Research sheds light on effectiveness of FDA's black box warning for asthma drug

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A University of Oklahoma study about a "black box warning" for the asthma drug Singulair continues to influence a national conversation about the medication and its reported neuropsychiatric side effects in

children and adolescents. The U.S. Food and Drug Administration assigns black box warnings, sometimes called boxed warnings, as the highest safety-related consumer warning the organization assigns to medications, intended to bring attention to the risks of taking the medication.

In 1998, the FDA approved Singulair, known as montelukast in its generic form, for treating asthma and hay fever. It became a frequently prescribed drug for children struggling with asthma and allergies because it is available in a cherry-flavored chewable pill and may decrease the need for steroids or daily inhaler use. However, in the 26 years since its approval, concerned parents have sounded the alarm about dramatic and sometimes deadly mental health changes they have seen in their children, prompting the FDA to issue a black box warning in 2020.

In their study published in *The Journal of Pediatric Pharmacology and Therapeutics*, researchers at OU-TU School of Community Medicine on the University of Oklahoma's Tulsa campus sought to understand whether Singulair's reported negative side effects—including depression, aggression and suicidal thoughts—decreased after the black box warning.

Researchers analyzed adverse events reported to the FDA two years before and two years after the warning was issued. In children ages one to 10, reports about most harmful side effects decreased after the warning was issued. However, for youth ages 11 to 17, the outcome was mixed. Reports about side effects actually increased for five of the eight mental health symptoms. Overall, prescriptions for Singulair have decreased only slightly since the black box warning was issued.

In February, the New York attorney general cited the OU findings among other research in a letter to the FDA urging the agency to sound a new, louder alarm about the negative side effects of Singulair in

children. Families, too, continue to push for more restrictions on the drug.

A limitation of the study is that the black box warning was issued at the beginning of the COVID-19 pandemic, which had its own effect on the mental health of youth. But for OU researchers, their study underscores the importance of conversations between doctors and families, said the study's lead author, Samer Abdelkader, D.O., a pediatrics resident physician in the OU-TU School of Community Medicine.

"As a clinician interested in public health, I hope we can maximize the intent of these warnings and mitigate potential negative impacts on our patients," Abdelkader said. "I think we can enhance our patient care with better conversations about the benefits and risks of this medication and come to a more informed decision on whether this is the right treatment for each patient."

Asthma is the most common chronic disease in children, and hay fever (also known as allergic rhinitis) affects the lives of one in five young people, according to the Centers for Disease Control and Prevention. Singulair treats the inflammation and airway swelling that can be dangerous in both conditions. The FDA approved the drug for treating asthma in children as young as 12 months old and for allergies in babies as young as six months old. It is prescribed to millions of children and adolescents each year.

Parents were the first to raise awareness about mental changes they saw in their children who were taking Singulair. Aggression, anxiety, depression, hyperactivity, sleep problems and suicidal thinking were among the symptoms, and several high-profile suicides brought further attention to the drug's reported problems. Without parents' advocacy, issues with the drug likely would not have come to light as soon, said Amy Hendrix-Dicken, a senior research assistant and co-author of the

paper.

"Parents are the greatest partners in providing health care to children," she said. "Parents know their kids; our health care providers see them for 15 minutes, and there's only so much you can glean from a 15-minute visit. We encourage families and patients to speak up, and if they feel like their provider isn't listening, to find someone who will."

New information like the black box warning can take a long time to make its way into doctors' offices large and small, and federal agencies may communicate potential drug problems in differing ways. But health care providers should take the initiative to learn everything they can about the drugs they prescribe, the study's authors said.

"I no longer say that a side effect cannot be from a medication," said study co-author and pharmacist Michelle Condren, a professor and vice chair of research in the OU Department of Pediatrics. "I may say, 'I haven't seen this side effect before' or 'Let me look in the medical literature,' but I'll never say that a side effect isn't possible. This has changed the way I communicate with patients and families. We never want to discount someone who is concerned that a medication could be causing a side effect, but to partner with them to figure things out."

More information: Samer Abdelkader et al, The Impact of Montelukast's Black Box Warning on Pediatric Mental Health Adverse Event Reports, *The Journal of Pediatric Pharmacology and Therapeutics* (2023). DOI: 10.5863/1551-6776-28.8.704

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