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Title page

Neuropsychiatric diagnoses after montelukast initiation in paediatric asthma patients

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Key messages

What is already known on this topic

Montelukast has been associated with various adverse neuropsychiatric outcomes, but the evidence base is inconclusive in children and young persons (CYP) with asthma.

What this study adds

In this cohort study of over 107,000 CYP, montelukast was associated with a 32% higher incidence of neuropsychiatric outcomes compared to those not exposed to montelukast, a statistically significant difference. Number needed to harm was 58.

How this study might affect research, practice or policy

Decision to prescribe montelukast in CYP with asthma should be based on a careful consideration of potential risks and benefits.

ABSTRACT

Background: The evidence base on montelukast-associated adverse outcomes is inconclusive in children and young persons (CYP) with asthma. We aimed to investigate 1-year incidence of neuropsychiatric diagnoses after initiation of montelukast as an adjunct therapy to inhaled corticosteroids in CYP aged 3–17 years with asthma.

Methods: This propensity score matched cohort study was conducted using electronic health records between 2015–2019 in the TriNetX Analytics Network patient repository in the USA. Neuropsychiatric diagnoses were identified using the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. We estimated risk ratios (RR), absolute risk increase (ARI), and number needed to harm (NNH) with 95% confidence intervals (95%CI).

Findings: The mean age [SD] at index prescription in the 107,384 CYP with asthma was 8.7 [4.0] years (93,461 [87%] mild to moderate asthma; 62,301 [58%] male; 53,485 [50%] white; 33,107 [31%] Black/African American). Montelukast was associated with excess incidence of any neuropsychiatric outcome (71 per 1000 persons with montelukast and 54 per 1000 persons with no montelukast; RR, 1.32 [95%CI, 1.25–1.39]; ARI per 100 persons, 1.71 [95%CI, 1.44–1.98]; 1-year NNH, 58 patients [95%CI, 51–69]). The highest excess risk in the montelukast group was for sleep disorders (RR, 1.63 [1.50–1.77]; ARI per 100 persons 1.17 [1.00–1.33]; NNH, 85 patients [75–100]). Montelukast use was also associated with excess incidence of anxiety disorders (RR, 1.10 [1.03–1.17]) and mood disorders (RR, 1.13 [1.03–1.24]).

Conclusions: In CYP with asthma who were treated with inhaled corticosteroids, adjunct treatment with montelukast was associated with a higher incidence of neuropsychiatric outcomes compared to those who were not exposed to montelukast.

INTRODUCTION

Inhaled corticosteroids (ICS) are the first-line therapy in children and young people (CYP) with chronic asthma.[1] Oral leukotriene receptor antagonists (LTRAs) can be used as an adjunct therapy in individuals who do not achieve adequate asthma control with daily ICS.[1] Montelukast is the most common LTRA prescribed worldwide and it is indicated for the maintenance treatment of asthma and for preventing asthma attacks in children aged 12 months and older. Other indications of montelukast are prevention of exercise-induced bronchoconstriction and relief of symptoms of allergic rhinitis. Montelukast is considered to be safe and well-tolerated, with mainly mild and infrequent side effects reported, such as headache and gastrointestinal symptoms.[2] In 2018, there were 2.3 million CYP under the age of 17 years in the U.S. who were prescribed montelukast.[3]

Asthma has been consistently associated with an increased risk of severe neuropsychiatric outcomes in CYP, including anxiety,[4,5] depression,[6,7] and even suicide.[8,9] The association between ICS and the risk of severe neuropsychiatric outcomes in CYP is not well established. However, ICS have been associated with hypothalamic-pituitary-adrenal (HPA) axis dysregulation.[10,11] It has been suggested that LTRAs could also be associated with HPA axis dysregulation, and that this could be the mechanism for montelukast-induced adverse drug reactions (ADRs) particularly in CYP.[12] Various severe neuropsychiatric outcomes have been associated with montelukast, including hallucinations, depression, and suicides.[13-18] Due to these concerns, the U.S. Food and Drug Administration (FDA) recommends limiting the use of montelukast in the treatment of allergic rhinitis to only those patients who cannot be treated effectively with alternative therapies.[3]

A total of 17 potential neuropsychiatric ADRs are listed in the labelling of LTRAs available in the U.S. as required by the FDA, along with a boxed warning of serious neuropsychiatric events reported in patients taking LTRAs.[3] The evidence based on the safety of LTRAs is almost exclusively based on montelukast because other LTRAs are rarely prescribed. In CYP with asthma, the most common ADRs associated with montelukast are anxiety, sleep problems, and various behavioural symptoms, including nervousness and aggression.[17] However, the evidence base in CYP is still considered inconclusive.[18] Therefore, further research is needed to clarify the nature and extent of the associations especially in CYP. The purpose of this study was to address this evidence gap by conducting a large propensity score matched cohort study of electronic medical records of over 800,000 paediatric asthma patients. We have previously shown that treatment with montelukast was associated with incident neuropsychiatric outcomes in

