Montelukast and Neuropsychiatric Events in Children with Asthma: A Nested Case–Control Study

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Objective To examine the association between montelukast prescription and neuropsychiatric events in children with asthma.

Study design A matched, nested case–control design was used to identify cases and controls from a cohort of children aged 5-18 years with physician-diagnosed asthma from 2004 to 2015, in Ontario, Canada, prescribed an asthma maintenance medication. Cases were children with a hospitalization or emergency department visit for a neuropsychiatric event. Cases were matched to up to 4 controls on birth year, year of asthma diagnosis, and sex. The exposures were dispensed prescriptions for montelukast (yes/no) and number of dispensed montelukast prescriptions in the year before the index date. Conditional logistic regression was used to measure the unadjusted OR and aOR and 95% CIs for montelukast prescription and neuropsychiatric events. Covariates in the adjusted model included sociodemographic factors and measures of asthma severity.

Results In total, 898 cases with a neuropsychiatric event and 3497 matched controls were included. Children who experienced a new-onset neuropsychiatric event had nearly 2 times the odds of having been prescribed montelukast, compared with controls (OR 1.91, 95% CI 1.15-3.18; $P = .01$). Most cases presented for anxiety (48.6%) and/or sleep disturbance (26.1%).

Conclusions Children with asthma who experienced a new-onset neuropsychiatric event had nearly twice the odds of having been prescribed montelukast in the year before their event. Clinicians should be aware of the association between montelukast and neuropsychiatric events in children with asthma, to inform prescribing practices and clinical follow-up. *(J Pediatr 2019;■:1-7)*.

Asthma affects at least 13% of children in the general population[1] and up to 300 million people worldwide.[2] It is marked by airway inflammation and recurring episodes of wheezing, dyspnea, chest tightness, and coughing.[3] Asthma typically is managed with a combination of long-term maintenance therapy (maintenance medications) and short-term therapy for the relief of acute asthma symptoms (reliever medications).[4] Leukotriene receptor antagonists (LTRAs), including montelukast, are one class of maintenance medications. LTRAs function by inhibiting inflammatory mediators of bronchoconstriction,[5] and they are prescribed primarily as adjunct therapy to inhaled corticosteroids in patients with moderate-to-severe asthma, although they also may be prescribed as an alternative to inhaled corticosteroids for mild persistent asthma.[6-8] In the US, 2.6 million children younger than the age of 16 years received dispensed prescriptions for montelukast in 2013.[9]

In 2009, the US Food and Drug Administration (FDA) announced a label change for montelukast, to include a warning regarding neuropsychiatric events under the "Precautions" section.[10] The label change was spurred by postmarketing case reports to the FDA Adverse Event Reporting System.[11] Specifically, patients prescribed montelukast reported episodes of depression, anxiety, sleep disturbance, aggression/agitation, suicidal ideation, suicide attempts, and/or completed suicide.[11-13] However, subsequent studies investigating the neuropsychiatric effects of montelukast have not defined conclusively the relationship between montelukast and neuropsychiatric events, and the relationship between number of montelukast prescriptions and neuropsychiatric events remains

ED	Emergency department
FDA	US Food and Drug Administration
LHIN	Local Health Integration Network
LTRA	Leukotriene receptor antagonist
ODB	Ontario Drug Benefits
ON-Marg	The Ontario Marginalization Index

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unclear.[12-18] Given the serious safety signals and the high prevalence of childhood asthma, we sought to investigate whether montelukast, a medication commonly used in pediatric asthma management, is associated with neuropsychiatric events in children. Our objective was to examine the association between montelukast prescription and neuropsychiatric events in children with asthma in Ontario, Canada.

Methods

A population-based, nested case–control study was conducted using prescription claims and an administrative healthcare data housed at the Institute for Clinical Evaluative Sciences. The Ontario Drug Benefit (ODB) Database was used to determine history of dispensed prescriptions. The ODB program offers publicly funded drug coverage for Ontario residents receiving social assistance, residing in long-term care facilities, or receiving professional home care services. Children with parents eligible for ODB also are covered under the program, and their subsidized dispensed prescriptions are captured in the database. Prescription drugs of interest were identified using their unique Drug Identification Number.[19]

Asthma prevalence was determined using the Ontario Asthma Surveillance Information System, which captures residents of Ontario diagnosed with asthma between 1996 and 2015 using a validated health administrative definition: at least 1 hospitalization for asthma or 2 outpatient visits for asthma within 2 consecutive years.[20,21] For children in Ontario, this health administrative definition for asthma has a sensitivity of 91.4% and a specificity of 82.9%.[20]

Data on emergency department (ED) visits, hospitalizations and same-day surgeries, and physician office visits in Ontario were obtained from the National Ambulatory Care Reporting System, Canadian Institute of Health Information Discharge Abstract Database, and Ontario Health Insurance Plan databases, respectively. Specific diagnoses and presenting complaints were identified using the *International Classification of Diseases and Health Related Problems, 10th Revision*, codes, *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, codes, and Ontario Health Insurance Plan billing codes (**Table I**; available at www.jpeds.com).

