JPPT | Adverse Drug Event Database Study

The Impact of Montelukast's Black Box Warning on Pediatric Mental Health Adverse Event Reports

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OBJECTIVE In March 2020, the US Food and Drug Administration (FDA) required a black box warning for montelukast due to serious mental health side effects. We hypothesized the warning would lead to an overall decrease in reports of mental health symptoms and disorders related to montelukast in both pre-adolescent and adolescent groups.

METHODS Adverse events of pre-adolescent and adolescent children taking montelukast sodium were reviewed from March 1, 2018 to March 3, 2020 and March 4, 2020 to February 28, 2022 using the FDA's Adverse Events Reporting System. The objective was to determine if mental health adverse event reports were influenced by placement of a Boxed Warning. Adverse reactions were grouped into 8 categories deemed to be related to mental health guided by the research team's interpretation of the FDA Sentinel Report. Chi-square tests were used to compare time periods and reports of the mental health categories.

RESULTS Of the 1570 reports assessed, 1295 (82.5%) included ≥1 mental health concern. Nine hundred ninety-six (84.2%) of the 1183 reports involving pre-adolescents and 299 (77.3%) of the 387 reports involving adolescents included ≥1 mental health reaction. Statistically significant changes for pre-adolescents were found in reports related to depression (χ^2 (1) = 4.30, p = 0.044), and sleep (χ^2 (1) = 5.74, p = 0.019), which both decreased between the pre and post periods. The only statistically significant change across categories for adolescents was a reduction in aggression reports between time periods (χ^2 (1) = 8.5, p = 0.004).

CONCLUSIONS After placement of an FDA black box warning on montelukast, total number of reports including mental health adverse events decreased in pre-adolescents; however, several categories assessed increased for adolescents.

ABBREVIATIONS FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration

KEYWORDS adverse effects; mental health; montelukast; pediatrics

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Introduction

According to the World Health Organization (WHO), asthma is the most common chronic disease observed in children and is characterized by the inflammation and swelling of small airways, which affected about 262 million people and resulted in about 461,000 deaths worldwide in 2019.[1,2] Additionally, allergic rhinitis, which is characterized by a heightened immune response localized to the upper respiratory tract, has been estimated by the Centers for Disease Control and Prevention to impact the lives of about 1 in 5 children.[3]

Leukotrienes are inflammatory mediators that play roles in airway inflammation in both asthma and allergic rhinitis. Over the past few decades, the blockage of leukotrienes has been an effective target in the treatment of asthma and allergic rhinitis. Per the Global Initiative for Asthma (2022), which routinely publishes guidelines for asthma management and prevention, leukotriene modulators were recognized as an option to reduce symptoms and the need for oral corticosteroids in young children with persistent asthma.[4] Montelukast sodium is an oral leukotriene receptor antagonist that works by blocking the receptor of the potent D4 leukotriene and is approved by the US Food and Drug Administration (FDA) for the treatment of asthma in children as young as 12 months of age and the treatment of allergies in children as young as 6 months of age.[5] The medication is estimated by the FDA to have been prescribed to about 2.3 million patients under 17 years of age in 2018.[5]

In 2008, 10 years after its initial approval, the FDA released a communication revealing there was a pending investigation regarding the possible association between montelukast sodium and behavior/mood changes, suicidality (suicidal thinking and behavior), and suicide.[5] After the FDA communication, there was a notable increase in reports in the FDA Adverse Event Reporting System (FAERS) database with an 18-fold

increase in adverse events reported in 2008 (n = 752), compared with the year prior (n = 41).[6] Subsequently, the FDA performed an analysis of completed suicides that had been reported and found many of the cases involved mental health adverse events being reported prior to the completion of suicide.[5] Investigations continued with additional analysis by the FDA using the Sentinel Distributed Database which, among a variety of analyses, looked at the comparison of depressive and suicidal symptoms in hospitalized montelukast users compared with inhaled corticosteroid (ICS) users.[5] Additional studies in animals revealed montelukast sodium had the ability to cross the blood brain barrier.[5] In March 2020, the FDA issued the *Boxed Warning*, which aimed to strengthen the existing warning regarding the risks of mental health adverse events that came with prescribing montelukast sodium (Figure 1).[5] The goal of this study was to determine whether the placement of the Boxed Warning impacted the number of mental health adverse events reported among pre-adolescents and adolescents when comparing the number of reports 2 years prior and 2 years after the warning.

