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# Montelukast Use and the Risk of Neuropsychiatric Adverse Events in Children

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**IMPORTANCE** Spontaneous reports have indicated that montelukast increases the risk of neuropsychiatric adverse events, and the US Food and Drug Administration added a boxed warning about these risks in 2020. However, the potential mechanism is not well understood, and the observational evidence is scarce, particularly in children.

**OBJECTIVE** To assess the potential association between the use of montelukast and the risk of neuropsychiatric adverse events in children and adolescents.

**DESIGN, SETTING, AND PARTICIPANTS** This nationwide register-based cohort study used data from Sweden from January 1, 2007, to November 30, 2021. Participants included children aged 6 to 17 years who used montelukast and long-acting β-agonists (LABA). Data analysis was performed from December 2023 to April 2024.

**EXPOSURE** Montelukast vs LABA.

**MAIN OUTCOMES AND MEASURES** The primary outcome, any neuropsychiatric adverse event, was a composite of secondary outcomes, including anxiety; depression; sleep-related disorders; suicide and suicidal actions; disrupted control of activity, attention, and behavior; and confusion and psychotic-like symptoms. Outcomes were defined on the basis of diagnosis codes and dispensings of prescription drugs for specific neuropsychiatric symptoms. Patients were followed up from drug initiation to discontinuation, and treatment and censoring weights were used to adjust for potential confounding on baseline and selection bias from informative censoring. Pooled logistic regression was used to estimate hazard ratios (HRs).

**RESULTS** The final cohort included 74 291 children (mean [SD] age, 12.3 [3.3] years; 35 446 female [47.7%]); 26 462 used montelukast and 47 829 used LABA. During a mean (SD) follow-up of 5.8 (3.2) months, 310 neuropsychiatric adverse events in the montelukast patients and 566 events in the LABA patients were identified. In the weighted cohort, the incidence rates of neuropsychiatric adverse events were 2.39 per 100 patient-years among the montelukast users and 2.41 per 100 patient-years among the LABA users. This translated to a weighted HR of 0.99 (95% CI, 0.84-1.16). No substantial differences were observed between the montelukast and LABA patients when analyzing the risk of specific neuropsychiatric adverse events: the HRs were 0.79 (95% CI, 0.54-1.14) for anxiety; 1.16 (95% CI, 0.70-1.95) for depression; 0.93 (95% CI, 0.76-1.13) for sleep-related disorders; 1.31 (95% CI, 0.64-2.69) for suicide and suicidal actions; 1.27 (95% CI, 0.84-1.90) for disrupted control of activity, attention, and behavior; and 0.51 (95% CI, 0.05-5.53) for confusion and psychotic-like symptoms. The risk of the primary outcome was consistent over subgroups and a range of sensitivity analyses.

**CONCLUSIONS AND RELEVANCE** In this large study of children and adolescents based on data from routine clinical practice, there was no association between use of montelukast and the risk of neuropsychiatric adverse events. In aggregation with other robust observational studies, these results can inform the management of asthma and allergic rhinitis in this patient group.

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Supplemental content

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The leukotriene receptor antagonist montelukast is efficacious and widely used in children and adolescents with asthma and allergic rhinitis.[1] Oral montelukast offers systemic anti-inflammatory action and is primarily used as an add-on treatment in patients with mild-to-moderate chronic disease who do not achieve disease control with inhaled corticosteroids (ICS) and short-acting β-agonists. The uptake of montelukast is high and has increased rapidly in many countries during the last decades.[2,3]

In 2008, a signal emerged from spontaneous reports in the US linking montelukast to an increased risk of neuropsychiatric adverse events, including depression, anxiety, sleep disturbance, aggression, and suicide.[4] Subsequently, the US Food and Drug Administration (FDA) announced a label change for montelukast and included a warning against these suspected adverse events, which was criticized for lacking support in observational data.[5,6] In 2020, the FDA added a boxed warning to montelukast and advised against use in patients with mild symptoms, mainly citing case reports.[3] The mechanism of montelukast is not well understood, but data from animal models suggest that it crosses the blood-brain barrier and causes a dysregulation of the hypothalamic-pituitary-adrenal axis, similarly to the mechanism of ICS.[7-9]

Since the signal emerged, several studies have been conducted to evaluate it. The analytical approaches, validity, and findings of these studies have been mixed. Post hoc analyses[10,11] of the clinical trials in adults and children performed by the manufacturer found no increased risk of behavior-related adverse experiences or suicidality, but the precision was low. A large cohort study[12] in adults and children performed by the FDA found no association between montelukast and the risk of hospitalization for depression or self-harm. Of 2 nested case-control studies in children investigating a composite of neuropsychiatric adverse events, one found an increased risk associated with montelukast[13] but the other one did not.[14] In summary, the available evidence on this safety concern is inconclusive, and the data among children are particularly scarce and heterogeneous.[15] The current study aimed to assess the potential association between the use of montelukast and the risk of neuropsychiatric adverse events in children and adolescents based on Swedish data.

### Key Points

**Question** Is use of montelukast associated with an increased risk of neuropsychiatric adverse events in children and adolescents?

**Findings** In this cohort study of 26 462 montelukast users and 47 829 long-acting β-agonist users aged 6 to 17 years, there was no association between montelukast and the risk of neuropsychiatric adverse events.

**Meaning** Aggregated results from this large-scale observational analysis and other studies can inform clinical practice and support the management of asthma and allergic rhinitis in children and adolescents.

## Methods

### Data Sources and Study Population

This cohort study was based on Swedish nationwide data from routine clinical practice. Key data sources included the Swedish Prescribed Drugs Register, the National Patient Register, and the Total Population Register. Extractions from the data sources were linked and patients were anonymized. The source population was all children and adolescents (aged 6-17 years) who resided in Sweden during the study period, January 1, 2007, to November 30, 2021. Patients from the source population were included in the study cohort on the basis of an incident dispensing of either montelukast or the comparator drug, long-acting β-agonists (LABA). Complete eligibility criteria are described below. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies. The study was approved by the Regional Ethics Committee in Stockholm, Sweden. Swedish law does not require informed consent for studies using national registers.