Data on participants' age, sex, and geographic residence were captured through the Registered Person's Database. Marginalization quintiles were obtained from The Ontario Marginalization Index (ON-Marg), described to follow.[22]

Study Population and Design

A nested case–control design was used to investigate the association between montelukast prescription and neuropsychiatric events (**Figure**; available at www.jpeds.com). The study cohort included Ontario children aged 5-18 years with physician-diagnosed asthma between April 1, 2004, and March 31, 2015, all of whom have been prescribed an asthma maintenance medication ("nest"). Children without a valid health card number and/or Ontario residence code were excluded from the study cohort. Those with an existing mental health condition, captured by the definition of hospitalization, same-day surgery (surgical procedure not requiring an overnight hospital stay), or ED visit coded for schizophrenia, bipolar disorder, depression/affective mood disorder, or anxiety in the year before their first known asthma prevalence date, also were excluded from the study cohort (**Table I**).

Cases were defined as children in the study cohort with a neuropsychiatric event (defined below) between April 1, 2004, and March 31, 2016. The index date for each case was the date of their first neuropsychiatric event following physician-diagnosed asthma. Each case was matched to a maximum of 4 controls, who had no neuropsychiatric event during the study period, on sex, year of asthma diagnosis (within 1 year), and year of birth (within 2 years). Controls were assigned the same index date as their matched case. We employed a 1-year lookback period to ascertain history of asthma medication prescription. Cases and controls had to have at least 1 record of a dispensed prescription for an asthma maintenance medication in ODB in the year prior to their index date (**Table II**; available at www.jpeds.com). If cases did not meet the criteria for pharmacologically treated asthma, they were excluded; if controls did not meet these criteria, they were returned to the pool of eligible controls to potentially be matched with a subsequent case. Cases and controls who had a dispensed prescription for zafirlukast (another LTRA) in the year before their index date also were excluded.

Exposure and Outcome Definitions

The exposure of interest was dispensed prescriptions for montelukast in the year before the index date, which was defined in 2 ways. Montelukast exposure was treated as a binary variable, based on whether the child had at least 1 dispensed prescription for montelukast in the year before the index date. In addition, montelukast exposure was treated as a categorical variable, defined as the number of dispensed prescriptions for montelukast in the year preceding the index date (0 dispensed prescriptions for montelukast, 1 dispensed prescription for montelukast, or 2+ prescriptions for montelukast). To be eligible for our study, children who were not prescribed montelukast were required to have had at least 1 dispensed prescription for another asthma maintenance medication during the same 1-year lookback period, to ensure they all had pharmacologically treated asthma.

The primary outcome was first neuropsychiatric event following physician-diagnosed asthma, defined as a hospitalization, same-day surgery, or ED visit coded for 6 groups of disorders: substance-related, schizophrenia, anxiety, sleep disturbance, mood and personality disorders, plus agitation (**Table I**). Except for outpatient physician visits, healthcare encounters from all sources were used to identify children with mental health visits. Mental health outcomes were ascertained from the admission records, whether the admission was for medical or surgical reasons. Presumably,

mental health diagnoses documented during the admission would be those considered as important by the clinical teams. Physician office visits were not included in the outcome definition, due to a lack of specificity in billing and diagnosis codes of interest. The outcome was defined as a binary variable.

Covariates

The Local Health Integration Network (LHIN) and rurality of each individual's primary residence were used to control for geographic differences. LHINs are regional health authorities responsible for allocating resources and coordinating healthcare services in Ontario, Canada. There are 14 distinct LHINs in Ontario. Rurality was defined as residing in a community with a population of 10 000 people or fewer.[23] Marginalization quintiles from ON-Marg were used as proxies for socioeconomic status (**Table III**; available at www.jpeds.com). The ON-Marg is a census-based index that measures inequalities in health and social well-being.[22] The 4 dimensions of ON-Marg are residential instability, material deprivation, dependency, and ethnic concentration.[22] A score is computed for each dimension and dimension-specific quintiles are produced, where the first quintile is the least marginalized and the fifth quintile is the most marginalized.[22] Number of dispensed prescriptions for long-term asthma maintenance medications (excluding montelukast), number of dispensed prescriptions for systemic corticosteroids, and number of hospitalizations, ED visits, and physician's office visits coded for asthma in the 1-year lookback period were investigated as potential covariates. We included number of prescriptions for oral corticosteroids in the model as a potential confounder, as corticosteroid use is associated frequently with psychiatric adverse events.