Materials and Methods

A retrospective review of previously reported adverse events related to montelukast sodium in the pediatric population (1–17 years of age) from 2018–2022 was conducted using the FDA's Adverse Events Reporting System (FAERs) Public Dashboard.[6] Search teams included: 'montelukast (P),' 'montelukast sodium (G),' 'montelukast sodium chewable (P),' 'montelukast\montelukast sodium (G),' and 'Singulair (P)' for individuals 0–17 years of age (n = 2228).

Exclusion Criteria. Cases were reviewed to remove reports without montelukast or Singulair as the suspected product when a product name was provided (n = 69). Cases including "Victim of Child Abuse," or "Child Abuse" were also excluded (n = 41) in an effort to reduce a confounding stressor known to impact mental health. Additionally, cases including other medications/active ingredients listed as a suspected ingredient in conjunction with montelukast were also excluded (n = 374) resulting in a final cohort of 1744 cases. During data cleaning an additional 13 cases were excluded for cases of children under the age of 1. Finally, the data were limited to March 1, 2018–February 28, 2022, for a total of 1570 cases.

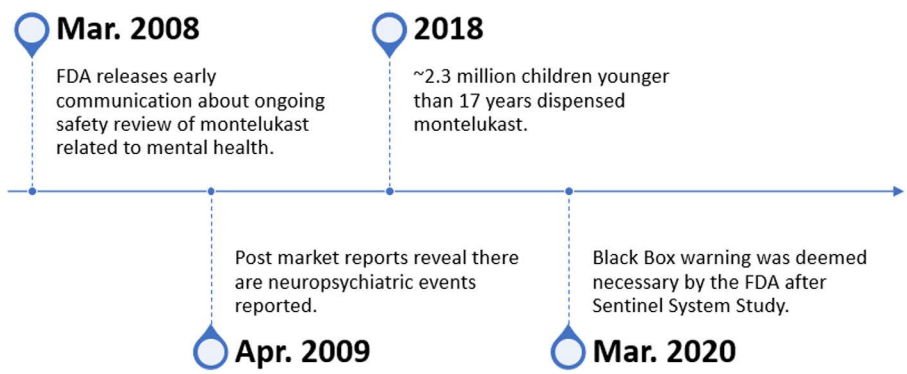
Grouping of Adverse Events. From this cohort a master list of over 500 reported reactions was created, including both mental health and non-mental health related events. This list was further reviewed to identify all mental health reactions. Once this review was completed, reactions were grouped into larger categories such as "Aggression Symptoms and Disorders," "Anxiety Symptoms and Disorders," "Depression Symptoms and Disorders," "Attention Deficit and Hyperactivity Disorder (ADHD) Symptoms and Disorders," "Sleep Symptoms and Disorders," "Suicidal Behavior," "Completed Suicide," and "Other Mental Health Symptoms and Disorders." These groupings were reviewed by all authors before being finalized for analysis. A complete list of reported events and groupings is provided in Supplement 1 (Table S1).

Statistical Analysis. Data were divided into a pre period (March 1, 2018–March 3, 2020) and post period (March 4, 2020–February 28, 2022) for the purpose of analysis. Cases were also grouped into 2 age categories, pre-adolescent (1–10 years) and adolescent (11–17 years).[9,10] Chi-square tests were used to test associations between time periods for each age group to assess changes in the mental health adverse event reporting using an alpha of 0.05 (5%) as a threshold for statistical significance.

