JPPT | Commentary

Public Interest in Montelukast Prior to and After Announcement of Black Box Warning and Associations With Adverse Event Reports

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ABBREVIATIONS ARIMA, autoregressive integrated moving average; FAERS, Food and Drug Administration Adverse Event Reporting System; FDA, US Food and Drug Administration; RSI, relative search interest

KEYWORDS adverse drug event; FDA Adverse Event Reporting System; internet trends; montelukast

J Pediatr Pharmacol Ther 2024;29(1):90–92

DOI: 10.5863/1551-6776-29.1.90

In follow-up to our work published in the December issue of *The Journal of Pediatric Pharmacology and Therapeutics*,[1] we used relative search interest (RSI) data for montelukast from Google Trends and data from the US Food and Drug Administration's (FDA's) Adverse Event Reporting System (FAERS) to determine if public interest after FDA placement of a black box warning (or "Boxed Warning") may have influenced adverse event reporting. Because the Boxed Warning is the strongest warning by the FDA to notify patients and health care professionals of potential risk of life-threatening or significantly life-altering side effects, its issuance for montelukast was subsequently covered by news and media outlets.[2] Given the critical nature of the warning, the subsequent media coverage, and the fact that the medication was available by prescription for such a long time, our objective was to assess public interest in the drug following the Boxed Warning, as well as the association between public interest and montelukast-related mental health adverse event reports.

To achieve our goal we extracted weekly search engine volume for the medication "montelukast" from Google Trends, which has been used in previous studies as a proxy for public interest, from March 1, 2016, through the week of December 27, 2020. The search class *medication* includes searches for brand-name medications. Cases from the FAERS[3] were reviewed, and those including mental health adverse event reports involving children from February 25, 2018, to December 27, 2020, were condensed into weekly counts. Google Trends provides search volume as RSI, based on the peak search volume (RSI = 100) within the given time span. We first constructed an autoregressive integrated moving average (ARIMA) model to forecast RSI if the Boxed Warning had not been designated to compare forecasted and actual RSI. We then used Pearson correlation to measure the association between RSI and mental health–related adverse event reports during this time span.

During the week of March 1, 2020, when the Boxed Warning was placed, RSI in montelukast peaked (RSI = 100) compared with the forecasted value of 56.92 (95% CI, 51.19–62.65), representing a 75.70% increase in search volume (Figure 1). The heightened search interest remained significantly above the forecasted value for 5 weeks. The correlation between montelukast-related mental health FDA adverse event reports and RSI showed a positive significant relationship ($R = 0.537$, $p < 0.001$; Figure 2).

Our analysis suggests that the placement of the FDA's most stringent warning increased public interest in montelukast. The issuance of the black box warning regarding potential risks of mental health adverse events likely prompted heightened vigilance among patients, caregivers, and health care providers for behavioral changes, mood swings, or any other concerning symptomatology among those using montelukast. Additionally, we found that increased search volume was also correlated with the frequency of adverse events reported through FAERS related to the medication from 2016 through 2020—also showing both values increase near the onset of spring allergy season.[4] This is when physicians are seeing an increased patient load for allergy symptoms and prescribing these medications; however, the largest spike in FAERS events was immediately following the Boxed Warning, thus, it likely performed as intended, by increasing public awareness of adverse events associated with montelukast use.

Our assessment of public interest is not without limitations. Reports from FAERS can be incomplete or duplicative and are not medically verified. While Google is a popular search engine, Google Trends does not

Figure 1. Relative search interest for montelukast in the United States from March 1, 2016, to December 27, 2020.

