Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice

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ABSTRACT Although montelukast is generally well tolerated, postmarketing studies have reported serious neuropsychiatric adverse drug reactions (ADRs) leading to a United States Food and Drug Administration warning. The objective of this study was to determine the incidence of neuropsychiatric ADRs leading to discontinuation of montelukast in asthmatic children.

We conducted a retrospective cohort study in children aged 1–17 years initiated on montelukast. In a nested cohort study, children initiated on montelukast as monotherapy or adjunct therapy to inhaled corticosteroids (ICS) were matched to those initiated on ICS monotherapy. A non-leading parental interview served to ascertain the occurrence of any ADRs with any asthma medication, and circumstances related to, and evolution of, the event.

Out of the 106 participants who initiated montelukast, most were male (58%), Caucasian (62%) with a median (interquartile range) age of 5 (3–8) years. The incidence (95% CI) of drug cessation due to neuropsychiatric ADRs was 16 (10–26)%, mostly occurring within 2 weeks. Most frequent ADRs were irritability, aggressiveness and sleep disturbances. The relative risk of neuropsychiatric ADRs associated with montelukast *versus* ICS was 12 (2–90).

In the real-life setting, asthmatic children initiated on montelukast experienced a notable risk of neuropsychiatric ADRs leading to drug cessation, that is significantly higher than that associated with ICS.

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Introduction

International guidelines recommend inhaled corticosteroids (ICS) as the preferred daily controller medication for children with asthma, with leukotriene receptor antagonists (LTRA) as second-line alternative [1–3]. Systemic adverse effects such as growth suppression and local effects including oropharyngeal candidiasis are well recognised in association with ICS [4–7]. With recent pragmatic studies showing greater adherence to, and effectiveness of, LTRA compared to ICS [8–10], the prospect of increased adherence resulting in better asthma control has renewed interest in the use of LTRA as monotherapy or adjunct therapy. Montelukast, the only LTRA licensed for use in children aged <12 years appears to be generally well tolerated with side-effects primarily limited to minor gastrointestinal disturbances, respiratory symptoms, skin reactions and headaches [11]; importantly, the absence of growth and adrenal suppression [5] increases its appeal for children with asthma. With similar drug effectiveness in the real-life setting, safety profiles and acceptability become key elements to guide the choice between ICS and LTRA monotherapy and LTRA *versus* long-acting β_2-adrenoceptor agonists (LABA) as adjunct therapy in children with asthma.

Since its commercialisation, information from several clinical trials and postmarketing cases [12–14] has led the United States Food and Drug Administration (FDA) to issue multiple warnings concerning an increased risk of neuropsychiatric events associated with montelukast, including aggressive behaviour, depression, hallucinations and suicidal behaviour [15–17]. In fact, in a Swedish postmarketing paediatric surveillance study, montelukast was one of five drug classes most frequently associated with neuropsychiatric adverse drug reactions (ADRs), representing 10% of all reports, closely followed by inhaled budesonide (6.5%) [18]. Yet postmarketing safety information remains quite limited in children [6], and importantly, such studies usually lack a denominator. Consequently, the incidence of neuropsychiatric ADRs associated with montelukast remains unclear in children.

The primary objective of this study was to determine the incidence of neuropsychiatric ADRs severe enough to lead to the cessation of montelukast in children with asthma. Secondary objectives included the characteristics and determinants of neuropsychiatric ADRs as well as the relative risk of drug cessation due to these ADRs in children initiated on montelukast *versus* ICS.

Methods

We assembled a retrospective cohort study of children who presented between February 2011 and April 2016 to the asthma clinic of the Sainte-Justine University Health Centre (Montreal, QC, Canada) and whose parents (representing 85% of approached patients) had previously provided written consent to enrol in the Pediatric Asthma Database and Biobank (PADB). The latter included detailed patient and treatment characteristics recorded in electronic medical charts and DNA banking; it was merged to databases of all medical services provided in our institution and to the reMed database providing data regarding all prescriptions served by any of the province of Quebec pharmacies, claimed by privately insured and a proportion of publicly insured patients *via* the Quebec drug plan. The study was approved by the institutional research ethics board. All parents gave verbal consent to participate in a telephone (or in-person) interview in the summers of 2014, 2015 or 2016.