Statistical Analyses

Descriptive statistics were calculated for the exposure and all identified covariates, by status (case or control). Continuous variables were described using medians, means, and SDs, as appropriate. Categorical variables were described using frequency distributions and percentages. Student t tests and χ^2 tests were used to assess the statistical significance of differences between cases and controls.

Univariate Analyses and Multivariable Model Building

Based on the matched design, conditional logistic regression was used to model the relationship between montelukast prescription and neuropsychiatric events. Univariate analyses were conducted for the exposure and all identified covariates, to assess the relationship between each variable and neuropsychiatric events. A forward model-building strategy was used to identify the most parsimonious multivariable conditional logistic regression model. Variables with a P value less than .25 in the univariate analyses were included in the full model. Variables with a P value greater than .05 in the full model were removed to produce a reduced model. The full model and reduced model were compared using a likelihood ratio test, to determine whether they were statistically different. The full model did not perform statistically significantly better than the reduced model; therefore, the reduced model was preferred for parsimony. To assess for confounding, eliminated variables were put back into the model one by one to see whether they appreciably changed (>10%) the beta estimate of the main exposure; none did. Finally, as a clinically important variable, corticosteroid use was forced back into the model. Both unadjusted ORs and aORs with 95% CIs were calculated. Covariates in the final model were LHIN, number of asthma medications, number of systemic corticosteroid prescriptions, asthma severity (defined as the number of ED visits and hospitalizations for asthma in the 1-year lookback period), and marginalization quintiles. All analyses were conducted using R statistical software (R Core Team, Vienna, Austria) (specifically the "lattice"[24] and "survival"[25] packages), and a P value of .05 was used as the threshold for statistical significance. The study was approved by Research Ethics Board of The Hospital for Sick Children (Toronto, Ontario). Per Ontario legislation, deidentified health administrative data could be used for this approved research project without obtaining individual consent.

Results

In total, 898 children with asthma, prescribed an asthma maintenance medication, with their first neuropsychiatric event occurring between April 1, 2004, and March 1, 2016, were identified. These cases were matched to 3497 controls, resulting in a total sample size of 4395 children with asthma. The presenting complaint(s) and/or diagnosis from the first neuropsychiatric event in cases are presented in **Table IV**, with most cases presenting for anxiety (48.6%) and/or sleep disturbance (26.1%). Almost one-half (42.4%) of neuropsychiatric events occurred within 90 days of the most recent dispensed asthma maintenance prescription, and an additional 22.2% of events occurred between 90 and 180 days from the most recent dispensed prescription.

The characteristics of cases and controls are presented in **Table V**. New-onset neuropsychiatric events occurred more often in the youngest and oldest age groups, following a bimodal distribution. Exposure to montelukast was more common in the cases, with 8.1% of cases having at least 1 dispensed prescription for montelukast, compared with 2.1% of controls ($P < .001$). With regard to asthma

Table IV. Presenting complaint and/or diagnoses for first neuropsychiatric event (N = 898)

First neuropsychiatric events	Cases (N = 898) n (%)
Anxiety	436 (48.6)
Sleep disturbance	234 (26.1)
Mood	153 (17.0)
Substance-related	99 (11.0)
Personality	14 (1.6)
Schizophrenia	13 (1.4)
Agitation	12 (1.3)

Table V. Descriptive statistics by outcome: cases with a neuropsychiatric event (N = 898) and controls (N = 3497)

