

Two Cases of Montelukast-Associated Psychosis in Children

Wisam Al Jumaili, MD; Nibras Al Gburi, MD; Narayan Chaudhary, MD; Kimberly Brown; and Shailesh Jain, MD

Montelukast is one of the most widely prescribed antiallergy medicines.¹ It is a selective leukotriene receptor antagonist used as monotherapy or adjunct for prophylactic treatment of allergic rhinitis and severe asthma. It is also used in the prevention of exercise-induced bronchospasm.^{1,2} Montelukast has many other off-label uses, including in chronic obstructive airway disease, acne, and obstructive sleep apnea.¹ The US Food and Drug Administration (FDA) approved the use of montelukast in children under 12 years old, as early as 6 months, and adults.^{2,3} In 2020, the FDA issued a black box warning of severe mental health complications in children associated with montelukast use.^{1,2} Montelukast-induced dose-dependent neuropsychiatric symptoms in children include depression, anxiety, irritability, sleep disturbance, nightmares, agitation, suicidal behavior, auditory/visual hallucinations, and/or full psychosis.¹ Stopping montelukast treatment abruptly can have varying effects on underlying neuropsychiatric symptoms and may increase the likelihood of recurrence after restarting montelukast.¹

Montelukast crosses the blood-brain barrier and blocks G-protein-coupled receptor (GPR172) on neurons and microglia, contributing to neuropsychiatric symptoms. Also, montelukast negatively affects prostaglandin E2 formation and reactive oxygenation species/oxygen-free radical clearance balance.⁴ Abrupt montelukast discontinuation might lead to immunologic overactivation, with hyperactivity of microglial and phagocyte cells leading to worsening

neuropsychiatric symptoms.⁴ Montelukast treatment has been linked to an increased risk of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).⁵ The correlation between montelukast therapy and PANDAS is not fully understood, but many streptococcal infections have occurred after discontinuing montelukast treatment.⁵ The use of montelukast has been shown to affect the connection between the hypothalamus and neuropeptides.^{6–8} Montelukast can cause a disturbance of blood-brain barrier permeability and negatively affects the serotonin-norepinephrine system.^{6–8} There is no specific treatment recommendation for montelukast use in psychiatric patients. We observed 2 cases where children with psychiatric care experienced auditory visual hallucinations after taking montelukast for 1–2 days. These side effects are rare but serious.

Case 1

An 11-year-old black boy with autism and attention-deficit/hyperactivity disorder (ADHD) presented to the psychiatric clinic with his parent. He was taking no psychotropics. The patient developed sudden auditory visual hallucinations of ugly picture and negative commanding voices, different from his preoccupation thought process, associated with paranoia and insomnia after 2 days of using montelukast for asthma. He had no previous medical condition. All his basic laboratory values, including brain magnetic resonance imaging, were within normal limits. He had no previous IQ evaluation. All his psychotic symptoms subsided within 2 days

after discontinuing montelukast. There were no other active medical conditions, use of illegal recreational substances or alcohol, previous psychosis, or any family history of a psychiatric condition.

Case 2

A 15-year-old white girl with major depressive disorder and obsessive-compulsive disorder experienced sudden auditory visual hallucinations. She had a worsening of depressive symptoms with comorbid psychosis after starting montelukast 10 mg as an adjunct treatment for allergic asthma. There were no reports of previous psychosis, suicidal attempts, or self-harm behavior. She needed hospitalization for her safety and stability. Her psychosis symptoms immediately improved after stopping montelukast. Her asthmatic symptoms were stable, and there were no underlying active medical concerns. She denied using illegal drugs or alcohol, previous psychosis, or any family history of mental illness.

Discussion

These case reports go with previous evidence of montelukast-induced psychosis,¹ indicating that mono or adjunct montelukast treatment can trigger acute psychosis. It can happen in any gender, race, or age group. Although rare, montelukast can cause severe and alarming psychosis for patients and their families. The Naranjo adverse drug reaction probability score⁹ was 7 in both cases. Montelukast-induced neuropsychiatric symptoms are more prominent in children than in adults.² Neuropsychiatric symptoms were observed in up to one-quarter of montelukast-treated patients, and the majority (75%) were seen within the

first 2 weeks of treatment.²

Neuropsychiatric symptoms, including psychosis, can result from the medication itself or because of abrupt discontinuation.¹⁰ The exact cause is unclear, but there is sound evidence of immunologic disturbance in children's developing brains, including brain neurohormonal disturbance involving different neuropeptide and neurotransmitter systems.^{6,7} Multiple observational and data analysis studies show montelukast's controversial long-term safety data on neuropsychiatric symptoms. However, despite multiple confounding factors and propensity score matching used to eliminate false positive results, the odds ratio (OR) is still higher than that in the general population.^{1,6} Psychotropic medication was more frequently prescribed in asthmatic patients on montelukast treatment compared to montelukast-free medication regimen patients.¹ Montelukast-based asthma treatment increases the risk of neuropsychiatric symptoms in children by 12 times compared to inhaled corticosteroid-based asthma treatment,² leading to greater financial burden and reduced quality of life.⁶ Montelukast-induced psychosis in children was reported in a few published case reports, which indicated that it can happen as early as 21 months of age.^{11–16} Sleep disturbance and irritability are among the most common neuropsychiatric symptoms seen in younger children, while depression and suicidality were frequently observed in late adolescence.^{2,11–15} In a 10-year study, Tsai and colleagues¹⁷ found no link between prenatal montelukast exposure and subsequent offspring risk for development of autism, ADHD, or tic disorder in a sample of 576,157 individuals aged 30–40 years. In a cohort study by Paljarvi et al¹ that included 77,473 asthmatic/allergic