Children were eligible if they were aged 1–17 years; had a physician-confirmed diagnosis of asthma [1, 19]; and made a clinic visit during which they were initiated on maintenance montelukast as monotherapy or as adjunct therapy to ICS or to ICS combined with LABA, providing that montelukast was the only new added medication. Patients were excluded if they denied having taken the medication of interest.

Within this cohort, we carried out a nested matched cohort study. Intervention patients were initiated on daily montelukast as monotherapy or as adjunct to ICS, whereas control patients were initiated on ICS monotherapy, both at an ICS dose of $\leqslant 250\ \mu g \cdot day^{-1}$ in hydrofluoroalkane-propelled beclomethasone or equivalent (where 1 µg of fluticasone=1 µg ciclesonide=2 µg dry powder budesonide) [1]. Neither group had been prescribed maintenance montelukast at any prior medical visit. Intervention patients initiated on montelukast were matched 1:1 to those initiated on ICS monotherapy, within (*i.e.* plus or minus) 90 days of the drug initiation date.

Parents of eligible patients were contacted by phone or in person by a trained research assistant. Using a non-leading interview script, a standardised questionnaire was administered to identify any ADR-related drug cessation, reported spontaneously or after prompting, using three approaches. First, we enquired about the occurrence and reason for any asthma drug cessation. Second, we asked if the child had experienced an ADR to any asthma medication. Finally, a list of neuropsychiatric ADRs was read to parents to determine if any of them had ever occurred with any asthma drug. If an ADR was reported in any of these three questions, parents were asked to describe the type and onset of symptoms, circumstances related to the event, dose adjustments or drug discontinuation resulting from the ADR, and,

when applicable, the evolution of the ADR after discontinuation of the drug (dechallenge) and after restarting the medication (rechallenge) [20]. In addition, the questionnaire enquired about the child's demographics, asthma controller medications used, predisposing medical conditions (*e.g.* attention deficit disorder), family history of neuropsychiatric conditions (*e.g.* depression) and prior adverse effects to other medications.

For all events suggesting neuropsychiatric ADRs, a structured coded report was submitted to an adjudication committee composed of six physicians and experts, along with a comprehensive list of ADRs associated with each drug of interest derived from the 2016 Canadian *Compendium of Pharmaceuticals and Specialties* [21]. Blinded to the drug name and class, two members of the adjudication committee independently reviewed the report to assess event severity, evolution and imputability using the Naranjo score [20], assuming alternatively that the drug was montelukast and an ICS. Briefly, the Naranjo algorithm evaluates the drug causality for an adverse drug reaction based on 10 questions. Each answer is assigned a value (−1 to +2) for a maximum score of 12, with causality considered definite if the total score is ⩾9, probable if 5–8, possible if 1–4 and doubtful if ⩽0. In case of disagreement, a consensus was reached after discussion.

The primary outcome was the incidence of parent-reported neuropsychiatric ADRs leading to drug cessation in the montelukast cohort. Secondary outcomes included the incidence of all neuropsychiatric ADRs and their characteristics including the type, delay to onset, delay until resolution and evolution following dechallenge and rechallenge, as well as severity, evolution and imputability as assessed by adjudicators. Host- and therapy-related determinants were explored for their potential association with ADRs. We focused on polymorphisms of two genes and alleles with a reported population prevalence of ⩾9%, namely CYP2C8*3, strongly associated with hepatic metabolism of montelukast [22, 23], and *SLCO2B1* that codes for the transporter OATP2B1 modulating intestinal and blood–brain barrier transport of montelukast [24, 25]. Finally, in the nested matched-controlled cohort, we ascertained the relative incidence of neuropsychiatric ADRs leading to drug cessation in the montelukast *versus* ICS groups.

Statistical analysis

A sample of 100 children initiated on montelukast would enable us to ascertain an incidence of ⩽18% with a two-sided 95% confidence interval width of 0.15.