Results

Of the 1570 reports assessed, 1295 (82.5%) included 1 or more mental health categories of interest. Reports predominantly included males (n = 938, 59.7%)

Figure 1. Timeline of events related to black box warning.[5,7,8]



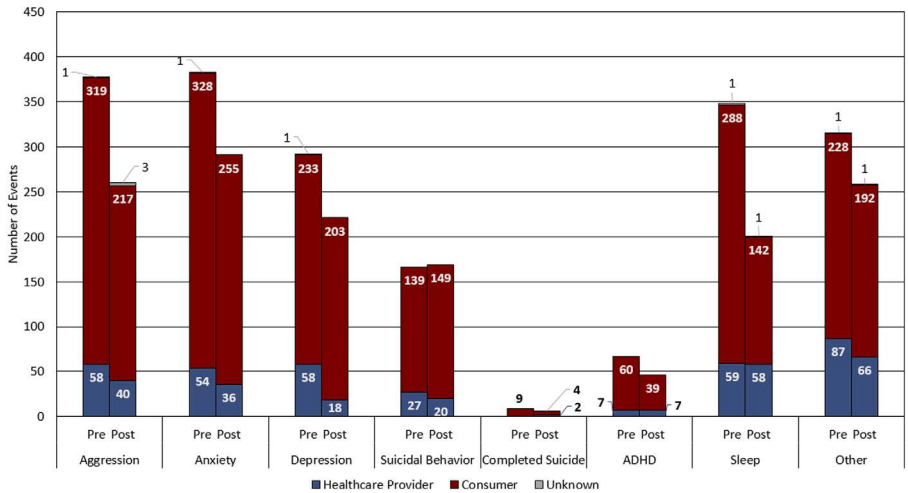
FDA, US Food and Drug Administration

compared with females (n = 574, 36.6%) with 58 (3.7%) reports not specifying the child's sex. Most reports were generated by consumers (n = 1083, 69%) with health care professionals generating only 30.6% (n = 481) of reports. Six (0.4%) reports did not specify a reporter type (Figure 2). The total number of reports decreased across time periods, as did the number of reports involving adverse mental health events; however, the percentage of reports that indicated a mental health adverse event increased between the pre (n = 711, 80.61%) and post (n = 584, 84.88%) periods. Nine hundred ninety-six (84.2%) of the 1183 reports involving pre-adolescent children and 299 (77.3%) of the 387 reports involving adolescent children included 1 or more mental health categories assessed. The total number of reports involving each category among pre-adolescents and adolescents during the pre and post periods are reflected in Figures 3 and 4, respectively.

ADHD Symptoms and Disorders. The pre period included 64 pre-adolescent reports including ADHD symptoms and disorders, which decreased to 36 during the post period; however, this change was not statistically significant (p = 0.455). Adolescent reports including ADHD increased between the pre (n = 3) and post (n = 10) periods; however, this change was also not statistically significant (p = 0.157).

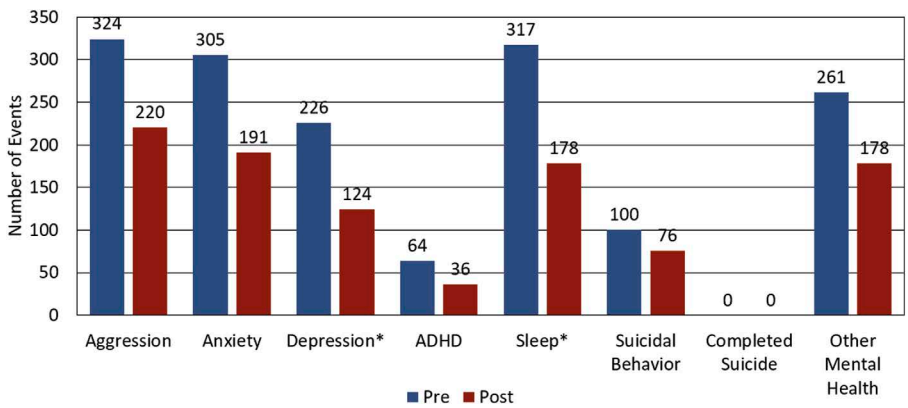
Aggression Symptoms and Disorders. Among pre-adolescents, the Aggression category was the most

Figure 2. Reports by reporter type and mental health category over time.