### Study Design

We used an active-comparator new user design where incident montelukast users were compared with incident users of LABA. Only patients without a history of either drug were analyzed (see definitions in eTable 1 in Supplement 1). The indications for montelukast and LABA are similar, and there is no evidence in support of choosing one over the other as add-on therapy in children with asthma.[16] Monotherapy with montelukast is also used as an alternative to low-dose ICS.[1] We restricted the cohort to patients aged 6 to 17 years because both drugs are indicated for this age range and most of the assessed outcome events were not relevant to study in younger children. We collected prescription dispensing data from the Swedish Prescribed Drug Register. The date of the first dispensing of montelukast or LABA was the index date. The following exclusion criteria were applied to all patients, according to status at baseline: history of any neuropsychiatric event, residing outside of Sweden in the last 5 years, and history of a life-limiting condition (eTable 1 in Supplement 1).

### Outcome

The primary outcome was any neuropsychiatric adverse event (including anxiety; depression; sleep-related disorders; suicide and suicidal actions; disrupted control of activity, attention, and behavior; and confusion and psychotic-like symptoms), which correspond to the adverse events in the montelukast summary of product characteristics (see detailed outcome definitions and corresponding adverse events in eTable 2 in Supplement 1). All components of the composite outcome were analyzed individually in secondary analyses. The outcome events were ascertained on the basis of diagnosis codes in specialist care and dispensings of prescription drugs as diagnosis proxies where applicable. The validity of a range of psychiatric diagnosis codes in the Swedish patient register has been established in previous studies, including depression and social anxiety disorder.[17-21] The event date was the date of the first event that occurred.



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### Statistical Analysis

Data analysis was performed from December 2023 to April 2024. We estimated the potential association between current treatment with montelukast and the risk of neuropsychiatric adverse events (ie, an as-treated analysis).[22,23] Previous data have indicated a fairly quick onset of neuropsychiatric adverse events during or shortly after montelukast treatment.[24]

Patients were censored at treatment stop. In the LABA group, patients were also censored if they initiated montelukast. Follow-up was defined in discrete time intervals of 14 days (ie, follow-up was analyzed in time intervals to enable time-dependent censoring weighting). Censoring and outcome events were identified by the follow-up interval when they occurred. Patients were considered to have stopped treatment when a dispensed prescription was not repeated within its duration and a grace period of 60 days (see detailed duration assumptions in eTable 3 in Supplement 1). In all analyses, the maximum follow-up was 1 year. Patients were also censored at the first of end of the study period (November 30, 2021), migration from Sweden, or death.

We adjusted for potential confounding at baseline with propensity score overlap weighting and for potential informative censoring from patients who stopped treatment with inverse probability of censoring weighting (see details in eMethods in Supplement 1).[25,26] With normalized overlap weights, we estimated the average treatment effect in the overlap population, avoided using extreme weights, and achieved nearly exact mean balance of covariates on baseline. In the treatment model, we adjusted for a large set of potential confounders and proxies for confounders, including age, sex, municipality of residence, socioeconomic status, calendar year of initiation, season, index prescription setting, indication, treatment history, comorbidities, and general health care use (see covariate details in eTable 4 in Supplement 1). The censoring model was adjusted for the baseline variables, exposure, and the time of censoring and its second-degree and third-degree polynomials. We estimated odds ratios (ORs) of the outcomes with weighted, pooled logistic regression, where all follow-up intervals of the patients in the cohorts were included.[27] The estimate of the OR associated with exposure can be interpreted as a hazard ratio (HR) because it is estimated in discrete follow-up intervals. The model was stratified by patient to account for the dependence between events introduced by the weighting.

We performed subgroup analyses by age group (6-11 and 12-17 years), sex, asthma indication, previous ICS use, and date of drug initiation (index in 2007-2011, 2012-2016, 2017-2021, until February 2020, and from March 2020). The latter analyses were performed to assess potential temporal trends and to determine whether there was a difference in association before and after the FDA issued a boxed warning in March 2020.[3] A number of sensitivity analyses were also performed. Grace periods of 30 and 90 days were applied (60 days in primary analysis) in an analysis where inverse probability of treatment weighting was used instead of overlap weighting to adjust for confounding and a naive as-treated analysis without censoring weighting was done (performed both with overlap weighting and inverse probability of treatment weighting on baseline). Sensitivity analyses with alternative outcome definitions were also performed, where only diagnoses or drug use were included in the outcome definition (sleep-related disorders) and where completed suicides and suicidal actions, as well as diagnosis codes for intentional self-harm and events of undetermined intent, were analyzed separately. Finally, we analyzed the secondary outcome of disrupted control of activity, attention, and behavior without *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis code F90.0X (attention-deficit/hyperactivity disorder, not other specified), as there is uncertainty regarding the use of this diagnosis in clinical practice. The analysis was performed in SAS Enterprise Guide version 8.3 (SAS Institute).

## Results

### Cohort

From the source population of all children and adolescents aged 6 to 17 years residing in Sweden during the study period, we identified 74 291 eligible patients (mean [SD] age, 12.3 [3.3] years; 35 446 female [47.7%]); 26 462 patients initiated montelukast and 47 829 initiated LABA (**Figure 1**). In the unweighted cohort, the patients taking montelukast were younger than the patients taking LABA (mean [SD] age, 11.2 [3.4] vs 12.9 [3.2] years), were less often female (11 810 patients [44.6%] vs 23 636 patients [49.4%]), had a higher prevalence of short-acting β-agonist use (19 617 patients [74.1%] vs 31 226 patients [65.3%]), had a higher proportion with no ICS use in the last 18 months (9821 patients [37.1%] vs 4391 patients [9.2%]), and generally had a higher health care use (eg, mean [SD] number of drugs, 4.2 [2.8] vs 3.5 [2.8]) (**Table 1**). In the weighted cohort, there was nearly exact balance on all baseline covariates according to key diagnostics (Table 1; eTable 5 and eFigure in Supplement 1). The mean (SD) follow-up time in this as-treated analysis where patients were censored at treatment cessation was 5.8 (3.2) and 5.9 (3.2) months in the montelukast and LABA group, respectively. The overall mean (SD) follow-up time was 5.8 (3.2) months.

### Primary and Secondary Outcomes

In the primary analysis, we identified 310 neuropsychiatric adverse events among the patients taking montelukast and 566 among the patients taking LABA during follow-up (**Table 2**). The unweighted HR of neuropsychiatric adverse events was 1.01 (95% CI, 0.88-1.16). In the weighted cohort, the incidence rates of neuropsychiatric adverse events were 2.39 per 100 patient-years in the montelukast group and 2.41 per 100 patient-years in the LABA group. We did not observe an increased risk in the patients taking montelukast; the weighted HR of neuropsychiatric adverse events was very similar to the unweighted HR (0.99; 95% CI, 0.84-1.16) (**Figure 2**).