patients with asthma and allergic rhinitis who were aged 15–64 years.[19] This new study adds to the evidence base by focusing on CYP aged 3–17 years with asthma, by including symptoms not fulfilling diagnostic criteria for mental health disorders, and by presenting the findings separately by sex and age group. We will use two complementary approaches to analyse the data to improve assessment of potential sources of bias occurring after baseline matching. In our primary analysis, which is in principle similar to per-protocol analysis used in RCTs, participant eligibility is retained throughout the study period. This approach attempts to control various factors potentially confounding the observed associations during the one-year follow-up, and is thus our main analysis of ADRs associated with montelukast exposure. In our secondary analysis, which is in principle similar to intention-to-treat analysis used in RCTs, any changes in eligibility after baseline are ignored. Consistent associations across these two approaches will support the validity of the findings. To our knowledge, this is one of the largest study to date to explore the association between montelukast and neuropsychiatric ADRs in CYP with asthma.

METHODS

We used the TriNetX (TriNetX LLC., Cambridge, MA 02140, USA, www.trinetx.com) patient repository and analytics platform to identify patients with asthma. The TriNetX Analytics Network provided access to pseudonymized information on diagnoses, dispensed prescription medicines, and clinical procedures on over 25 million patients aged 3–17 years from 105 health care organizations (HCOs) mainly in the USA. This study is a secondary analysis of existing data, it does not involve intervention or interaction with human subjects, and is de-identified in line with the de-identification standard defined in Section §164.514(a) of the Health Insurance Portability and Accountability Act (HIPAA, 1996) Privacy Rule. The HIPAA Privacy Rule establishes the conditions under which protected health information may be used for research purposes. Based on the Privacy Rule, this retrospective study was exempt from Institutional Review Board approval and from informed consent.

Data were accessed and analysed via the TriNetX platform by using the TriNetX built-in query builder and algorithms. All diagnoses were identified using the International Classification of Diseases, tenth revision, clinical modification (ICD10-CM) codes. Dispensed prescription medicines were identified using the Veterans Affairs (VA) National Formulary codes and the normalized nomenclature for clinical drugs (RxNorm) codes. Clinical procedures were identified using the Current Procedural Terminology (CPT) codes. During the years 2015–2019, there were 844,429 patients aged 3–17 years with asthma. From this population, we defined two separate asthma groups: one of patients treated with ICS and montelukast (i.e., montelukast group), and another of patients treated with ICS but not with montelukast (i.e., control group). Each study year (2015—2019), we used the first dispensed montelukast prescription in the data as the index prescription for asthma patients exposed to montelukast; whereas, for the control group, we used the first dispensed prescription for ICS or inhaled bronchodilators, whichever came first, as the index prescription.

Patients were eligible at baseline if they were aged 3–17 years at index prescription, had an asthma-related visit and were prescribed ICS during the same year, and had no recorded history of LTRA prescriptions (i.e., had incident/new prescription for montelukast or did not have known previous exposure to LTRAs in the control group). All participants were required to have at least six months of recorded patient history in the participating HCOs, defined as any patient encounter, before the index prescription. Nearly all (95% in the montelukast group and 98% in the control

group) of the CYPs had a recorded patient history of up to two years before the index prescription, including the minimum period of six months (eFigure 1).

Primary analysis. The main results are based on analyses where participants were required to remain in their original treatment group (i.e., those in the control group were not allowed to have montelukast treatment during the one-year follow-up to avoid exposure misclassification/contamination bias), were required to have persistent asthma during follow-up to avoid confounding by asthma status (i.e., had an asthma-related visit or were prescribed asthma medication also in the following year after the index year), had recorded follow-up information for the full study period (i.e., were not lost to follow-up for the outcomes), did not have diagnosed obstructive sleep apnoea (OSA) and did not have tonsillectomy or adenoidectomy during follow-up. Those with tonsillectomy or adenoidectomy during follow-up and those with diagnosed OSA were excluded to reduce confounding particularly in sleep-related outcomes but also in relation to anxiety and depression. Furthermore, excluding those with OSA excluded patients for whom montelukast was possibly prescribed off-label to treat symptoms of OSA rather than to treat symptoms of asthma. There were 53,793 patients in the montelukast group who fulfilled the eligibility criteria and 313,490 patients in the control group who fulfilled the eligibility criteria and were thus included in propensity score matching (eFigure 2). Over 99% (364903/367283) of these patients were in the USA. After matching, there were 53,692 CYPs included per group.