Variable	Cases (N = 898) n (%)	Controls (N = 3497) n (%)	*P* value*
Age at asthma diagnosis, y			
0-5	341 (38.0)	1290 (36.9)	.76
6-12	355 (39.5)	1429 (40.9)	
13-18	202 (22.5)	778 (22.2)	
Age at index date, y			
6-7	167 (18.6)	591 (17.0)	.71
8-9	123 (13.7)	504 (14.4)	
10-11	103 (11.5)	404 (11.6)	
12-14	221 (24.6)	913 (26.1)	
15-18	284 (31.6)	1085 (31.0)	
Sex: female	476 (53.0)	1874 (53.6)	.78
Urban residence	794 (88.4)	3285 (93.9)	**<.001**
Socioeconomic status quintiles			
Deprivation quintile			
1: least	67 (7.5)	266 (7.7)	.26
2	96 (10.8)	300 (8.6)	
3	122 (13.7)	506 (14.6)	
4	178 (19.9)	629 (18.1)	
5: most	430 (48.2)	1774 (51.1)	
Dependency quintile			
1: least	259 (29.0)	1157 (33.3)	**.02**
2	186 (20.8)	789 (22.7)	
3	156 (17.5)	588 (16.9)	
4	147 (16.5)	481 (13.8)	
5: most	145 (16.2)	460 (13.2)	
Ethnic concentration quintile			
1: least	109 (12.2)	274 (7.9)	**<.001**
2	121 (13.5)	318 (9.2)	
3	157 (17.6)	369 (10.6)	
4	195 (21.8)	633 (18.2)	
5: most	311 (34.8)	1881 (54.1)	
Instability quintile			
1: least	77 (8.6)	393 (11.3)	.28
2	113 (12.7)	427 (12.3)	
3	152 (17.0)	536 (15.4)	
4	238 (26.7)	933 (26.8)	
5: most	313 (35.1)	1186 (34.1)	
Asthma severity (hospitalizations and/or ED visits for asthma)			
Median (IQR)	0 (0-2.96)	0 (0-0.47)	**<.001**
Mean (SD)	1.25 (2.54)	0.13 (0.50)	
Number of other asthma maintenance medication prescriptions			
Median (IQR)	6 (1.07-19.57)	2 (0.74-4.52)	**<.001**
Mean (SD)	10.32 (13.72)	2.63 (2.80)	
Number of other asthma maintenance medication prescriptions			
0-1	105 (11.7)	1593 (45.6)	**<.001**
2-3	186 (20.7)	1183 (33.8)	
4+	607 (67.6)	721 (20.6)	
Number of corticosteroid prescriptions			
0	528 (58.8)	3022 (86.4)	**<.001**
1	177 (19.7)	363 (10.4)	
2+	193 (21.5)	112 (3.2)	
Number of corticosteroid prescriptions, in corticosteroid users			
Median (IQR)	2 (1.00-8.65)	1 (0.75-2.13)	**<.001**
Mean (SD)	3.18 (8.12)	1.44 (1.03)	
n (%)	370 (41.2)	475 (13.6)	
Number of montelukast prescriptions			
0	825 (91.87)	3423 (97.88)	**<.001**
1	17 (1.89)	19 (0.54)	
2+	56 (6.24)	55 (1.57)	
Number of montelukast prescriptions, in montelukast users			
Median (IQR)	4 (1.98-15.40)	2.50 (1.23-6.17)	**.001**
Mean (SD)	8.69 (9.96)	3.70 (3.66)	
n (%)	73 (8.1)	74 (2.1)	
Time from most recent (or montelukast) prescription to event date, d			
0-90	381 (42.4)	1392 (39.8)	.15
>90-180	199 (22.2)	879 (25.1)	
>180	318 (35.4)	1226 (35.1)	
Time from first known prevalent asthma date to event date, d			
Median (IQR)	1326 (766.03-2253.97)	1339 (784.38-2271.62)	.65
Mean (SD)	1510 (1103.81)	1528 (1103.30)	

All percentages are adjusted for missing values. Bold values are statistically significant at the $P < .05$ level.
*Determined by a χ^2 test (categorical variables) or 2-sided t test (discrete variables).

severity, cases had significantly more ED visits and hospitalizations for asthma in the year before the index date (cases—mean 1.25, SD 2.54; controls—mean 0.13, SD 0.50; $P < .001$). A greater proportion of cases had a dispensed prescription for systemic corticosteroids (41.2% for cases vs 13.6% for controls; $P < .001$), and a greater number of prescriptions for other asthma maintenance medications (67.6% of cases had 4 or more other dispensed asthma medication prescriptions, compared with 20.6% of controls; $P < .001$).

Results of the univariate and multivariable conditional logistic regression are presented in Table VI. Exposure to montelukast was significantly associated with 4.5 times increased odds of a neuropsychiatric event (unadjusted OR 4.5, 95% CI 3.1-6.5) in the unadjusted model. Similarly, a greater number of dispensed montelukast prescriptions in the year before the index date was significantly associated with increased odds of a neuropsychiatric event, compared with no prescriptions for montelukast (1 prescription: unadjusted OR 3.89, 95% CI 1.95-7.73; 2 or more prescriptions: unadjusted OR 4.70, 95% CI 3.09-7.14).

Exposure to montelukast was significantly associated with neuropsychiatric events, after we controlled for LHIN, marginalization quintiles, number of other asthma medication prescriptions, number of corticosteroid prescriptions, and number of hospitalizations and ED visits for asthma. Children with a dispensed prescription for montelukast had nearly 2 times increased odds of a neuropsychiatric event in the adjusted model (aOR 1.91; 95% CI 1.15-3.18). The direction of the effect estimate for montelukast and neuropsychiatric events did not change when exposure to montelukast was treated as a categorical variable; however, the association was no longer statistically significant.

