurse practitioners, are communicating to families.

So there is clearly a strong acknowledgement of the concern of these symptoms that are being described that continue to be described today. There is a clear message of the desire to evaluate the risk and the benefit ratio given different indications and different disease modalities and how those diseases are being managed with other medications. I heard a consistent general support for the use of medication guide or other such processes that would better try to ensure communication to families, yet diverse opinions on the risk and benefits of a box warning.

Finally, I think, as always, we consistently ask for more thorough research and difficult research brought to light today, pharmacogenomics and the biological mechanisms that support neurotoxicity of this medication or any medication. Yet the time it will take to get those data is prolonged, and, therefore, I think we would recommend moving forward with finding ways to improve communication to both providers, pharmacists, and families through the variety of mechanisms that were brought forth. I think the only thing I would personally add is that we often develop family medication guides for asthma, how to track your incentive spirometry, how to be in your yellow, green, red zones for asthma.

There is lots of family information, and that is one topic that has not been brought forth is there are neuropsychiatric side effect warnings for a variety of asthma medications and that that may be another avenue of material that's already getting into the home about asthma management to try to get information about

medication management, medication storage, medication side effects, length of medication, those kind of thoughts. So with that, we will now adjourn the meeting. I will remind you to take all personal belongings with you. The room will be cleaned at the end of the meeting, and materials may be left on the table. And they will then be disposed of. Again, thank you to everyone for attending the meeting today.

[MEETING ADJOURNED]

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