Secondary analysis. In the secondary analysis, we used only baseline information to define eligibility and ignored potential changes in eligibility after baseline. Results from these analyses were used to validate the findings from the main analyses by comparing consistency of observed associations. The baseline eligible groups were matched for the same set of covariates as those in the primary analysis, which resulted in 73,443 matched CYPs per group. Of the patients in the control group, 1886 CYPs (2.6%) were prescribed montelukast during the one-year follow-up and thus changed their exposure status during the outcome measurement period. For 15,606 (21,2%) CYPs in the control group and 10,973 (14.9%) CYPs in the montelukast group, persistent asthma status could not be determined during follow-up because they did not have an asthma-related visit or had prescriptions for asthma medication during the following year after the index prescription. These post-baseline changes in eligibility could potentially affect the observed associations. The mean follow-up time, defined by the last known fact in the EHR, was 11.4 months

(standard deviation, 2.4) in the montelukast group and 11.4 (standard deviation, 2.5) in the control group, meaning that lost to follow-up did not likely bias the associations.

Primary outcome measures were 12-month incident psychotic disorders (ICD10-CM: F20–F29), mood disorders (F30–F39), anxiety disorders (F40–F48), sleep disorders (F51, G47), and suicidality defined by codes for intentional self-harm, suicidal ideation, and events of undetermined intent (X71–X83, T14.91, R45.851, Y21–Y33). For potential mental health symptoms not fulfilling diagnostic criteria for any of the primary diagnoses, we created two symptom groups using the ICD10-CM codes for emotional state (R45) and categorised these into externalising symptoms (nervousness, restlessness and agitation, irritability and anger, hostility, violent behaviour, impulsiveness, and homicidal ideations) and internalising symptoms (unhappiness, demoralisation and apathy, low self-esteem, worries, excessive crying, anhedonia, and emotional lability). We used dispensed prescriptions for sedatives and hypnotics, antidepressants, antipsychotics, stimulants, and medicines commonly prescribed for sleep problems as proxies for clinically important neuropsychiatric symptoms receiving treatment (eTable 1).

Sensitivity analyses were conducted within the main categories of neuropsychiatric outcomes: within mood disorders (bipolar disorder, major depression, dysthymic disorder, other and unspecified mood disorders), within anxiety disorders (phobic anxiety, generalised anxiety, obsessive-compulsive disorder (OCD), other and unspecified anxiety), within sleep disorders (insomnia, hypersomnia, parasomnias, movement disorders, other and unspecified sleep disorders), and suicidality (intentional self-harm, suicidal ideation, and events of undetermined intent). Furthermore, models for the primary outcomes were stratified by sex and age at index prescription (aged 3–9 years and 10–17 years at index prescription, for which the cut-off age was based on the mean age at index prescription) to observe potential differences between males and females and by age group. A post-hoc sensitivity analysis was conducted separately for those whose race was recorded as Black or African American because this group represented 31% of the study population.

Statistical methods

Propensity score matching was used to control for various confounders that could bias the comparisons between the montelukast and control groups. These covariates included demographics, severity of asthma, covariates associated with treatment allocation, and various neuropsychiatric and somatic comorbidities (Table 1). For the propensity

score matching, we used 1:1 nearest neighbour matching with a caliper of 0.1 standard deviations. Based on standard differences (≥0.1) before matching, distributions of patient characteristics differed across the montelukast group and the control group, e.g., in terms of asthma severity, covariates associated with montelukast indication, history of neuropsychiatric diagnoses, and somatic comorbidities (Table 1). Of the patients in the montelukast group, over 99% (53692/53793) were successfully matched with a patient in the control group. After matching, the groups were balanced for all the covariates included, i.e., all standard differences were below 0.1. We calculated risk ratios (RR) with 95% confidence intervals (95%CI) for the associations between montelukast and neuropsychiatric outcomes. For RRs above one, we calculated absolute risk increase (ARI) with 95% CI and number needed to harm (NNH, calculated as 1/ARI) with 95%CI. For the RRs, statistical significance was defined as 95%CIs not crossing 1; and for the ARIs, 95%CIs not crossing 0. There were no missing information on age, 0.1% had missing information on sex, and 12% had missing information on race. Those with missing information on sex or race were included in the propensity score matching as 'unknown sex' or 'unknown race' to balance the cohorts for missing information (Table 1). All sensitivity analyses were matched for the same set of covariates as the main models.

FINDINGS

Of the 107,384 patients who were included in the primary analysis, 62,301 (58%) were males; 53,485 (50%) were white; 33,107 (31%) were Black or African American; their mean age was 8.7 years (standard deviation (SD), 4.0) at the index prescription; 93,461 (87%) had mild to moderate asthma; 61,673 (57%) had vasomotor or allergic rhinitis; 35,320 (33%) had dermatitis or eczema; and 68,458 (64%) had a history of oral glucocorticoid prescriptions (Table 1). The most common neuropsychiatric comorbidity was disruptive behaviour disorder (attention deficit hyperactivity disorder (ADHD), (8198 patients, 8%) or conduct disorder (CD) (2710, 3%)), followed by sleep disorders (6799, 6%) and generalised anxiety disorder (4718, 4%). Patients in the montelukast group had a median of two dispensed prescriptions (mean, 2.2; SD, 2.6) during the 1-year follow-up period (data not shown).