rhinitis adult patients, anxiety and insomnia were the only neuropsychiatric symptoms that were statistically significantly correlated with montelukast treatment after 1 year (OR = 0.98 for asthmatic vs OR = 1.07 for allergic rhinitis). There are no other similar studies in the pediatric population.¹ More studies are needed to confirm whether montelukast treatment is safe for psychiatric patients, especially children. When prescribing montelukast, pediatric clinicians should monitor at-risk patients for psychosis, sleep disturbance, nightmares, depression, and suicidality. They should also discuss the potential adverse effects and warnings with patients and their families.

Article Information

Published Online: May 28, 2024.

<https://doi.org/10.4088/PCC.23cr03694>

© 2024 Physicians Postgraduate Press, Inc.

Prim Care Companion CNS Disord 2024;26(3):23cr03694

Submitted: January 1, 2024; accepted February 26, 2024.

To Cite: Al Jumaili W, Al Gburi N, Chaudhary N, et al. Two cases of montelukast-associated psychosis in children. *Prim Care Companion CNS Disord*. 2024;26(3):23cr03694.

Author Affiliations: Texas Tech University Health Sciences Center at Permian Basin, Lubbock, Texas (Al Jumaili, Brown, Jain); Core Clinical Research, Everett, Washington (Al Gburi, Chaudhary).

Corresponding Author: Wisam Al Jumaili, MD, Texas Tech University Health Sciences Center at Permian Basin, 3601 4th St, Lubbock, TX 79430 (wajumail@ttuhsc.edu).

Relevant Financial Relationships: None.

Funding/Support: None.

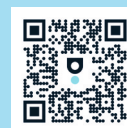
Patient Consent: The patients and their guardians consented to publish the case reports, and information has been de-identified to protect anonymity.

References

1. Paljarvi T, Forton J, Luciano S, et al. Analysis of neuropsychiatric diagnoses after montelukast initiation. *JAMA Netw Open*. 2022;5(5):e2213643.
2. Urdaneta E. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. *Eur Respir J*. 2017;50(5):1701984.
3. Merck & Co., Inc. *Singulair Package Insert*. Accessed September 5, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021409s0361bl.pdf

4. Marschallinger J, Schäffner I, Klein B, et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat Commun*. 2015;6:8466.
5. Wilbur C, Bitnun A, Kronenberg S, et al. PANDAS/PANS in childhood: controversies and evidence. *Paediatr Child Health*. 2019;24(2):85–91.
6. Umetsu R, Tanaka M, Nakayama Y, et al. Neuropsychiatric adverse events of montelukast: an analysis of real-world datasets and drug-gene interaction network. *Front Pharmacol*. 2021;12:764279.
7. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. *Pharmacol Res Perspect*. 2017;5(5):e00341.
8. Eriksson Y, Boström M, Sandelius Å, et al. The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. *Cell Death Dis*. 2018;9(7):775.
9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.
10. Pediatric Advisory Committee. *FDA Briefing Document*. Accessed September 5, 2024. Page 14. <https://www.fda.gov/media/131035/download>
11. Calapai G, Casciaro M, Miroldi M, et al. Montelukast-induced adverse drug reactions: a review of case reports in the literature. *Pharmacology*. 2014;94(1-2):60–70.
12. Wallerstedt SM, Brunlöf G, Sundström A, et al. Montelukast and psychiatric disorders in children. *Pharmacoepidemiol Drug Saf*. 2009;18(9):858–864.
13. Ekhardt C, van Hunsel F, Sellick V, et al. Neuropsychiatric reactions with the use of montelukast. *BMJ*. 2022;376:e067554.
14. Taşkıran G, Aslı Sürer A, Perihan Turhan G. Psychotic symptoms associated with montelukast in a 21-month-old girl. *Psychiatry Clin Psychopharmacol*. 2019;29:145–146.
15. Kovesi T. Neuropsychiatric side effects of montelukast. *J Pediatr*. 2019;212:248.
16. Jordan A, Toennesen LL, Eklöf J, et al. Psychiatric adverse effects of montelukast – a nationwide cohort study. *J Allergy Clin Immunol Pract*. 2023;11(7):2096–2103.e1.
17. Tsai HJ, Wu CS, Chang YC, et al. Use of leukotriene-receptor antagonists during pregnancy and risk of neuropsychiatric events in offspring. *JAMA Netw Open*. 2023;6(3):e231934.

Scan Now



Cite and Share
this article at
Psychiatrist.com