The primary outcome, the incidence of neuropsychiatric ADRs serious enough to warrant drug cessation was reported with a 95% confidence interval estimated using a Poisson distribution. We conducted three sensitivity analyses: 1) focusing on cases for which the imputability was assessed as definite or probable by the adjudicators; 2) assuming that none of the nonparticipants who denied having taken montelukast despite confirmed drug claims had any neuropsychiatric ADR-related drug cessation; and 3) none of all nonparticipants had any neuropsychiatric ADR-related drug cessation. Group differences in patient characteristics were compared using a Chi-squared test, Fisher's exact test or t-test, as indicated. A modified multivariable logistic regression (to deal with lack of convergence) [26] served to estimate the relative risk of neuropsychiatric ADR-related drug cessation in the nested matched cohort study comparing montelukast as monotherapy or adjunct therapy to ICS monotherapy. Two *post hoc* analyses were conducted in unmatched groups comparing ICS monotherapy to montelukast, first in children using only monotherapy, and second in those using montelukast as monotherapy or adjunct therapy to ICS or ICS/LABA. In all cases, potential host- (age, sex, ethnicity, asthma control, phenotype, personal and family predisposing behavioural problems) and treatment- (delay between drug initiation and interview and co-intervention) related confounders were offered as candidate variables along with those with baseline group differences. Standard bivariate and multivariable logistic regression models served to explore potential determinants of ADRs in the montelukast cohort, including, in addition to the host and co-intervention variables listed above, pharmacogenetics (P450 CYP2C8*3 and transporter SLCO2B1) and weight-adjusted montelukast dose ($mg \cdot kg^{-1}$). The final models resulted from the stepwise selection of determinants.

Analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA). No imputation for missing covariates in the multivariable models was planned. A significance level of 0.05 was used for all statistical tests.

Results

Out of the 1010 patients enrolled in the PADB with a medical visit before April 1, 2016, 223 received a prescription for initiation of montelukast either as monotherapy or adjunct to ICS or ICS/LABA. Of these, 117 were not reached, denied any intake of montelukast or refused participation, among which 50 denied having taken the medication; 106 eligible children completed the interview (figure 1). Nonparticipants