Discussion

Our study answers the call for epidemiologic research to quantify the risk of neuropsychiatric events for children prescribed montelukast, using the most recent population-level administrative health data in Ontario, Canada. In this nested case–control study, exposure to montelukast was significantly associated with a 2-fold increase in the odds of a

Table VI. Results of unadjusted and adjusted conditional logistic regression, for the outcome of new-onset neuropsychiatric event (N = 4395)

Variable	Unadjusted OR	95% CI	*P* value	aOR*	95% CI	*P* value
Montelukast use (ref = no)						
Yes	4.48	3.10-6.46	**<.001**	1.91	1.15-3.18	**.01**
Number of montelukast prescriptions (ref = 0)						
1	3.89	1.95-7.73	**<.001**	2.38	0.98-5.77	.06
2+	4.70	3.09-7.14	**<.001**	1.74	0.96-3.16	.07
Deprivation quintile (ref = 1)						
2	1.29	0.91-1.84	.16	1.19	0.76-1.88	.45
3	0.98	0.70-1.37	.89	0.68	0.44-1.08	.10
4	1.13	0.83-1.55	.45	0.88	0.57-1.36	.56
5	0.96	0.72-1.28	.80	0.75	0.49-1.14	.18
Missing	0.95	0.35-1.59	.92	1.50	0.39-5.75	.55
Dependency quintile (ref = 1)						
2	1.05	0.86-1.30	.62	0.88	0.67-1.15	.34
3	1.20	0.96-1.49	.12	0.77	0.57-1.03	.08
4	1.38	1.10-1.73	**.006**	0.79	0.57-1.09	.16
5	1.39	1.11-1.75	**.005**	0.81	0.58-1.15	.24
Missing	1.05	0.39-2.78	.93	–	–	–
Ethnic quintile (ref = 1)						
2	0.98	0.71-1.34	.88	1.18	0.78-1.78	.45
3	1.08	0.79-1.44	.67	1.18	0.78-1.79	.43
4	0.79	0.60-1.04	.10	1.00	0.66-1.52	.98
5	0.42	0.33-0.55	**<.001**	0.53	0.34-0.82	**.004**
Missing	0.62	0.23-1.69	.35	–	–	–
Instability quintile (ref = 1)						
2	1.33	0.97-1.84	.08	1.15	0.75-1.77	.51
3	1.43	1.06-1.94	**.02**	1.36	0.89-2.06	.15
4	1.29	0.97-1.72	.08	1.40	0.93-2.12	.11
5	1.33	1.01-1.76	**.04**	1.80	1.19-2.73	**.006**
Missing	1.19	0.44-3.22	.74	–	–	–
Number of other asthma medication prescriptions (ref = 0-1)						
2-3	2.37	1.83-3.06	**<.001**	2.03	1.53-2.68	**<.001**
4+	13.45	10.57-17.11	**<.001**	9.66	7.29-12.81	**<.001**
Number of corticosteroid prescriptions (ref = 0)						
1	2.84	2.30-3.50	**<.001**	0.96	0.72-1.26	.75
2+	10.13	7.75-13.25	**<.001**	1.41	0.99-2.02	.06
Asthma severity (hospitalizations/SDS and ED visits for asthma)	3.18	2.79-3.63	**<.001**	2.09	1.82-2.40	**<.001**

SDS, same-day surgery. Bold values are statistically significant at the $P < .05$ level.
*aORs were estimated using the model with the binary primary exposure variable (yes vs no dispensed prescriptions for montelukast). Model was also adjusted for the patient's regional health authority (LHIN).

neuropsychiatric event, compared with other asthma maintenance medications, after we controlled for sociodemographic factors and measures of asthma severity and treatment.

Our results are corroborated by early analyses of voluntary adverse event reporting databases, including the World Health Organization's VigiBase and Sweden's SWEDIS.[12,14] Both studies, which relied on Individual Case Safety Reports and adverse drug reaction reports and therefore had no comparison group, detected a positive signal wherein children prescribed montelukast had an increased risk of neuropsychiatric events.[12,14] Our findings are also in line with a recent nested case–control study of children with asthma in Quebec, Canada, which found that individuals on montelukast had significantly greater risk of neuropsychiatric adverse drug reactions than those on inhaled corticosteroids.[17] The findings of our study contrast with 2 other nested case–control studies, which found no association between montelukast and neuropsychiatric events or suicide attempts.[13,15] Both studies used health insurance claim databases in the US, and their study populations differed from ours in terms of socioeconomic status and asthma severity.[13,15] Neither study used a validated health administrative definition for physician-diagnosed asthma, and instead, defined asthma as a single claim for asthma during the study period.[13,15] One study used suicide attempts as their primary outcome, which was not explored in our study.[15] The other used a broad definition of neuropsychiatric events, including all psychiatric disorders except developmental disorders.[13] The nonspecific definition of a neuropsychiatric event, which was not aligned with adverse event reports for montelukast, may have contributed to the null findings.[13]