No substantial differences were observed between the montelukast and LABA groups when analyzing the risk of specific neuropsychiatric adverse events (Table 2). The HRs for secondary outcomes were 0.79 (95% CI, 0.54-1.14) for anxiety; 1.16 (95% CI, 0.70-1.95) for depression; 0.93 (95% CI, 0.76-1.13) for



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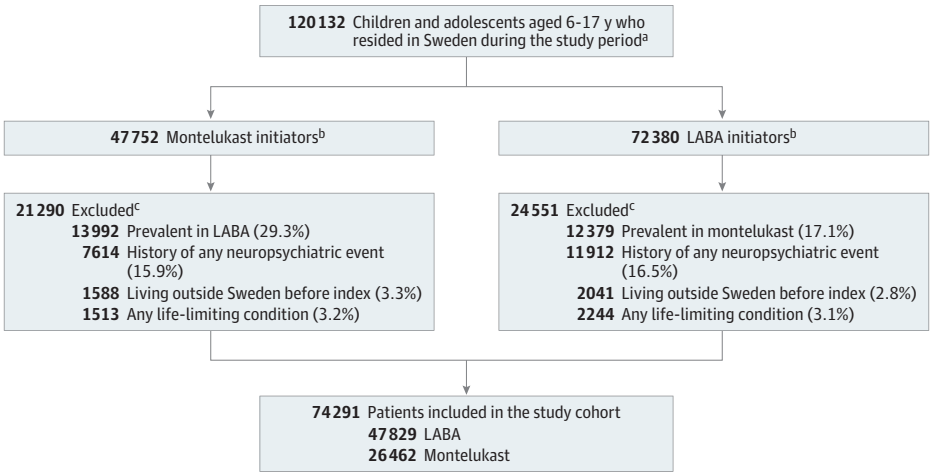
Figure 1. Patient Enrollment Flowchart




LABA indicates long-acting β-agonists.

[a]The study period was January 1, 2007 to November 30, 2021.

[b]New use was defined on the basis of all available look-back data.

[c]Exclusion criteria were not mutually exclusive.

sleep-related disorders; 1.31 (95% CI, 0.64-2.69) for suicide and suicidal actions; 1.27 (95% CI, 0.84-1.90) for disrupted control of activity, attention, and behavior; and 0.51 (95% CI, 0.05-5.53) for confusion and psychotic-like symptoms. Note that only 2 events of confusion and psychotic-like symptoms were observed in each group.

### Subgroup and Sensitivity Analyses

We identified no subgroups with substantially different relative risk compared with the primary analysis (**Figure 3**). In the weighted cohort, the HRs were 1.15 (95% CI, 0.88-1.50) for patients aged 6 to 11 years, 0.93 (95% CI, 0.75-1.15) for patients aged 12 to 17 years, 1.11 (95% CI, 0.87-1.42) for boys, and 0.91 (95% CI, 0.73-1.14) for girls. The results were similar between the groups with and without confirmed asthma on baseline, and with and without previous use of ICS, but the risk tended to be higher in patients taking montelukast without confirmed asthma and with previous ICS use. When performing the analysis by date of drug initiation, we observed no difference in association between the periods before and after the boxed warning was issued by the FDA in March 2020, although there were only 47 exposed events in the latter period. Similarly, there were no substantial differences in association when comparing consecutive 5-year periods. However, it is worth noting that rates increased in both treatment groups over time (eg, the weighted incidence rates in the patients taking montelukast were 1.69 events per 100 patient-years from 2007 to 2011 and 3.03 events per 100 patient-years from 2017 to 2021).

In the sensitivity analyses where sleep-related disorders were ascertained only on the basis of diagnosis codes or drug use, we observed similar results as with the main definition, with HRs of 0.94 (95% CI, 0.57-1.55) for analysis of only diagnosis codes and 0.92 (95% CI, 0.75-1.13) for analysis of only drug use. The sensitivity analysis of suicide and suicidal actions showed that no completed suicides were observed in either of the groups. When restricting the outcome definition to only intentional self-harm diagnoses or events of undetermined intent, we observed a higher point estimate for the former (HR, 2.00; 95% CI, 0.57-6.95) than for the latter (HR, 1.06; 95% CI, 0.46-2.46). However, as with the main definition of suicide and suicidal actions, few events were observed: 6 and 9 for intentional self-harm and 14 and 17 for event of undetermined intent in the montelukast and LABA groups, respectively. In the sensitivity analysis of outcome disrupted control of activity, attention and behavior, we excluded the code diagnosis F90.0X (attention-deficit/hyperactivity disorder, not other specified) and observed a similar result as with the main definition (HR, 1.37; 95% CI, 0.88-2.14). Finally, we observed no substantial differences when the grace period or the weighting method were altered.

## Discussion

In this nationwide cohort study based on unselected data from Swedish routine clinical practice, we investigated the potential association between montelukast and the risk of neuropsychiatric adverse events in children and adolescents. On the basis of an eligible set of more than 105 000 patients aged 6 to 17 years, we found no support for an increased risk of the primary outcome any neuropsychiatric adverse event or any of the 6 specific events. The findings were consistent over subgroups and a range of sensitivity analyses.

Suspected neuropsychiatric adverse effects of montelukast have been a major concern for patients, clinicians, and regulators since the signal emerged from spontaneous report in 2008 and FDA announced a boxed warning in 2020 advising against the use in patients with mild disease. However, there is still a lack of observational studies confirming the signal; in particular, the need for pediatric evidence has been emphasized.[15] Disproportionality analyses of spontaneous reports do not provide conclusive evidence on risk, owing to the lack of denominators, appropriate comparators, and bias adjustment.[28,29] These limitations are critical when assessing the risk of neuropsychiatric adverse events because the