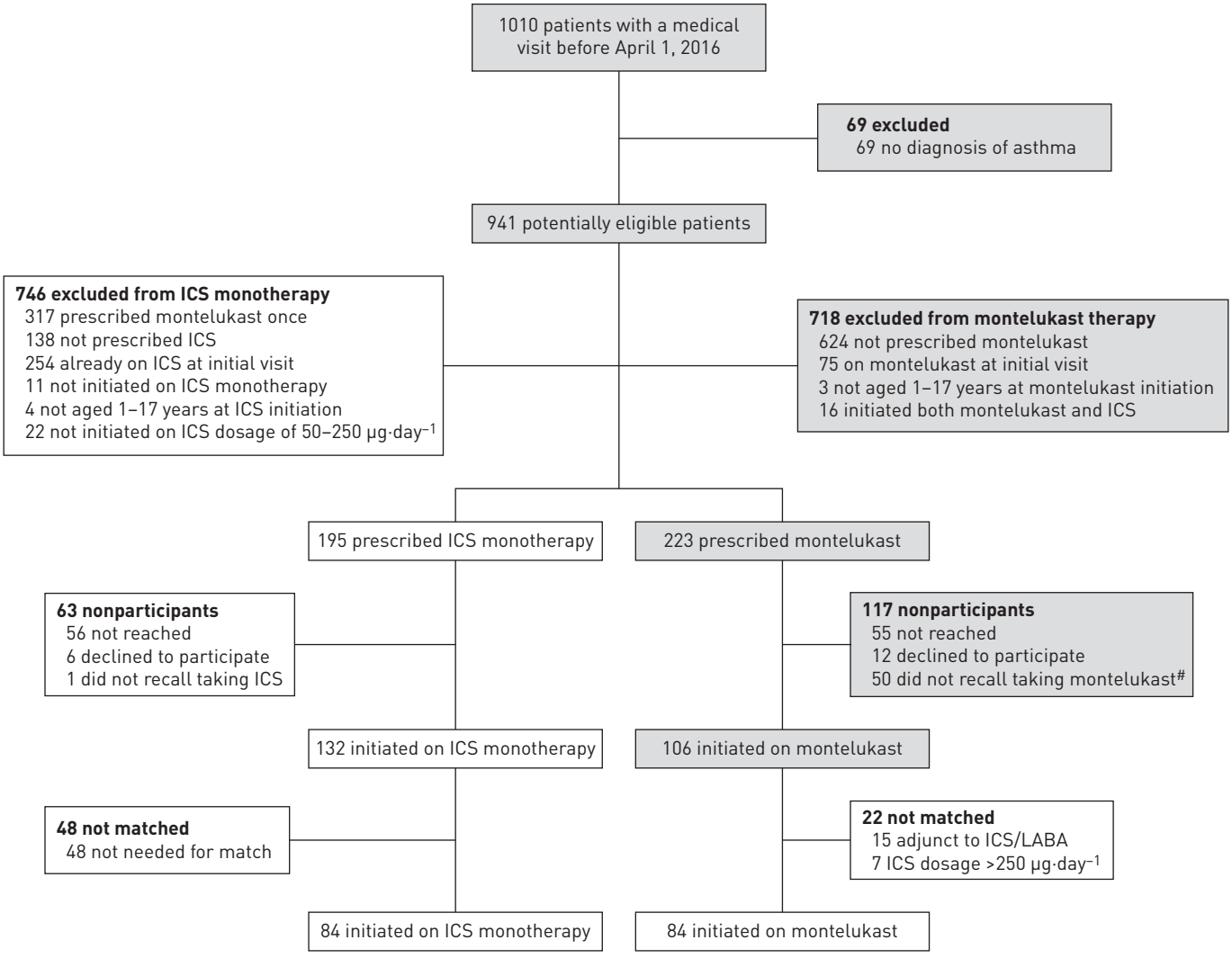

FIGURE 1 Patient selection. The flow of patients initiated on montelukast and on inhaled corticosteroid (ICS) monotherapy is depicted from screening to analysis. #: in the 50 nonparticipants prescribed montelukast but who did not recall intake, we obtained pharmacy confirmation of drug served with 3 months of the prescription in 18 out of 41 patients, with no data on the remaining nine patients. One nonparticipant prescribed ICS did not recall any intake. A total of 132 patients were initiated on ICS monotherapy and 106 on montelukast as monotherapy or as adjunct to ICS or ICS/long-acting β_2-adrenoceptor agonist (LABA). 84 patients in each group were matched on the date±90 days of drug initiation.

were comparable to participants in age, sex, asthma phenotype, triggers, control and atopy; more non-Caucasians declined participation (56% *versus* 38%, p=0.008) (online supplementary table E1).

Most participants were male (58%), Caucasian (62%), with persistent asthma (83%) with a median (interquartile range (IQR)) age of 5 (3–8) years. They had been initiated on montelukast as monotherapy (43%) or as adjunct therapy to ICS (43%) or ICS/LABA (14%). A notable proportion (20%) of children initiated on montelukast suffered from attention deficit disorder (table 1).

The main outcome was ascertained in all participants. 17 (16%, 95% CI 10–26%) children stopped montelukast due to neuropsychiatric ADRs (table 2). Restricting the analysis to those assessed by adjudicators as definitely (n=0) or probably (n=13) related to montelukast, the incidence was 12%. The incidences of drug cessation were 14% and 8%, assuming no drug cessation in nonparticipants who did not recall having taken montelukast despite confirmed pharmacy dispensation, and in all nonparticipants, respectively.

Overall, 25 (24%) patients reported a total of 57 neuropsychiatric ADRs. The most frequently reported ADRs were irritability (n=9), aggressiveness (n=8) and sleep disturbances (n=7) (table 3). The median (IQR) delay from treatment initiation to onset of any ADRs was 7 (2–14) days and 2 (0–3.5) days from drug cessation to symptom resolution. No patients reported suicidal ideation. Adjudicators assessed most (70%) side-effects as mild, requiring only drug cessation; the remainder (30%) were assessed to be very

TABLE 1 Description of participants of the main cohort

Patients	106
Age years	5 (3–8)
Male	62 (58)
Ethnicity	
Caucasian	66 (62)
North African	21 (20)
Black	4 (4)
Asian	3 (3)
East Indian	3 (3)
Hispanic	3 (3)
Interracial/others	6 (6)
Medical history in past year	
Patients with ⩾1 acute care visit	63 (59)
Patients with ⩾1 hospital admission	16 (15)
Medication prescribed at index visit	
Montelukast	106 (100)
Dose (n=104)	
4 mg	53 (51)
5 mg	47 (45)
10 mg	4 (4)
Formulation[#] (n=55)	
Chewable tablet	52 (95)
Granules	2 (4)
Tablet	1 (2)
ICS	61 (58)
LABA	15 (14)
Physician assessment at index visit	
Asthma symptoms (n=100)	
Persistent	83 (83)
Episodic	17 (17)
Unclear	0 (0)
Trigger pattern (n=93)	
Single trigger	16 (17)
Multiple trigger	77 (83)
Physician's assessment of asthma control (n=103)	
Excellent	10 (10)
Good	52 (50)
Unsatisfactory	28 (27)
Poor	13 (13)
Atopy[¶]	32 (30)
Child's predisposing conditions	
Any	39 (37)
Migraine	3 (3)
Attention deficit disorder	21 (20)
Depression	1 (1)
Anxiety	11 (10)
Autism	4 (4)
Sleep disorder	6 (6)
Learning disabilities	1 (1)
Family predisposing conditions[+]	
Any	59 (56)
Migraine	40 (38)
Behavioural problems	15 (14)
Sleep disorders	18 (17)
Psychological or psychiatric disorders	17 (16)