During the 1-year follow-up, 3240 (7%) patients in the montelukast group and 2462 (5%) patients in the control group experienced at least one of the neuropsychiatric outcomes (incidence rate, 71 per 1000 persons vs 54 per 1000 persons, respectively), corresponding to about 30% excess risk (RR, 1.32 [95%CI, 1.25–1.39]; ARI per 100 persons, 1.71 [95%CI, 1.44–1.98]; NNH, 58 patients [95%CI, 51—69]) (Table 2). The highest excess risk in the montelukast group was for sleep disorders (RR, 1.63 [1.50–1.77]; ARI per 100 patients, 1.17 [1.00–1.33]; NNH, 85 patients [75—100]). Excess risks were also observed for other neuropsychiatric outcomes, including anxiety and mood disorders, and externalising and internalising symptoms, but with lower ARIs and higher NNHs. Similar findings of excess risks in the montelukast group were observed for incident psychotropic medicines across all drug groups (Table 3).

The sensitivity analyses by diagnostic subgroups showed that the excess risk in sleep disorders applied to subcategories of sleep disorder diagnoses, including hypersomnia and insomnia (eTable 2). Similarly, excess risks were seen across anxiety-related diagnoses, including generalised anxiety and OCD. A relatively large proportion of the diagnoses in sleep disorders, anxiety disorders, and mood disorders were in the diagnostic categories of ‘other’ or ‘unspecified’ disorders. Incident suicidal ideation, rather than self-harm, was more common in the montelukast group than in the control group, but the association was not statistically significant (RR, 1.25 [0.98–1.61]). When the models for main neuropsychiatric outcomes were stratified by sex and age, increased risks were observed in the montelukast group in males and females (eTable 3), and in those aged 3—9 years and 10—17 years (eTable 4). In CYP

whose race was Black or African American, montelukast was associated with a comparable excess risk of any neuropsychiatric outcome (RR, 1.29 [1.17–1.42]) (eTable 5) than what was observed in the total population.

The associations observed for the main neuropsychiatric outcomes in the secondary analysis showed that the RRs for anxiety disorders, mood disorders, sleep disorders, and for any neuropsychiatric outcomes showed comparable associations as in the primary analysis (results presented in Table 2 vs. eTable 6). However, differences in ARIs and thus also in the NNH were observed between the two study designs. In the primary analysis, the NNH was 58 (95%CI, 51–69) for any neuropsychiatric outcome, whereas in the secondary analysis it was 45 (95%CI, 41–52), respectively. The largest difference was seen in the NNH for sleep problems (85 (95%CI, 75–100) in the primary analysis and 52 (95%CI, 47–57) in the secondary analysis). In other words, the changes in eligibility after baseline did not change the proportionate risk difference across the groups for the main outcomes, but the primary and secondary analysis populations likely differed in their baseline risks, as suggested by the differences in ARIs. However, the consistency of associations in the RRs between the two designs support the validity of the observed increased risks associated with montelukast treatment.

DISCUSSION

We compared the incidence of neuropsychiatric diagnoses between those with and without montelukast as an adjunct therapy to ICS in CYP with asthma. Patients treated with montelukast had a 32% higher 1-year incidence of any neuropsychiatric outcomes compared to those treated with ICS alone. The highest excess incidence was for sleep disorders. NNH to cause one excess neuropsychiatric outcome was 58 in the montelukast group. The NNH was lowest for sleep disorders (NNH, 85), followed by anxiety disorders (NNH, 200), and mood disorders (NNH, 417). The observed associations were consistent across males and females, and across age groups.

These findings support the conclusion that montelukast is associated with neuropsychiatric outcomes in CYP with asthma, and that sleep problems and anxiety are common ADRs during treatment with montelukast.[17,20-23] In contrast with some previous studies,[17,18] we found an increased incidence of mood disorders in CYP with asthma who were treated with montelukast. Although the increased risk of mood disorders was smaller than for sleep disorders or anxiety, these disorders have a marked impact on the overall health and wellbeing of affected individuals; particularly if the symptoms are intensive and persistent, and occur during critical transitioning phases of childhood and adolescence. The excess incidence of antidepressant prescriptions in the montelukast group support the finding of increased symptoms of depression and anxiety. In our previous study, in a population of mainly adults, we did not find an increased risk of depression.[19] It is, therefore, possible that montelukast exacerbates a pre-existing HPA axis dysregulation particularly in CYP who have an initial suboptimal asthma symptom control, for which montelukast is commonly prescribed for.[12]