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Table 1. Baseline Characteristics of Unweighted and Weighted Study Cohort of Montelukast and LABA Users

| Characteristic | Unweighted cohort | | | Weighted cohort | | |
|---|---|---|---|---|---|---|
| | Montelukast, participants, No. (%) (n = 26 462) | LABA, participants, No. (%) (n = 47 829) | SMD between groups, % | Montelukast, % (n = 26 462) | LABA, % (n = 47 829) | SMD between groups, % |
| Age, mean (SD), y | 11.2 (3.4) | 12.9 (3.2) | 52.5 | 11.9 (3.3) | 11.9 (3.3) | 0.1 |
| Sex | | | | | | |
| Female | 11 810 (44.6) | 23 636 (49.4) | 9.6 | 46.2 | 46.2 | 0 |
| Male | 14 652 (55.4) | 24 193 (50.6) | 9.6 | 53.8 | 53.8 | 0 |
| Calendar year | | | | | | |
| 2007-2009 | 4251 (16.1) | 15 816 (33.1) | 40.3 | 22 | 22 | 0.1 |
| 2010-2012 | 4669 (17.6) | 9492 (19.8) | 5.6 | 19.4 | 19.4 | 0 |
| 2013-2015 | 5154 (19.5) | 6983 (14.6) | 13.0 | 18.2 | 18.2 | 0 |
| 2016-2018 | 6095 (23.0) | 6969 (14.6) | 21.8 | 19.8 | 19.7 | 0.1 |
| 2019-2021 | 6293 (23.8) | 8569 (17.9) | 14.5 | 20.6 | 20.6 | 0 |
| Index season | | | | | | |
| Winter | 5822 (22.0) | 11 371 (23.8) | 4.2 | 23 | 23 | 0 |
| Spring | 9108 (34.4) | 15 176 (31.7) | 5.7 | 32.5 | 32.4 | 0 |
| Summer | 5217 (19.7) | 8479 (17.7) | 5.1 | 18.5 | 18.5 | 0 |
| Fall | 6315 (23.9) | 12 803 (26.8) | 6.7 | 26 | 26 | 0 |
| Disposable family income quartile | | | | | | |
| First | 5881 (22.2) | 12 691 (26.5) | 10.1 | 23.7 | 23.7 | 0 |
| Second | 5575 (21.1) | 10 503 (22.0) | 2.2 | 21.8 | 21.8 | 0 |
| Third | 8066 (30.5) | 13 002 (27.2) | 7.3 | 29.2 | 29.2 | 0 |
| Fourth | 6940 (26.2) | 11 633 (24.3) | 4.4 | 25.3 | 25.3 | 0 |
| Parental education, y | | | | | | |
| ≤9 | 573 (2.2) | 1266 (2.6) | 3.1 | 2.3 | 2.3 | 0 |
| 10-12 | 7677 (29.0) | 15 912 (33.3) | 9.2 | 31.2 | 31.2 | 0 |
| ≥13 | 18 212 (68.8) | 30 651 (64.1) | 10.0 | 66.5 | 66.5 | 0 |
| Municipality population density | | | | | | |
| Low | 6437 (24.3) | 12 567 (26.3) | 4.5 | 26.1 | 26.1 | 0 |
| Medium | 10 487 (39.6) | 16 705 (34.9) | 9.7 | 38 | 38 | 0 |
| High | 9538 (36.0) | 18 557 (38.8) | 5.7 | 35.9 | 35.9 | 0 |
| Indication | | | | | | |
| Asthma | 5309 (20.1) | 9583 (20.0) | 0.1 | 22.6 | 22.6 | 0 |
| Rhinitis | 6390 (24.1) | 9592 (20.1) | 9.9 | 17.7 | 17.7 | 0 |
| Asthma and rhinitis | 11 279 (42.6) | 15 827 (33.1) | 19.7 | 45.1 | 45.1 | 0 |
| Undetermined | 3484 (13.2) | 12 827 (26.8) | 34.6 | 14.6 | 14.7 | 0.1 |
| Health care setting of index prescription | | | | | | |
| Specialized care | 15 353 (58.0) | 21 943 (45.9) | 24.5 | 56.1 | 56.1 | 0 |
| Primary care | 9737 (36.8) | 22 763 (47.6) | 22.0 | 38.4 | 38.5 | 0 |
| Other | 1372 (5.2) | 3123 (6.5) | 5.7 | 5.4 | 5.4 | 0 |
| Short-acting β-agonist | 19 617 (74.1) | 31 226 (65.3) | 19.3 | 78.6 | 78.5 | 0.1 |
| Oral corticosteroids | 3970 (15.0) | 5693 (11.9) | 9.1 | 14.4 | 14.4 | 0 |
| No. of inhaled corticosteroids dispensings | | | | | | |
| 0 | 9821 (37.1) | 4391 (9.2) | 70.2 | 19.3 | 19.2 | 0.2 |
| 1 | 5593 (21.1) | 24 047 (50.3) | 63.8 | 29.9 | 29.9 | 0.1 |
| 2 | 4316 (16.3) | 7901 (16.5) | 0.6 | 19.7 | 19.8 | 0 |
| ≥3 | 6732 (25.4) | 11 490 (24.0) | 3.3 | 31.1 | 31.1 | 0 |
| Type 1 diabetes | 99 (0.4) | 194 (0.4) | 0.5 | 0.4 | 0.4 | 0 |
| Celiac disease | 259 (1.0) | 429 (0.9) | 0.8 | 1 | 1 | 0 |
| Inflammatory bowel disease | 32 (0.1) | 74 (0.2) | 0.9 | 0.1 | 0.1 | 0 |
| Atopic dermatitis | 2770 (10.5) | 3774 (7.9) | 8.9 | 10.1 | 10.1 | 0 |
| Obesity | 495 (1.9) | 868 (1.8) | 0.4 | 2 | 2 | 0 |

(continued)



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Table 1. Baseline Characteristics of Unweighted and Weighted Study Cohort of Montelukast and LABA Users (continued)

| Characteristic | Unweighted cohort | | | Weighted cohort | | |
|---|---|---|---|---|---|---|
| | Montelukast, participants, No. (%) (n = 26 462) | LABA, participants, No. (%) (n = 47 829) | SMD between groups, % | Montelukast, % (n = 26 462) | LABA, % (n = 47 829) | SMD between groups, % |
| No. of prescription drugs, mean (SD) | 4.2 (2.8) | 3.5 (2.8) | 24.7 | 4.1 (2.8) | 4.1 (2.8) | 0.1 |
| No. of outpatient hospital contacts, mean (SD) | 2.3 (3.1) | 1.8 (2.7) | 17.2 | 2.2 (3.0) | 2.2 (3.0) | 0 |
| No. of inpatient admissions, mean (SD) | 0.1 (0.3) | 0.1 (0.3) | 2.3 | 0.1 (0.3) | 0.1 (0.3) | 0 |

Abbreviations: LABA, long-acting β-agonists; SMD, standardized mean difference.