Data are presented as n, median (interquartile range) or n (%). ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist. [#]: confirmed by data claims in the subgroup of chidren with a private drug plan; [¶]: defined as diagnosed allergic conjunctivitis, allergic rhinitis or eczema; [+]: in a first-degree relative (parent or sibling).

mild. Adjudicator-assessed imputability was high; ADRs were deemed probably or possibly related to montelukast in 16 (64%) and six (24%) patients, respectively. Of note, the imputability remained identical whether adjudicators assumed the drug taken to be montelukast or ICS.

TABLE 2 Incidence of cessation of montelukast due to a neuropsychiatric adverse drug reaction (ADR)

	ADR n	Montelukast cohort	Sensitivity analyses	
			Including nonparticipants who denied montelukast intake, but had confirmed drug claims[#]	Including all nonparticipants[¶]
Patients n		106	124	223
ADR reported by parents	17	16 (10–26)	14 (9–22)	8 (5–12)
ADR confirmed by the adjudication committee[+]	13	12 (7–21)	10 (6–18)	6 (3–10)

Data are presented as incidence (95% CI), unless otherwise stated. [#]: assuming that none of the 18 out of 50 nonparticipants who denied having taken montelukast (but in whom we had confirmed dispensing in the drug claim database) had a drug cessation due to a neuropsychiatric ADR; [¶]: assuming that none of the 117 nonparticipants (not contacted, refused to participate or who denied having taken montelukast) had a drug cessation due to a neuropsychiatric ADR; [+]: ascertained as definite (≥9; n=0) or probably (5–8; n=13) related to the drug on the Naranjo causality scale. Of note, the causality assessment was identical whether the adjudicator assumed that the ADR was related to inhaled corticosteroid or to montelukast.

In the nested cohort study, 195 patients were prescribed ICS monotherapy and 132 interviewed. The matched montelukast and ICS cohorts were each composed of 84 patients. With two exceptions, montelukast-treated children were similar to ICS-treated children; montelukast-initiated children had better asthma control and more first-degree relatives with sleep disorders or any predisposing conditions (online supplementary table E2). The risk of neuropsychiatric ADRs leading to drug cessation was significantly greater with montelukast than ICS (relative risk (RR) 12.0, 95% CI 1.60–90.2), a finding sustained when considering only probably related ADRs (RR 9.0, 95% CI 1.2–69.5) (table 4). No potential confounders or variables with baseline group imbalance were significantly associated with ADR. *Post hoc* analyses confirmed the higher risk of parent-reported ADR-related drug cessation when comparing children treated with montelukast as monotherapy (RR 5.9, 95 CI 1.5–22.5) or with montelukast as monotherapy or adjunct therapy to ICS or ICS/LABA (RR 7.1, 95% CI 2.1–23.4) compared to ICS monotherapy, without matching (online supplementary table E3).

In children in whom neuropsychiatric ADRs were ascertained as probably related to montelukast, cotreatment with ICS/LABA was associated with more than a five-fold increased odds (online supplementary table E4). Repeating these analyses in those in whom the ADR was probably or possibly related to montelukast, children cotreated with ICS/LABA and non-Caucasians showed a six- and three-fold increased odds, respectively (online supplementary table E5).

Discussion

In this paediatric cohort, the incidence of drug cessation due to neuropsychiatric ADRs associated with the initiation of montelukast was 16% and was robust to several conservative sensitivity analyses. When compared to the 1% risk observed with ICS monotherapy, the risk of neuropsychiatric ADR-related drug cessation was 12-fold higher with montelukast; a significant excess risk remained in all *post hoc* analyses. Reported adverse effects were ascertained as very mild to mild, with 75% occurring within 14 days of initiation and disappearing within 3.5 days of cessation.