In sleep, anxiety, and mood disorders, diagnostic codes assigned for other and unspecific disorders were frequently used. This likely reflects diagnostic challenges on one hand and practices in assigning working diagnoses for neuropsychiatric symptoms in paediatric populations on the other hand. Increased risk of unspecific anxiety associated with montelukast has been reported previously.[20] These diagnostic challenges may partly explain the conflicting evidence from previous studies in CYP, together with other methodological limitations, such as small and selected study populations and limited control for confounders.[18] Potential montelukast associated neuropsychiatric ADRs are often identified and reported as symptoms rather than diagnoses.[17] Subjective symptom experience and presentation of symptoms in CYP may produce challenges in identifying neuropsychiatric symptoms and thus correctly diagnosing these symptoms. Certain ADRs, such as sleep disorders, are more likely to

be diagnosed, because a single symptom, such as difficulty falling asleep, can be used for a diagnosis of insomnia. However, as sleep problems are a known potential ADR of montelukast, clinicians may discontinue treatment with montelukast without a formal diagnosis of sleep disorders once these symptoms occur. There may also be considerable delay in arriving with a psychiatric diagnosis particularly in younger children, meaning that a longer follow-up than what is typically used in RCTs is needed to capture ADRs. Disruptive behaviours (ADHD and CD) were the most common baseline comorbidities in our data. Hyperactivity is commonly reported as a potential ADR associated with montelukast, but montelukast has not been found be associated with an ADHD diagnosis.[24] This is not surprising as ADHD is a neurodevelopmental disorder. Hyperactivity or restlessness observed in CYP treated with montelukast is thus more likely associated with anxiety or sleep disorders. Our consistent findings on various neuropsychiatric outcomes, thus, strengthen the partly mixed evidence base from larger observational studies in paediatric populations.[21,25,26]

Methodological considerations

As with all studies based on register data, this study had limitations. We did not have information on the duration of montelukast treatment, adherence, or for the indication for which montelukast had been prescribed for (e.g., whether primarily for asthma or allergic rhinitis). If patients received treatment from HCOs not participating in the TriNetX, before or after index prescription, this may have introduced bias due to misclassification in exposure status or loss to follow-up for the outcomes. However, because our eligibility criteria required a visit during the following year after the index prescription, lost to follow-up for the outcomes is unlikely. Because we used recorded diagnoses to identify neuropsychiatric outcomes, we only identified patients receiving treatment for these conditions. This has likely underestimated the number of patients experiencing these outcomes because patients with less severe symptoms may have not been identified. We focused on new treatment episodes with montelukast to reduce bias, because history of montelukast treatment is an indication of tolerability. Therefore, the associations may be different among patients with continuous long-term exposure to montelukast. It is possible that some residual confounding by indication remained in the models by unmeasured risk factors not captured by the data. Some case studies have reported that adverse montelukast-associated symptoms have resolved after cessation of treatment and returned after restarting treatment.[27] Our data did not enable us to establish a potential dechallenge-rechallenge association. We did not have information on outpatient deaths, meaning that we did not identify

completed suicides, if the individual was not treated in hospital before death. The HCOs participating in the TriNetX cannot be considered as representative of all HCOs in the USA., meaning that the true incidence of ADRs associated with montelukast remains unknown. Finally, it should be noted that the FDA issued safety warnings and other publicity around potential montelukast-associated adverse neuropsychiatric outcomes may have increased sensitivity of guardians and clinicians to monitor for and report neuropsychiatric symptoms in CYP treated with montelukast. This limitation applies to all observational studies on montelukast. A major strength of our data was the large number of CYP initially prescribed with montelukast, which allowed us to control for various potential baseline confounders and to establish the associations for various rare neuropsychiatric outcomes. Practically all patients in the montelukast group were successfully matched with a patient in the control group, which further reduced potential bias. Finally, consistent associations were observed across the two analysis approaches based on the principles of per-protocol and intention-to-treat analyses, which further supported the validity of our findings.

CONCLUSIONS

Although the observed overall risk increase for any adverse neuropsychiatric outcomes associated with montelukast was relatively small in absolute terms, these findings have important implications. First, because over 1/100 individuals experienced adverse outcomes during treatment, adverse neuropsychiatric outcomes associated with montelukast can be considered to be common in CYP with asthma. Whether these excess risks warrant change in clinical practice at individual level requires consideration by clinicians, patients, and their families in light of the risk profile reported here. Thus, a careful risk-benefit assessment should be made before the decision on prescribing montelukast in CYP with persistent asthma.[28,29] Second, given the wide use of montelukast and the relatively low overall NNH of 58 in those treated with montelukast, suggests that there is a large number of montelukast-associated adverse neuropsychiatric outcomes at population level. The potential association with suicidal ideation warrants further research in larger populations exposed to montelukast. Because we observed only diagnosed conditions, i.e., those that were most severe or disruptive, the actual NNH is likely to be lower. Given the existing alternative add-on therapies, e.g., inhaled corticosteroids – long acting beta agonist combination therapy, these population level effects are important to consider when establishing treatment choices in consensus guidelines.

STATEMENTS

Contributions

TP, SF, and JF designed the study. SL provided methodological support. TP did the statistical analyses. TP wrote the first draft of the manuscript. All authors (TP, JF, CT, SL, KH, and SF) reviewed and revised the manuscript. SF is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. TP and SL 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.