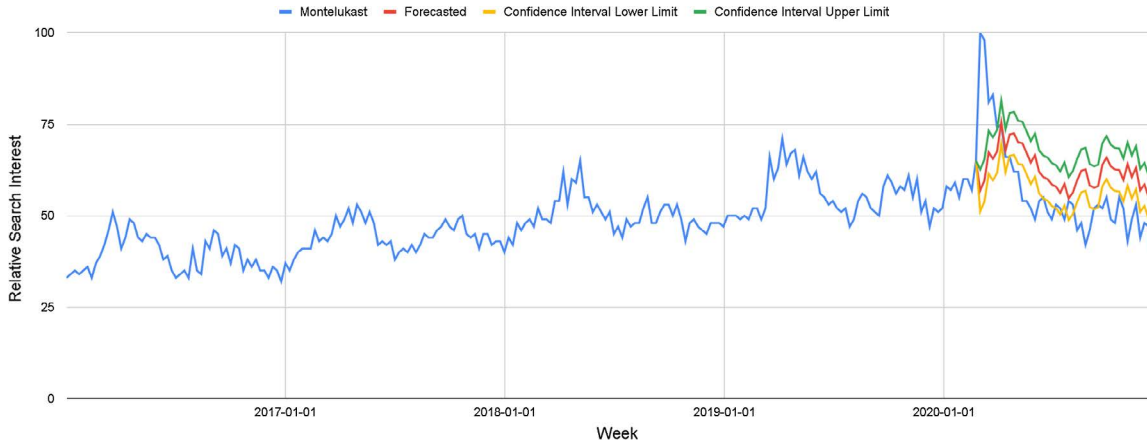
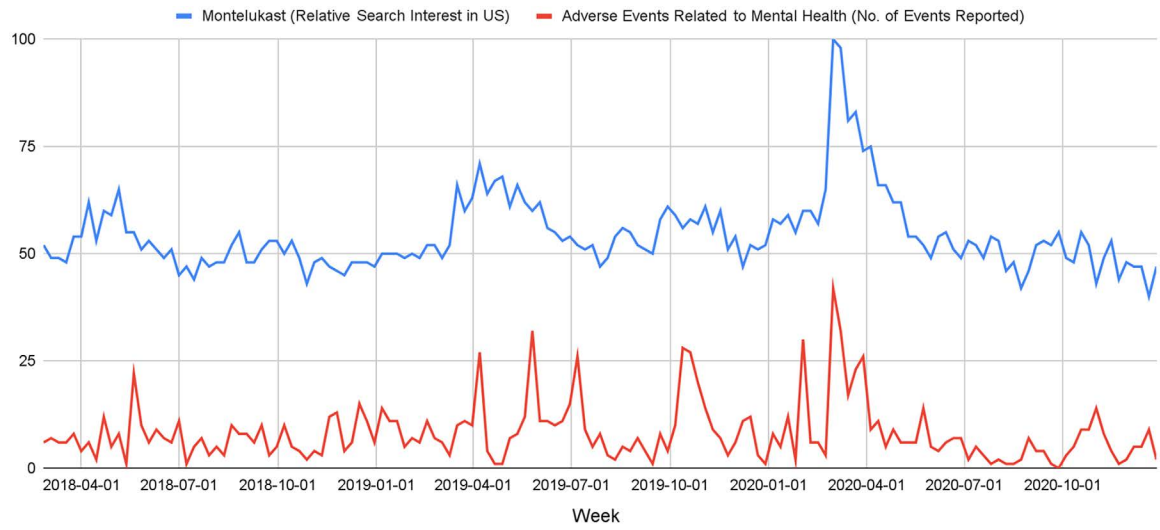


Figure 2. Montelukast relative search interest and adverse event reports related to mental health from February 25, 2018, to December 27, 2020.



capture user demographics, thus limiting the generalizability of our findings.[5] As such, further research into the effect of public awareness on adverse event reporting is needed.

From a public health perspective, the black box warning can be a powerful tool to heighten parent awareness related to specific medication adverse events. Given the significance of this warning, it is more likely to catch the attention of the media, allowing for a broader discussion of medication side effects outside of the medical community. This is critical because parents are essential partners with pediatric care teams and provide important information related to behavior and mood changes in their children. Given that initial reports related to mental health issues linked to montelukast were downplayed in 2009,[6] one cannot assume a layperson would link a child's sudden shifts in mood or behavior to an allergy medication. Further, our findings related to RSI indicate the public's desire to better understand information related to medication; however, that information is still not easily accessible or understandable outside of that relayed by media. It is essential that the medical community reflect on the important lessons that we've learned from montelukast over the last 2½ decades to increase patient safety and well-being.

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Disclosure. Micah Hartwell receives funding from the Human Resources Services Administration for research (U4AMC44250-01-02, PI: Audra Haney; R41MC45951 PI: Hartwell) unrelated to the current work. Amy Hendrix-Dicken owns personal stocks in Catalyst Pharmaceuticals, Johnson & Johnson, and AstraZeneca totaling less than $50. 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 communication, institutional review board/ethics committee review and informed consent were not required.

Submitted. September 29, 2023

Accepted. November 17, 2023

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