Table 2. Association Between Use of Montelukast and the Risk of the Primary and Secondary Outcomes in the Unweighted and Weighted Study Cohort[a]

| Outcomes | Unweighted cohort | | | | Weighted cohort | |
|---|---|---|---|---|---|---|
| | Patients, No. | Events, No. | Incidence rate, events/100 PY | HR (95% CI) | Incidence rate, events/100 PY | HR (95% CI) |
| Primary outcome, any neuropsychiatric event | | | | | | |
| Montelukast | 26 462 | 310 | 2.44 | 1.01 (0.88-1.16) | 2.39 | 0.99 (0.84-1.16) |
| LABA | 47 829 | 566 | 2.41 | 1 [Reference] | 2.41 | 1 [Reference] |
| Secondary outcomes | | | | | | |
| Anxiety | | | | | | |
| Montelukast | 26 462 | 51 | 0.40 | 0.69 (0.50-0.96) | 0.44 | 0.79 (0.54-1.14) |
| LABA | 47 829 | 136 | 0.58 | 1 [Reference] | 0.55 | 1 [Reference] |
| Depression | | | | | | |
| Montelukast | 26 462 | 25 | 0.20 | 0.74 (0.46-1.17) | 0.25 | 1.16 (0.70-1.95) |
| LABA | 47 829 | 63 | 0.27 | 1 [Reference] | 0.22 | 1 [Reference] |
| Sleep-related disorders | | | | | | |
| Montelukast | 26 462 | 208 | 1.64 | 0.95 (0.80-1.12) | 1.58 | 0.93 (0.76-1.13) |
| LABA | 47 829 | 405 | 1.72 | 1 [Reference] | 1.72 | 1 [Reference] |
| Suicide and suicidal actions | | | | | | |
| Montelukast | 26 462 | 19 | 0.15 | 1.35 (0.75-2.44) | 0.15 | 1.31 (0.64-2.69) |
| LABA | 47 829 | 26 | 0.11 | 1 [Reference] | 0.13 | 1 [Reference] |
| Disrupted control of activity, attention and behavior | | | | | | |
| Montelukast | 26 462 | 59 | 0.46 | 1.53 (1.09-2.16) | 0.43 | 1.27 (0.84-1.90) |
| LABA | 47 829 | 71 | 0.30 | 1 [Reference] | 0.34 | 1 [Reference] |
| Confusion and psychotic-like symptoms | | | | | | |
| Montelukast | 26 462 | 2 | 0.02 | 1.84 (0.26-13.05) | 0.01 | 0.51 (0.05-5.53) |
| LABA | 47 829 | 2 | 0.01 | 1 [Reference] | 0.01 | 1 [Reference] |

Abbreviations: HR, hazard ratio; LABA, long-acting β-agonists; PY, person-year.

[a] All analyses were weighted with overlap weights and censoring weights. HRs were estimated with pooled logistic regression over all time intervals of follow-up.

underlying disease, its severity, and concomitant use of ICS all likely affect the risk.[7,30] In the current study, we evaluated this safety signal and assessed the potential association between current or recent montelukast treatment and the suspected neuropsychiatric adverse effects described in the product label. We used LABA as active comparator to reduce confounding through the design and censoring weights to reduce the risk of selection bias as we followed patients with ongoing treatment. LABA is a more suitable active comparator than ICS because, like montelukast, it is an add-on drug; a majority of patients have previously used ICS when initiating montelukast, and they are regarded as equivalent therapeutic alternatives in this age group, according to guidelines.[16,31] We conservatively excluded patients with any psychiatric history during the previous 5 years to avoid analyzing prevalent patients.

The findings of previous studies addressing this safety concern have been mixed, but most methodologically sound studies have shown no association between montelukast and neuropsychiatric adverse events. A recent cohort study[12] based on data from the Sentinel database in the US in children and adults (aged ≥5 years) found no association between montelukast use and the risk of hospitalization for depression (HR, 1.06; 95% CI, 0.90-1.24) or self-harm (HR, 0.92; 95% CI, 0.69-1.21), compared with users of ICS. In a manufacturer-led post hoc analysis[11] of clinical trials, the risk of behavior-related adverse experiences was analyzed using data from 35 and 11 placebo-controlled trials in adults and children, respectively, including 11 673 patients who received montelukast. Overall, the OR of behavior-related adverse experiences vs placebo was 1.12 (95% CI, 0.93-1.36).



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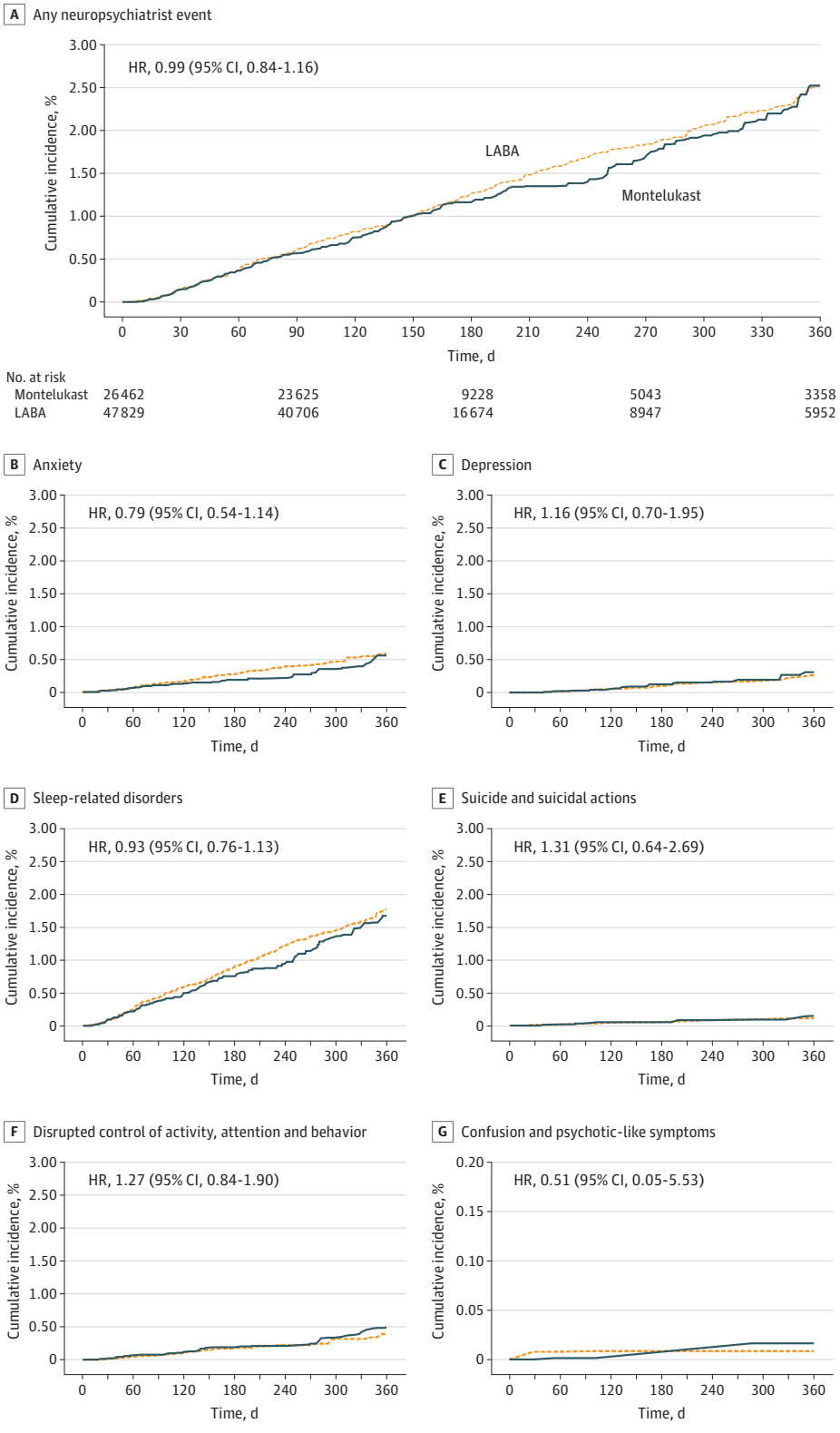
Figure 2. Cumulative Incidence of Any Neuropsychiatric Event and Specific Neuropsychiatric Events for Montelukast and Long-Acting β-Agonist (LABA) Users in the Weighted Cohort