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Competing interests

The authors have no conflict of interests to declare. SL and CT were employees of the TriNetX at the time when the study was conducted.

Ethics approval

Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval and from informed patient consent according to the U.S. federal law (Health Insurance Portability and Accountability Act 1996).

Data sharing

Data was provided by TriNetX (www.trinetx.com), a federated data network. Access to TriNetX's de-identified patient data is available for the purpose of health care research with an approved user license.

REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org. Accessed October 2023.
2. Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, Knorr B, Noonan G. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. Pediatr Pulmonol. 2009 Jun;44(6):568-79. doi: 10.1002/ppul.21018.
3. 3-4-2020 FDA Drug Safety Communication. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. Available from: www.fda.gov. Accessed October 2023.
4. Dudeney J, Sharpe L, Jaffe A, Jones EB, Hunt C. Anxiety in youth with asthma: A meta-analysis. Pediatr Pulmonol. 2017 Sep;52(9):1121-1129. doi: 10.1002/ppul.23689.
5. Ye G, Baldwin DS, Hou R. Anxiety in asthma: a systematic review and meta-analysis. Psychol Med. 2021 Jan;51(1):11-20. doi: 10.1017/S0033291720005097.
6. Gao YH, Zhao HS, Zhang FR, Gao Y, Shen P, Chen RC, et al. The Relationship between Depression and Asthma: A Meta-Analysis of Prospective Studies. PLoS One. 2015 Jul 21;10(7):e0132424. doi: 10.1371/journal.pone.0132424.
7. Simões Cunha M, Amaral R, Pereira AM, Almeida R, Alves-Correia M, Loureiro CC, et al. Symptoms of anxiety and depression in patients with persistent asthma: a cross-sectional analysis of the INSPIRERS studies. BMJ Open. 2023 May 5;13(5):e068725. doi: 10.1136/bmjopen-2022-068725.
8. Barker E, Kõlves K, De Leo D. The relationship between asthma and suicidal behaviours: a systematic literature review. Eur Respir J. 2015 Jul;46(1):96-106. doi: 10.1183/09031936.00011415.
9. Hoffman KW, Visoki E, Argabright ST, Schultz LM, Didomenico GE, Tran KT, Gordon JH, Chaiyachati BH, Moore TM, Almasy L, Barzilay R. Association between Asthma and Suicidality in 9-12-Year-Old Youths. Brain Sci. 2022 Nov 23;12(12):1602. doi: 10.3390/brainsci12121602.
10. Zöllner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)--the risk as determined by gold standard adrenal function tests: a systematic review. Pediatr Allergy Immunol. 2007 Sep;18(6):469-74. doi: 10.1111/j.1399-3038.2007.00539.x.
11. Smith RW, Downey K, Gordon M, Hudak A, Meeder R, Barker S, Smith WG. Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. Paediatr Child Health. 2012 May;17(5):e34-9. doi: 10.1093/pch/17.5.e34.
12. Marques CF, Marques MM, Justino GC. The mechanisms underlying montelukast's neuropsychiatric effects - new insights from a combined metabolic and multiomics approach. Life Sci. 2022 Dec 1;310:121056. doi: 10.1016/j.lfs.2022.121056.
13. Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. Pharmacology. 2014;94(1-2):60-70. doi: 10.1159/000366164.
14. Aldea Perona A, García-Sáiz M, Sanz Álvarez E. Psychiatric Disorders and Montelukast in Children: A Disproportionality Analysis of the VigiBase. Drug Saf. 2016 Jan;39(1):69-78. doi: 10.1007/s40264-015-0360-2.
15. FDA Briefing Document. Neuropsychiatric Events with Use of Montelukast in Pediatric Patients. Pediatric Advisory Committee Meeting September 27, 2019. Available from: www.fda.gov. Accessed October 2023.
16. Sansing-Foster V, Haug N, Mosholder A, Cocoros NM, Bradley M, Ma Y, et al. Risk of Psychiatric Adverse Events Among Montelukast Users. J Allergy Clin Immunol Pract. 2021 Jan;9(1):385-393.e12. doi: 10.1016/j.jaip.2020.07.052. Epub 2020 Aug 11. PMID: 32795564.
17. Dixon EG, Rugg-Gunn CE, Sellick V, Sinha IP, Hawcutt DB. Adverse drug reactions of leukotriene receptor antagonists in children with asthma: a systematic review. BMJ Paediatr Open. 2021 Oct 13;5(1):e001206. doi: 10.1136/bmjpo-2021-001206.
18. Lo CWH, Pathadka S, Qin SX, Fung LWY, Yan VKC, Yiu HHE, et al. Neuropsychiatric events associated with montelukast in patients with asthma: a systematic review. Eur Respir Rev. 2023 Sep 27;32(169):230079. doi: 10.1183/16000617.0079-2023.