ADHD, attention-deficit/hyperactivity disorder

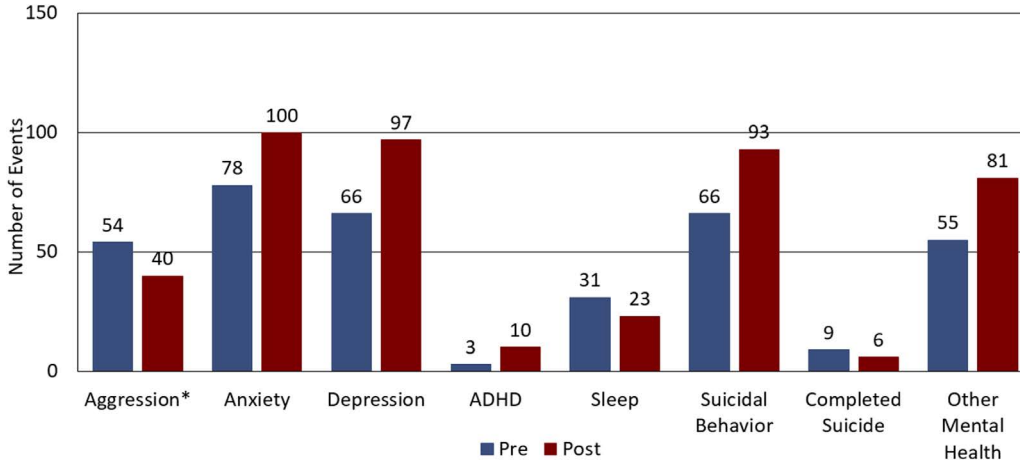
Figure 3. Reports by mental health category of pre-adolescent children before and after black box warning placement.



ADHD, attention-deficit/hyperactivity disorder

* Statistically significant changes between pre and post periods (p < 0.05).

Figure 4. Reports by mental health category of adolescent children before and after black box warning placement.



ADHD, attention-deficit/hyperactivity disorder

* Statistically significant changes between pre and post periods ($p < 0.05$).

reported of the eight mental health categories evaluated in the pre period. The number of aggression reports among pre-adolescents decreased between the pre (n = 324), and post (n = 220) periods; however, the change was not statistically significant (p = 0.812). Aggression reports involving adolescents also decreased between the pre (n = 54) and post (n = 40) periods. This change was statistically significant ($\chi^2(1) = 8.5$, p = 0.004).

Anxiety Symptoms and Disorders. Reports involving anxiety and pre-adolescents decreased from the pre (n = 305) and post (n = 191) periods; however, the change was not statistically significant (p = 0.400). Anxiety was the most reported mental health category among adolescents during the pre period (n = 78). These reports increased during the post period (n = 100); however, the increase was not statistically significant (p = 0.838).

Depression Symptoms and Disorders. Reports involving depression and pre-adolescents underwent a statistically significant decrease from pre (n = 226) and post (n = 124) periods ($\chi^2(1) = 4.30$, p = 0.044). Reports involving adolescents increased from the pre (n = 66) and post (n = 97) periods; however, this increase was not statistically significant (p = 0.214).

Sleep Symptoms and Disorders. Reports involving pre-adolescents and sleep disorders significantly decreased between the pre (n = 317) and post (n = 178) periods ($\chi^2(1) = 5.74$, p = 0.019). Reports involving adolescents decreased from the pre (n = 31) and post (n = 23) periods; however, the decrease was not statistically significant (p = 0.054).