Our findings also differed from those of a Merck-funded reanalysis of clinical trial data.[16] Despite their conclusion that behavior-related adverse events were rare in clinical trials of montelukast, they may have been under-reported and overlooked, because the trials were focused on drug efficacy and were not powered nor specifically probed for neuropsychiatric symptoms or events.[16] In addition, the average follow-up time was less than 2 months, which may have underestimated the risk, given that time to onset of neuropsychiatric adverse events can vary from hours to months after initiation of therapy.[12,16]

One limitation of our study was the reliance on the ODB database to capture dispensed prescription medications. Children eligible for ODB may not be representative of the general pediatric population, as they generally come from families of lower socioeconomic status. However, because this holds true for both cases and controls, it should not systematically bias the results. Furthermore, for children older than 5 years, the cost of montelukast is not covered by the ODB's general benefit formulary.[19] To access drugs not covered by the ODB's general benefit formulary, a request must be submitted to the Exceptional Access Program. The Exceptional Access Program will only approve montelukast for children and adolescents aged 5-18 years if they are already on an inhaled corticosteroid and long-acting beta-2 agonist and their asthma remains uncontrolled.[26] For this reason, children in our cohort may have had more severe and/or poorly controlled asthma compared with the general population. We addressed this issue by controlling for proxy measures of asthma severity, although there may have been residual confounding related to disease severity. As our study used health administrative data, we did not have definitive measures of adherence to therapy. The inclusion criteria did ensure that all children had dispensed prescriptions for asthma maintenance medications and thus were intended to be treated pharmacologically. In addition, if prescriptions for montelukast were paid for out-of-pocket, they would not be captured in the ODB database.

Despite these limitations, the ODB database was the best-available source for population-level prescription data in Ontario. The ODB population also provides important insights, because children of low socioeconomic status with severe asthma may be particularly vulnerable to neuropsychiatric events.[27,28] Because we employed a case–control design, and children may be transiently eligible for socially funded medications under the ODB, we a priori chose to focus on time interval from most recent montelukast prescription to neuropsychiatric event. Future research should explore the correlation between duration of montelukast exposure and risk of neuropsychiatric events.

Another potential limitation was the use of hospitalizations, same-day surgeries, and ED visits for our outcome of neuropsychiatric events, which may have missed cases who presented only at a physician's office. However, recent literature suggests up to 53% of children in Ontario present to the ED as their first point of contact for mental health,[29] and many others are being referred to the ED after seeing their primary care physician. Hospitalizations, same-day surgeries and ED visits were also used to define existing mental health conditions. If a child had a visit coded for schizophrenia, bipolar disorder, depression/affective mood disorder, or anxiety in the year before their first known asthma prevalence date, they were excluded from the study cohort. This definition would not have excluded all existing mental health conditions. However, the definitions of neuropsychiatric events and existing mental health conditions allowed us to capture new-onset neuropsychiatric events, or mental health conditions that increased in urgency or severity. Previous research has established an association between uncontrolled asthma and psychiatric symptoms,[30] which may have been captured by our outcome definition. In an effort to produce an unbiased estimate of the neuropsychiatric effect of montelukast, we controlled for proxy measures of asthma severity between the 2 groups, to the best that a large database study with no complete health records allows. Finally, the relatively small sample size precluded us from investigating each event type individually, beyond a composite outcome measure. The small sample size and relatively rare montelukast exposure also limited the power of our study when looking at our exposure as a categorical variable, the number of dispensed prescriptions for montelukast.

At present, the biological mechanisms underlying the neuropsychiatric effects of montelukast are not understood; however, previous research has shown clinical resolution of adverse events when montelukast therapy was discontinued.[31] The pathophysiology of montelukast-induced neuropsychiatric effects is an important direction for future research.

In summary, children prescribed montelukast for asthma management had nearly twice the odds of neuropsychiatric events, compared with those on other asthma maintenance medications. Our recommendations echo those of the FDA's Pediatric Advisory Committee, who discussed montelukast in 2014 and ultimately recommended increased provider awareness and continued monitoring of neuropsychiatric adverse events.[9] Clinicians should be aware of the potential risks of montelukast, as it may inform their prescribing practices and clinical follow-up visits. ■