All analyses were weighted with overlap weights and censoring weights. Hazard ratios (HRs) were estimated with pooled logistic regression over all time intervals of follow-up. The vertical axis was changed for outcome confusion and psychotic-like symptoms due to few events.

The age-stratified corresponding ORs were 0.85 (95% CI, 0.58-1.25) for children younger than 6 years, 1.41 (95% CI, 0.67-3.07) for children aged 6 to 11 years, and 2.17 (95% CI, 0.71-7.89) for children aged 12 to 17 years.[11] The study was



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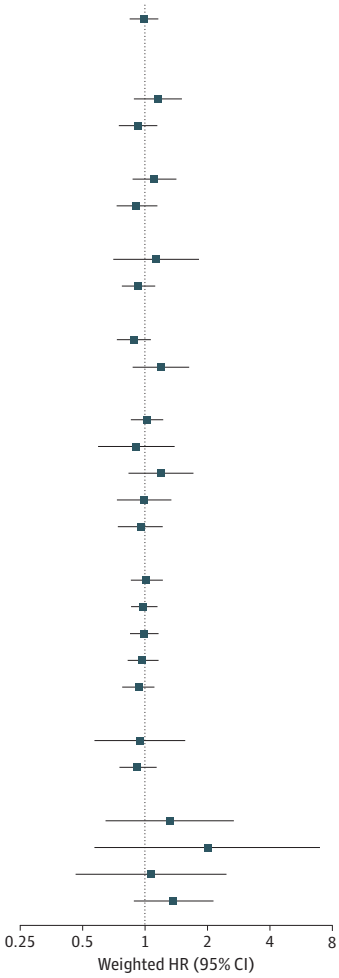
Figure 3. Subgroup and Sensitivity Analyses of the Association Between Use of Montelukast and the Risk of Any Neuropsychiatric Event in the Weighted Study Cohort

| Main analysis | Montelukast | | LABA | | Weighted HR (95% CI) |
|---|---|---|---|---|---|
| | Unweighted events/ patients, No. | Weighted events/100 patient-years | Unweighted events/ patients, No. | Weighted events/100 patient-years | |
| Any neuropsychiatric event | 310/26 462 | 2.39 | 566/47 829 | 2.41 | 0.99 (0.84-1.16) |
| Subgroup analysis | | | | | |
| Age, y | | | | | |
| 6-11 | 150/15 849 | 1.89 | 130/18 183 | 1.61 | 1.15 (0.88-1.50) |
| 12-17 | 160/10 613 | 3.00 | 436/29 646 | 3.28 | 0.93 (0.75-1.15) |
| Sex | | | | | |
| Male | 152/14 652 | 2.06 | 209/24 193 | 1.79 | 1.11 (0.87-1.42) |
| Female | 158/11 810 | 2.77 | 357/23 636 | 3.14 | 0.91 (0.73-1.14) |
| Previous ICS | | | | | |
| Yes | 112/9821 | 2.58 | 29/4391 | 2.29 | 1.14 (0.71-1.82) |
| No | 198/16 641 | 2.31 | 537/43 438 | 2.42 | 0.93 (0.78-1.12) |
| Asthma | | | | | |
| Yes | 192/16 588 | 2.25 | 335/25 410 | 2.45 | 0.89 (0.73-1.07) |
| No | 118/9874 | 2.64 | 231/22 419 | 2.24 | 1.19 (0.87-1.63) |
| Index | | | | | |
| Until February 2020 | 263/22 822 | 2.26 | 467/42 132 | 2.19 | 1.02 (0.85-1.22) |
| From March 2020 | 47/3636 | 3.56 | 99/5693 | 3.98 | 0.90 (0.59-1.38) |
| 2007-2011 | 64/7356 | 1.69 | 178/22 657 | 1.46 | 1.19 (0.83-1.72) |
| 2012-2016 | 107/8798 | 2.53 | 163/12 153 | 2.52 | 0.99 (0.73-1.33) |
| 2017-2021 | 139/10 308 | 3.03 | 225/13 019 | 3.16 | 0.95 (0.74-1.22) |
| Sensitivity analyses | | | | | |
| 30-d Grace | 244/26 462 | 2.44 | 437/47 829 | 2.38 | 1.01 (0.85-1.22) |
| 90-d Grace | 367/26 462 | 2.39 | 676/47 829 | 2.44 | 0.98 (0.85-1.14) |
| No censoring weights | 310/26 462 | 2.39 | 566/47 829 | 2.41 | 0.99 (0.84-1.16) |
| IPTW | 310/23 376 | 2.37 | 566/47 763 | 2.41 | 0.97 (0.82-1.16) |
| IPTW and no censoring weights | 310/26 376 | 2.24 | 566/47 763 | 2.41 | 0.93 (0.78-1.11) |
| Sleep-related disorders | | | | | |
| Only diagnosis codes | 33/26 462 | 0.26 | 52/47 829 | 0.26 | 0.94 (0.57-1.55) |
| Only drug dispensings | 189/26 462 | 1.41 | 379/47 829 | 1.56 | 0.92 (0.75-1.13) |
| Suicide and suicidal actions | | | | | |
| Only hospital contacts | 19/26 462 | 0.15 | 26/47 829 | 0.13 | 1.31 (0.64-2.69) |
| Only intentional self-harm | 6/26 462 | 0.07 | 9/47 829 | 0.04 | 2.00 (0.57-6.95) |
| Only events of undetermined intent | 14/26 462 | 0.09 | 17/47 829 | 0.09 | 1.06 (0.46-2.46) |
| Disrupted control of activity attention and behavior, not F90.0X | 52/26 462 | 0.36 | 57/47 829 | 0.28 | 1.37 (0.88-2.14) |