Suicidal Behavior and Completed Suicide. Reports including suicidal behavior decreased among the pre-adolescent group between the pre (n = 100) and post (n = 76) periods; however, the change was not statistically significant (p = 0.360). Reports of suicidal behavior increased for the adolescent group between the pre (n = 66) and post (n = 93) periods; however, this change was also not statistically significant (p = 0.351). Pre-adolescents had no reports including completed suicide during the entirety of the study time frame. Reports of completed suicide among adolescents decreased from the pre (n = 9) and post (n = 6) periods. This change was not statistically significant (p = 0.290).

Other Mental Health Symptoms and Disorders. When assessing reports including other mental health symptoms and disorders, reports involving pre-adolescents decreased during the pre (n = 261) and post (n = 178) periods; however, the change was not statistically significant (p = 0.806). The opposite trend was observed regarding reports involving adolescents, which increased from the pre (n = 55) and post (n = 81) periods; however, the change was also not statistically significant (p = 0.284).

Discussion

The FDA's placement of a black box warning regarding adverse mental health effects associated with montelukast in all ages equipped clinicians with an opportunity for better informed clinical decision-making. The warning was intended to provide heightened awareness of the benefit-risk ratio involved with prescribing montelukast to both providers and patients. This analysis suggests a general decrease in reports for pre-adolescents and a mixed trend amongst

adolescents in which 5 of 8 observed mental health groups were noted to have increased after placement of the Boxed Warning.

These findings could be due to a variety of factors that include but are not limited to better informed decision making among providers leading to more cautious prescribing in the younger of the 2 observed populations. With the implementation of a stronger warning, increased sensitivity and awareness of potential mental health adverse effects may have reduced the threshold for older pediatric patients to report side effects. Additionally, it is worth mentioning the placement of the warning occurred near the time the COVID-19 pandemic started to have implications on everyday life in the United States, which undoubtedly had an impact on pediatric mental health. For instance, during the first months of the pandemic the Centers for Disease Control and Prevention reported a 24% increase in children 5 to 11 having a mental-health related visit to an emergency department while rates for children 12 to 17 increased by 31%.[11] Finally, although notable trends were observed in the data presented, FAERS data cannot be used to infer causation or correlation.

Limitations of Data and Next Steps

While these findings are important, the current study is not without limitations. A variety of factors could have impacted the mental health of children during this time period as noted previously. Increased public awareness and other factors may have increased the likelihood of children and parents reporting adverse events or concerns to FAERS or their medical provider. Additionally, the FAERS database is a public database with the potential for duplicate and incomplete reports documented. A submission of a report to the FAERS database does not indicate medical confirmation that the drug involved had definitive contribution to the reported event. As such, the rates of actual occurrence cannot be confirmed through use of the FAERS database.

Further research is needed to determine if more selective prescribing played a significant role in the reduction of adverse mental health events reported among preadolescents. Research is also necessary to determine factors contributing to the increase in reports among adolescents. Finally, future studies should expand the time frame of assessment to better determine and control for the impact COVID-19 had on pediatric mental health.

Conclusion

While the overall number of reports regarding adverse mental health events amongst pediatric patients decreased after the placement of an FDA black box warning, the percentage of reports including an adverse mental health event increased. Further, an analysis of older children demonstrated mixed trends in observed mental health reports. Providers still need to offer continuing patient/family education and monitoring regarding the potential for mental health adverse events that come with montelukast prescribing.

Article Information

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Disclosure. Amy Hendrix-Dicken, MA, owns personal stocks in Catalyst Pharmaceuticals, Johnson & Johnson, and AstraZeneca. Michelle Condren, PharmD has been a consultant for Wolters Kluwer and Pediatric and Neonatal Lexi-Comp. The other authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

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