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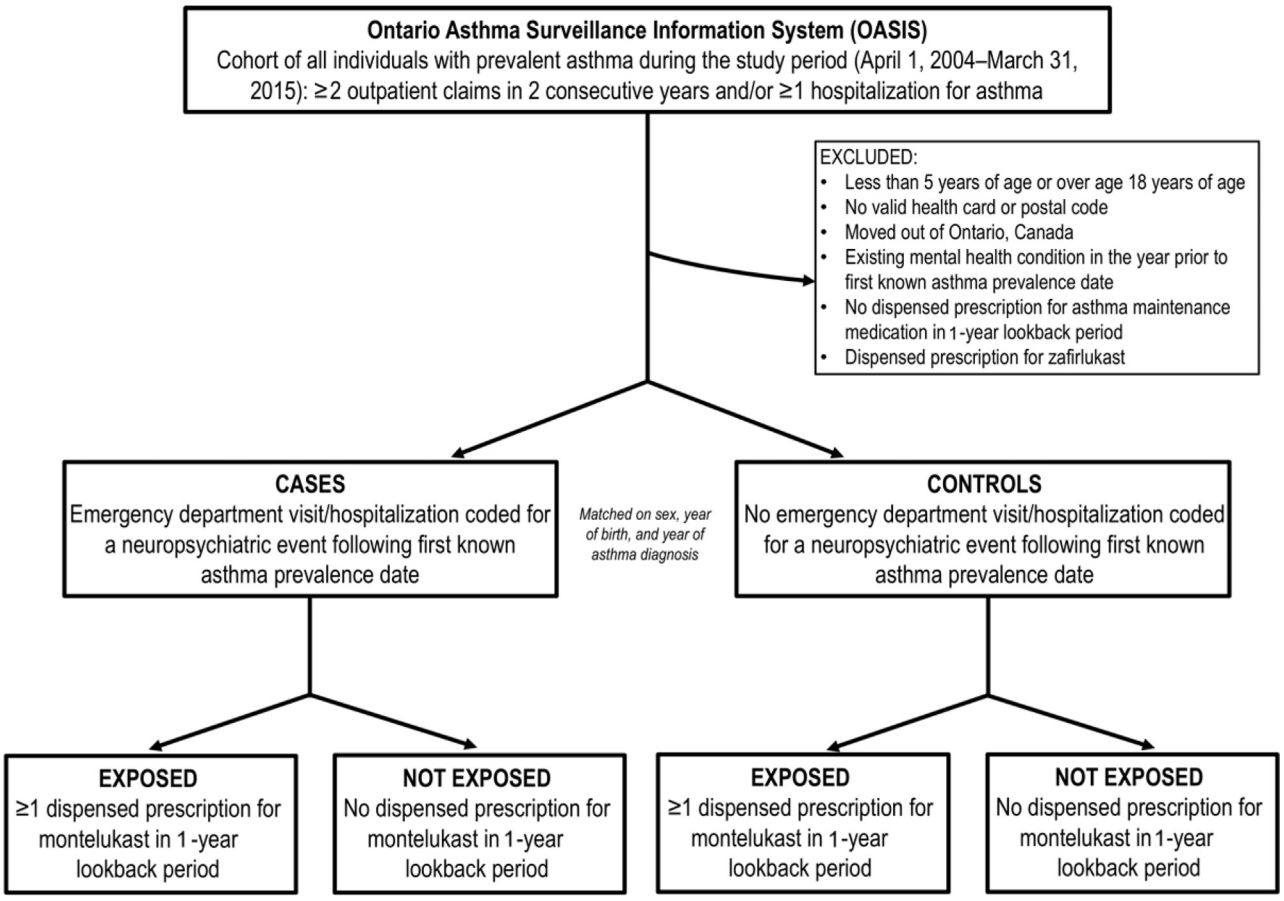

Figure. Flowchart of study population and data sources. Outpatient claims were obtained from the Ontario Health Insurance Plan database. Hospitalizations were obtained from the Canadian Institute of Health Information Discharge Abstract Database. ED visits were obtained from the National Ambulatory Care Reporting System. Prescription data were obtained from the ODB Program database. All datasets are housed at the Institute for Clinical Evaluative Sciences.

Table I. ICD-10 codes, DSM-IV codes, and OHIP billing codes used for outcome definition, exclusion criteria, and covariates

Disorder groups	ICD-10 codes	DSM-IV codes	OHIP billing codes
Neuropsychiatric event (outcomes)			
Substance-related	F55, F10- F19	291.(0, 1, 2, 3, 5, 81, 89, 9), 292.0, 292.11, 292.12, 292.81, 292.82, 292.83, 292.84, 292.89, 292.9, 303.(00, 90), 304.(00, 10, 20, 30, 40, 50, 60, 80, 90), 305.(00, 10-90)	-
Schizophrenia	F20 (excluding F20.4), F22-F25, F28, F29	295.(10, 20, 30, 40, 60, 70, 90), 297.1, 297.3, 298.8, 298.9	-
Anxiety	F40-F43, F48.8, F48.9, F93.0	300.(00. 01, 02, 21, 22, 23, 29), 300.3, 308.3, 309.21, 309.81	-
Sleep disturbance	F51, G47	307.44, 307.42, 347, 780.59, 307.45, 307.47, 327.03, 307.46, 780.54, 780.52	-
Agitation	R45.1	N/A	-
Mood disorders	F30-F34, F39	293.83, 296.0x, 296.2x, 296.3x, 296.4x, 296.5x, 296.6x, 296.7, 296.80, 296.89, 296.90, 300.4, 301.13, 311	-
Personality disorders	F60-F62, F68, F69, F21	301.0, 301.20, 301.11, 301.4, 301.50, 301.6, 301.7, 301.81, 301.82, 301.83, 301.9	-
Existing mental health condition (exclusion criteria)			
Schizophrenia	F20 (excluding F20.4), F22-F25, F28, F29	295.(10, 20, 30, 40, 60, 70, 90), 297.1, 297.3, 298.8, 298.9	-
Bipolar	F31	296.80, 296.4x, 296.5x, 296.6x, 296.0x, 296.89	-
Depression/ affective mood disorder	F32-F34, F39	296.2x, 296.3x, 311	-
Anxiety	F40-F43, F48.8, F48.9, F93.0	300.(00. 01, 02, 21, 22, 23, 29), 300.3, 308.3, 309.21, 309.81	-
Covariates			
Asthma	J45.00, J46	N/A	493
Allergic rhinitis	J30	N/A	-