All analyses were weighted with overlap weights and censoring weights. Weights were estimated individually for each subgroup. Hazard ratios (HRs) were estimated with pooled logistic regression over all time intervals of follow-up. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis code F90.0X, attention-deficit/ hyperactivity disorder, not other specified, was used. ICS indicates inhaled corticosteroids; IPTW, inverse probability of treatment weighting; LABA, long-acting β-agonists.

limited by the post hoc definition and ascertainment of outcome events.

Two nested case-control studies investigated this safety concern based on US insurance claims data[13] and Canadian administrative health care data,[14] respectively. The first study[13] included children aged 1 to 17 years and found no association between montelukast use and the risk of neuropsychiatric events (OR, 1.01; 95% CI, 0.88-1.14), in comparison with no use; in contrast, the second study[14] of children aged 5 to 18 years found an association between montelukast use and increased risk of these events (OR, 1.91; 95% CI, 1.15-3.18).

Finally, a recent Korean self-controlled study[32] found an association with any neuropsychiatric event in adolescents aged 12 to 18 years (incidence rate ratio, 1.28; 95% CI, 1.05-1.55), but an opposite association in children aged 3 to 11 years (incidence rate ratio, 0.66; 95% CI, 0.53-0.80). It is worth noting that incidence rate ratio in adolescents (point estimate) was higher in the time period after the FDA announced the safety concerns regarding montelukast (incidence rate ratio, 1.32; 95% CI, 1.06-1.62) vs the period before the FDA announcement (incidence rate ratio, 1.10; 95% CI, 0.65-1.75). Furthermore, the self-controlled design was a limitation of that analysis because there is no adjustment for time-varying factors within patients that might lead to confounding by indication.[33]

Other observational studies assessing this safety concern had limitations, including small samples,[34,35] poor outcome measures,[34,36] and inadequate design.[35-37] As in previous



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studies,[10,38] it was not possible to assess the risk of completed suicides because the sample was too small.

### Limitations

This study has limitations. Outcome events were primarily ascertained on the basis of diagnosis codes from specialized care, and misclassification is a potential issue, in particular low sensitivity.[17-20] There is a risk of subclinical events, and there might be a lag between the onset of symptoms and when the patients seek health care. The sensitivity also likely varies according to the type and severity of symptoms; for example, externalizing symptoms (eg, hyperactivity and irritability) are more easily observed and have higher sensitivity than internalizing symptoms (eg, anxiety and depression). To increase the sensitivity, we included incident medication use as proxy measures in the definition of sleep-related disorders, as these are commonly treated in primary care. In the definition of suicide and suicidal actions, we included both intentional self-harm and events of undetermined intent because of the underreporting of intentional events.[39-41] The sensitivity of outcome definitions is likely not differential between treatment groups in our analysis since we used an active comparator design and adjusted for factors that might influence surveillance, including health care setting of index prescription, municipality of residence, and general health care use. However, awareness of suspected adverse effects of montelukast, which gradually increased over the course of the study period, might induce outcome misclassification. Increased monitoring of patients taking montelukast could bias the association away from the null, but awareness could also lead to channeling of patients deemed at higher risk to alternative treatments, inducing bias in the opposite direction. Because a null result was observed in the current study, this potential bias was not a serious concern and the subgroup analyses by date of drug initiation showed no temporal patterns in association. Nonetheless, the analysis showed that the rates of neuropsychiatric adverse events increased in both treatment groups over the study period, which can be due to factors such as differences in screening, diagnostic practices, and awareness.

Exposure misclassification is another potential limitation. We assumed that dispensed drugs were used, and lack of consumption would bias a potential association toward the null. However, we assessed the association with current treatment and censored patients who did not refill their prescription within a short grace period of 60 days, which reduced the potential bias of low adherence.

## Conclusions

In this nationwide cohort study of children and adolescents, we found no support for an association between montelukast and the risk of neuropsychiatric adverse events, defined as a composite of specific events. In addition to other relevant pediatric studies, this large-scale observational study can inform regulatory agencies and clinical practice. Robust safety data on montelukast are crucial given its role in the management of asthma and allergic rhinitis.


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**Author Contributions:** Dr Wintzell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Concept and design*: All authors.
*Acquisition, analysis, or interpretation of data*: Wintzell, Halldner, Gong, Almqvist.
*Drafting of the manuscript*: Wintzell.
*Critical review of the manuscript for important intellectual content*: All authors.
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### REFERENCES


1. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2022. Accessed December 9, 2024. http://www.ginasthma.org

2. Socialstyrelsens statistikdatabas. Läkemedel. 2023. Accessed September 1, 2023. https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikdatabasen/

3. US Food and Drug Administration. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. March 4, 2020. Accessed December 9, 2024. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug

4. US Food and Drug Administration. Early communication about an ongoing safety review of montelukast (Singulair). 2008. Accessed December 13, 2024. https://wayback.archive-it.org/7993/20170112033551/http:/www.fda.gov/Drugs/DrugSafety/




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PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070618.htm

5. US Food and Drug Administration. Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast (marketed as Accolate), and zileuton (marketed as Zyflo and Zyflo CR). 2009. Accessed December 13, 2024. https://wayback.archive-it.org/7993/20170111080414/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm165489.htm

6. [No authors listed.] Joint statement on FDA investigation of Singulair from the ACAAI and AAAAI. *Eur Ann Allergy Clin Immunol*. 2008;40(2):64.