19. Paljarvi T, Forton J, Luciano S, Herttua K, Fazel S. Analysis of Neuropsychiatric Diagnoses After Montelukast Initiation. JAMA Netw Open. 2022 May 2;5(5):e2213643. doi: 10.1001/jamanetworkopen.2022.13643.
20. Wallerstedt SM, Brunlöf G, Sundström A, Eriksson AL. Montelukast and psychiatric disorders in children. Pharmacoepidemiol Drug Saf. 2009 Sep;18(9):858-64. doi: 10.1002/pds.1794.
21. Glockler-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case-Control Study. J Pediatr. 2019 Jun;209:176-182.e4. doi: 10.1016/j.jpeds.2019.02.009.
22. Benard B, Bastien V, Vinet B, Yang R, Krajinovic M, Ducharme FM. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. Eur Respir J. 2017 Aug 17;50(2):1700148. doi: 10.1183/13993003.00148-2017.
23. Al-Shamrani A, Alharbi S, Kobeisy S, AlKhater SA, Alalkami H, Alahmadi T, Almutairi A, Alharbi AS, Yousef AA. Adverse Drug Reactions (ADRs) of Montelukast in Children. Children (Basel). 2022 Nov 21;9(11):1783. doi: 10.3390/children9111783.
24. Huang PY, Yang YH, Huang YH, Kuo HC, Wang LJ, Chien SJ, et al. Montelukast does not increase the risk of attention-deficit/hyperactivity disorder in pediatric asthma patients: A nationwide population-based matched cohort study. J Formos Med Assoc. 2021 Jun;120(6):1369-1376. doi: 10.1016/j.jfma.2020.10.018.
25. Ali MM, O'Brien CE, Cleves MA, Martin BC. Exploring the possible association between montelukast and neuropsychiatric events among children with asthma: a matched nested case-control study. Pharmacoepidemiol Drug Saf. 2015 Apr;24(4):435-45. doi: 10.1002/pds.3758.
26. Glockler-Lauf SD, Finkelstein Y, Zhu J, Feldman LY, To T. Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case-Control Study. J Pediatr. 2019 Jun;209:176-182.e4. doi: 10.1016/j.jpeds.2019.02.009.
27. Watson S, Kaminsky E, Taavola H, Attalla M, Yue QY. Montelukast and Nightmares: Further Characterisation Using Data from VigiBase. Drug Saf. 2022 Jun;45(6):675-684. doi: 10.1007/s40264-022-01183-2.
28. Chauhan BF, Jeyaraman MM, Singh Mann A, Lys J, Abou-Setta AM, Zarychanski R, et al. Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma. Cochrane Database Syst Rev. 2017 Mar 16;3(3):CD010347. doi: 10.1002/14651858.CD010347.pub2.
29. Mayoral K, Lizano-Barrantes C, Zamora V, Pont A, Miret C, Barrufet C, et al. Montelukast in paediatric asthma and allergic rhinitis: a systematic review and meta-analysis. Eur Respir Rev. 2023 Oct 18;32(170):230124. doi: 10.1183/16000617.0124-2023.

Table 1. Characteristics of montelukast and control groups before and after matching.