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; *ICD*, International Classification of Diseases and Health Related Problems, 10th Revision; *N/A*, not available; *OHIP*, Ontario Health Insurance Plan.

Data on ED visits, hospitalizations, and physician office visits in Ontario were obtained from the National Ambulatory Care Reporting System, Canadian Institute of Health Information Discharge Abstract Database, and Ontario Health Insurance Plan databases, respectively. Asthma prevalence is captured by the Ontario Asthma Surveillance Information System. All datasets are housed at the Institute for Clinical Evaluative Sciences.

Table II. List of asthma maintenance medications used in cohort creation, and systemic corticosteroids used as a covariate

Drug classes	Medication
LTRAs	Montelukast
ICS	Beclomethasone dipropionate
	Budesonide
	Triamcinolone acetonide
	Flunisolide
	Fluticasone propionate
	Ciclesonide
	Fluticasone furoate
	Mometasone
	Beclomethasone
LABA	Formoterol
	Indacaterol
	Salmeterol
	Umeclidinium
	Glycopyrronium
	Tiotropium
	Aclidinium
ICS/LAMA	Fluticasone furoate/vilanterol
ICS/LABA	Mometasone/formoterol
	Salmeterol xinafoate and fluticasone propionate
	Budesonide and formoterol fumarate dihydrate
LABA/LAMA	Umeclidinium/vilanterol
	Aclidinium/formoterol
	Tiotropium/olodaterol
	Indacaterol/glycopyrronium
Short-acting beta-2 agonists/ short-acting muscarinic antagonists	Ipratropium bromide & salbutamol sulfate
Anti-IgE	Omalizumab
Methylxanthines	Oxtriphylline
	Theophylline
PDE-4 inhibitors	Roflumilast
Interleukin-5 inhibitors	Mepolizumab
Corticosteroids (covariate)	Prednisone
	Dexamethasone
	Hydrocortisone
	Methylprednisolone
	Methylprednisolone acetate
	Fludrocortisone acetate
	Prednisolone sodium phosphate
	Triamcinolone acetonide

ICS, inhaled corticosteroids; *LABA*, long-acting beta-2 agonists; *LAMA*, long-acting muscarinic antagonists; *PDE-4*, phosphodiesterase 4.
Prescription drugs of interest were identified using their unique Drug Identification Number.

Table III. ON-Marg dimensions and indicators

Dimensions	Indicators
Material deprivation	Proportion of the population aged 20 + years without a high-school diploma
	Proportion of families who are lone parent families
	Proportion of the population receiving government transfer payments
	Proportion of the population aged 15 + years who are unemployed
	Proportion of the population considered low-income
	Proportion of households living in dwellings that are in need of major repair
Dependency	Proportion of the population who are aged 65 years and older
	Dependency ratio (total population 0-14 and 65+/total population 15-64 years)
	Proportion of the population not participating in labor force (aged 15+ years)
Residential instability	Proportion of the population living alone
	Proportion of the population who are not youth (aged 16+ years)
	Average number of persons per dwelling
	Proportion of dwellings that are apartment buildings
	Proportion of the population who are single/divorced/widowed
	Proportion of dwellings that are not owned
	Proportion of the population who moved during the past 5 years
Ethnic concentration	Proportion of the population who are recent immigrants (arrived in the 5 years before the census
	Proportion of the population who self-identify as a visible minority

ON-Marg seeks to measure differences in marginalization across geographic areas and population groups. It is based on the Census of Canada and is calculated across geographies in Ontario. The 4 dimensions of the ON-Marg are listed here, along with the indicators used in the calculation of each dimension. All dimensions are divided into quintiles, ranked from 1 (least marginalized) to 5 (most marginalized).
Reference: Matheson et al.[22]