7. Smith RW, Downey K, Gordon M, et al. Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. *Paediatr Child Health*. 2012;17(2):e34-e39. doi:10.1093/pch/17.5.e34

8. 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;310:121056. doi:10.1016/j.lfs.2022.121056

9. 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. doi:10.1038/ncomms9466

10. Philip G, Hustad C, Noonan G, et al. Reports of suicidality in clinical trials of montelukast. *J Allergy Clin Immunol*. 2009;124(4):691-6.e6. doi:10.1016/j.jaci.2009.08.010

11. Philip G, Hustad CM, Malice MP, et al. Analysis of behavior-related adverse experiences in clinical trials of montelukast. *J Allergy Clin Immunol*. 2009;124(4):699-706.e8. doi:10.1016/j.jaci.2009.08.011

12. Sansing-Foster V, Haug N, Mosholder A, et al. Risk of psychiatric adverse events among montelukast users. *J Allergy Clin Immunol Pract*. 2021;9(1):385-393.e12. doi:10.1016/j.jaip.2020.07.052

13. 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;24(4):435-445. doi:10.1002/pds.3758

14. 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;209:176-182.e4. doi:10.1016/j.jpeds.2019.02.009

15. Lo CWH, Pathadka S, Qin SX, et al. Neuropsychiatric events associated with montelukast in patients with asthma: a systematic review. *Eur Respir Rev*. 2023;32(169):32. doi:10.1183/16000617.0079-2023

16. Scottish Intercollegiate Guidelines Network BTS. British guideline on the management of asthma. 2019. Accessed December 9, 2024. https://www.sign.ac.uk/our-guidelines/british-guideline-on-the-management-of-asthma/

17. Sellgren C, Landén M, Lichtenstein P, Hultman CM, Långström N. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. *Acta Psychiatr Scand*. 2011;124(6):447-453. doi:10.1111/j.1600-0447.2011.01747.x

18. Vilaplana-Pérez A, Isung J, Krig S, et al. Validity and reliability of social anxiety disorder diagnoses in the Swedish National Patient Register. *BMC Psychiatry*. 2020;20(1):242. doi:10.1186/s12888-020-02644-7

19. Fazel S, Wolf A, Chang Z, Larsson H, Goodwin GM, Lichtenstein P. Depression and violence: a Swedish population study. *Lancet Psychiatry*. 2015;2(3):224-232. doi:10.1016/S2215-0366(14)00128-X

20. Idring S, Rai D, Dal H, et al. Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. *PLoS One*. 2012;7(7):e41280. doi:10.1371/journal.pone.0041280

21. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450. doi:10.1186/1471-2458-11-450

22. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med*. 2017;377(14):1391-1398. doi:10.1056/NEJMsm1605385

23. Hernán MA, Hernández-Díaz S. Beyond the intention-to-treat in comparative effectiveness research. *Clin Trials*. 2012;9(1):48-55. doi:10.1177/1740774511420743

24. Ekhart C, van Hunsel F, Sellick V, de Vries T. Neuropsychiatric reactions with the use of montelukast. *BMJ*. 2022;376:e067554. doi:10.1136/bmj-2021-067554

25. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550-560. doi:10.1097/00001648-200009000-00011

26. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. *Am J Epidemiol*. 2019;188(1):250-257. doi:10.1093/aje/kwy201

27. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000;11(5):561-570. doi:10.1097/00001648-200009000-00012

28. Montastruc JL, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br J Clin Pharmacol*. 2011;72(6):905-908. doi:10.1111/j.1365-2125.2011.04037.x

29. Kasliwal R. Spontaneous reporting in pharmacovigilance: strengths, weaknesses and recent methods of analysis. *J Clin Prev Cardiol*. 2012;1:20-23.

30. Brew BK, Osvald EC, Gong T, et al. Paediatric asthma and non-allergic comorbidities: a review of current risk and proposed mechanisms. *Clin Exp Allergy*. 2022;52(9):1035-1047. doi:10.1111/cea.14207

31. Wintzell V, Svanström H, Pasternak B. Selection of comparator group in observational drug safety studies: alternatives to the active comparator new user design. *Epidemiology*. 2022;33(5):707-714. doi:10.1097/EDE.0000000000001521

32. Park JS, Cho YJ, Yun JY, et al; Korean childhood Asthma REsearch (KARE) team. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents and young adults: a self-controlled case series. *Eur Respir J*. 2022;60(5):2102467. doi:10.1183/13993003.02467-2021

33. Hallas J, Pottegård A. Use of self-controlled designs in pharmacoepidemiology. *J Intern Med*. 2014;275(6):581-589. doi:10.1111/joim.12186

34. 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;50(2):50. doi:10.1183/13993003.00148-2017

35. Yilmaz Bayer O, Turktas I, Ertoy Karagol HI, Soysal S, Yapar D. Neuropsychiatric adverse drug reactions induced by montelukast impair the quality of life in children with asthma. *J Asthma*. 2022;59(3):580-589. doi:10.1080/02770903.2020.1861626

36. Zhou EH, Kaplan S, Mosholder A, et al. Antidepressant medication dispensing among montelukast initiators. *J Asthma*. 2013;50(9):990-995. doi:10.3109/02770903.2013.823445

37. Paljarvi T, Forton J, Luciano S, Herttua K, Fazel S. Analysis of neuropsychiatric diagnoses after montelukast initiation. *JAMA Netw Open*. 2022;5(5):e2213643. doi:10.1001/jamanetworkopen.2022.13643

38. Schumock GT, Stayner LT, Valuck RJ, Joo MJ, Gibbons RD, Lee TA. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. *J Allergy Clin Immunol*. 2012;130(2):368-375. doi:10.1016/j.jaci.2012.04.035

39. Reuter Morthorst B, Soegaard B, Nordentoft M, Erlangsen A. Incidence rates of deliberate self-harm in Denmark 1994-2011. *Crisis*. 2016;37(4):256-264. doi:10.1027/0227-5910/a000391

40. Tøllefsen IM, Helweg-Larsen K, Thiblin I, et al. Are suicide deaths under-reported? nationwide re-evaluations of 1800 deaths in Scandinavia. *BMJ Open*. 2015;5(11):e009120. doi:10.1136/bmjopen-2015-009120

41. Tøllefsen IM, Thiblin I, Helweg-Larsen K, et al. Accidents and undetermined deaths: re-evaluation of nationwide samples from the Scandinavian countries. *BMC Public Health*. 2016;16:449. doi:10.1186/s12889-016-3135-5



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