	Before matching			After matching		
Characteristics. %	**Montelukast group (n=53793)**	**Control group (n=313490)**	**Std diff**	**Montelukast group (n=53692)**	**Control group (n=53692)**	**Std diff**
Mean age at index prescription (SD)	8.6 (4.0)	9.2 (4.2)	0.126	8.6 (4.0)	8.7 (4.0)	0.009
Male	58.1	56.9	0.023	58.1	57.9	0.014
Unknown sex	0.1	0.04	0.018	0.1	0.1	0.010
White	49.2	46.3	0.059	49.2	50.5	<0.001
Black or African American	31.2	33.6	0.056	31.2	30.5	0.026
Other Race	7.6	9.0	0.016	7.6	7.3	0.015
Unknown race	12.1	11.1	0.030	12.1	11.7	0.005
Mild intermittent asthma	36.8	47.1	0.201	36.9	36.5	0.011
Mild persistent asthma	27.5	22.4	0.138	27.5	28.0	0.010
Moderate persistent asthma	23.1	11.6	0.323	23.0	22.1	0.012
Severe persistent asthma	3.7	1.0	0.184	3.6	3.0	0.023
Bronchodilators. inhalants	90.9	96.4	0.227	90.9	91.3	0.034
Glucocorticoids. oral	63.7	62.9	0.031	63.7	63.8	0.015
Wheezing	21.4	24.0	0.059	21.4	21.0	0.006
Acute upper respiratory infections	51.7	61.1	0.186	51.7	51.1	0.009
Vasomotor and allergic rhinitis	57.4	43.1	0.291	57.3	57.5	0.012
Chronic rhinitis. nasopharyngitis and pharyngitis	9.9	6.8	0.115	9.9	9.7	0.006
Snoring	10.5	8.9	0.053	10.5	10.1	0.009
Dermatitis and eczema	33.1	36.1	0.057	33.2	32.6	0.011
Suppurative and unspecified otitis media	26.1	31.5	0.116	26.1	25.5	0.020
Headache	7.4	9.5	0.075	7.4	7.2	0.014
Other headache syndromes	3.9	5.4	0.076	3.9	3.8	0.007
Overweight and obesity	8.2	10.6	0.080	8.2	7.9	0.007
Other functional intestinal disorders	14.1	16.4	0.060	14.1	13.6	0.014
Other and unspecified noninfective gastroenteritis and colitis	11.5	13.8	0.070	11.5	11.2	0.014
Gastro-oesophageal reflux disease	9.4	9.3	0.020	9.4	9.2	0.009
Nocturnal enuresis	1.5	2.1	0.041	1.5	1.5	0.007
Congenital malformations. deformations and chromosomal abnormalities	11.7	13.7	0.057	11.7	11.4	0.006
Depressive episode	1.9	3.1	0.069	1.9	1.8	0.008
Generalised anxiety disorder	4.5	6.1	0.065	4.5	4.3	0.009
Adjustment disorders	1.3	2.0	0.053	1.3	1.3	0.007
Sleep disorders not due to a substance or known physiological condition	0.8	0.9	0.016	0.8	0.8	0.007
Sleep disorders	5.7	5.6	0.010	5.7	5.4	0.003
Attention-deficit hyperactivity disorders	7.6	9.8	0.075	7.6	7.6	0.010
Conduct disorders	2.6	3.8	0.071	2.6	2.5	0.003
Injuries to the head	11.5	15.4	0.111	11.5	11.1	0.010
Suicidal ideations	0.4	0.8	0.041	0.4	0.4	0.011
Suicide attempt	0.1	0.1	0.011	0.1	0.1	0.010
Intentional self-harm	0.1	0.2	0.018	0.1	0.1	<0.001
Visit: Emergency	35.4	42.6	0.146	35.4	34.6	<0.001
Visit: Inpatient encounter	17.2	16.8	0.032	17.2	16.7	0.017

Std diff, standardised mean difference; SD, standard deviation of the mean. Asthma patients aged 3–17 years at index prescription in years 2015–2019. Covariates recorded at or before index prescription.

Table 2. One-year incident neuropsychiatric outcomes.

	Montelukast group		Control group				
	Patients in group	**Patients with outcome**	**Patients in group**	**Patients with outcome**	**RR (95%CI)**	**ARI (95%CI)**	**NNH (95%CI)**
Psychotic disorder	53394	50	53369	50	1.00 (0.68, 1.48)	n/a	n/a
Mood disorder	51987	898	52031	773	1.16 (1.05, 1.29)	0.0024 (0.0011, 0.0037)	417 (270, 909)
Anxiety disorder	50061	1842	50036	1591	1.16 (1.08, 1.24)	0.0050 (0.0031, 0.0069)	200 (145, 323)
Sleep disorder	50315	1519	50473	935	1.63 (1.50, 1.77)	0.0117 (0.0100, 0.0133)	85 (75, 100)
Suicidality[a]	52971	324	53147	258	1.25 (0.98, 1.61)	0.0013 (0.0005, 0.0020)	769 (500, 2000)
Externalising symptoms	52900	240	52987	192	1.25 (1.02, 1.53)	0.0009 (0.0003, 0.0016)	1111 (625, 3333)
Internalising symptoms	52919	207	52841	151	1.36 (1.09, 1.71)	0.0011 (0.0005, 0.0017)	909 (588, 2000)
Any neuropsychiatric outcome	45735	3240	45828	2462	1.32 (1.25, 1.39)	0.0171 (0.0144, 0.0198)	58 (51, 69)

n/a, not applicable; RR, rate ratio; CI, confidence interval; ARI, absolute risk increase; NNH, number needed to harm calculated as 1/ARI.

[a]Suicidality including suicidal ideation, intentional self-harm, and events of undetermined intent. Asthma patients aged 3–17 years at index prescription in years 2015–2019. The same individual could have multiple incident diagnoses from different diagnostic groups during follow-up.

Table 3. One-year incident prescriptions for psychotropics.

	Montelukast group		Control group		
Psychotropics	**Patients in group**	**Patients with outcome**	**Patients in group**	**Patients with outcome**	**RR (95%CI)**
Sedatives	49468	1467	48990	1170	1.24 (1.13, 1.35)
Antidepressants	51525	1084	51711	792	1.37 (1.25, 1.51)
Antipsychotics	52937	306	53040	228	1.34 (1.13, 1.59)
Stimulants	50362	1194	50298	876	1.36 (1.25, 1.48)
Sleep medications	52274	725	52383	517	1.40 (1.24, 1.58)
Any selected psychotropic	45316	2787	45095	2198	1.26 (1.19, 1.33)

RR, rate ratio; CI, confidence interval. Asthma patients aged 3–17 years at index prescription in years 2015–2019. The same individual could have multiple incident prescriptions from different drug classes during follow-up.