The observed incidence of drug cessation due to neuropsychiatric ADRs associated with montelukast is markedly superior than previously reported. In a retrospective analysis of adult and paediatric placebo-controlled trials, behaviour-related ADRs occurred in 2.73% of patients treated with montelukast and were not more frequent than with placebo (odds ratio 1.12, 95% CI 0.93–1.36) [12]. ADRs lead to few (<1%) study discontinuations in placebo [12] or comparative trials [27]. However, in most trials children were generally underrepresented, and patients with significant psychiatric disorders were specifically excluded. A 2014 meta-analysis of paediatric randomised controlled trials exploring the risk of all ADRs associated with any asthma medication revealed the paucity of reported ADRs in general, and neuropsychiatric ADRs specifically [6]. Although children initiated on ICS had poorer control than those on montelukast with fewer family predisposing conditions, no evidence of confounding effect was observed when these and other variables were offered to the multivariable model.

Four main hypotheses may explain the high incidence of drug cessation due to neuropsychiatric ADR observed in our cohort compared to randomised controlled trials, namely 1) a true effect, that is, an accurate ascertainment of montelukast-related ADR in a real-life population; 2) a synergistic effect of montelukast with other asthma controllers; 3) an increased recognition of the association between

TABLE 3 Characteristics of adverse drug reactions (ADRs) with montelukast as ascertained by the adjudication committee[#]

	Patients[¶]	Severity[+]			Evolution			Causality[§]			
		Very mild	Mild	Missing[f]	Ongoing	Resolved	Missing/ unknown[f]	Probable	Possible	Improbable	Missing[f]
Sleep disturbance in general	7	2	4	1	1	5	1	6			1
Insomnia	1		1			1		1			
Nightmares	2	1	1		1	1		2			
Drowsiness	2	2			2			2			
Behaviour problems	4		4		1	3		4			
Irritability	9	4	5		2	7		8		1	
Depressive state	1		1			1		1			
Aggressiveness	8	2	5	1	2	4	2	4	3		1
Anxiety	3		2	1		1	2		2		1
Agitation/hyperactivity	6	2	3	1	1	3	2	3	2		1
Mood swings	5	2	3			4	1	3	1	1	
Headaches	5	1	4		1	4		3	2		
Stomachaches	4		4		1	3		3	1		

Data are presented as n. [#]: according to the consensus of two members of the independent adjudication committee; [¶]: number of patients reporting an adverse drug reaction in each category. 25 out of 106 patients reported one or more neuropsychiatric ADRs for a total 57 reported ADRs; [+]: very mild: an ADR that does not necessarily require drug cessation; mild: an ADR requiring drug cessation. No ADRs were assessed as moderate (requiring an antidote or medical intervention) or severe (deadly, life-threatening or requiring hospitalisation); [§]: link to montelukast assessed by the Naranjo score (9–10: definite; 5–8: probable; 1–4: possible; 0: doubtful). Note that the causality was assessed blindly, that is, the adjudicators were asked to assess the causality twice, once assuming the patient was taking inhaled corticosteroids and once that the patient was taking montelukast; [f]: four ADRs in four patients were inadvertently not submitted to the adjudication committee and are referred to as missing. Due to insufficient information, the adjudication committee was unable to confirm the evolution in a remaining four ADRs.

neuropsychiatric ADR and montelukast; and 4) lower family tolerance to ADRs. Indeed, although children with asthma and their families have a higher rate of psychiatric conditions, particularly depression and anxiety, than unaffected ones [28, 29], such conditions are often underrepresented in drug trials due to concerns about adherence [12]. Yet oral montelukast is particularly attractive to improve adherence in these patients, possibly explaining the notable proportion of children and parents with mood and behaviour disorders in our cohort. Most paediatric trials tested montelukast as monotherapy [30]; few tested it as adjunct therapy [27]. In contrast, 72% of children in our trial used montelukast as adjunct therapy to ICS or ICS/LABA [1, 3]. Furthermore, after the 2008 FDA-requested updated labels for montelukast, there was an increase in reporting of various neuropsychiatric ADRs in comparison with other ADRs for montelukast [31]. Our observations may reflect the higher recognition by parents and physicians that neuropsychiatric symptoms may be associated with montelukast, a fact largely unrecognised when most montelukast trials were conducted. Regarding the fourth hypothesis, perhaps lower parental tolerance to additional behaviour problems in families with attention deficit disorder and

TABLE 4 Incidence of drug cessation due to adverse drug reaction (ADR) associated with montelukast and inhaled corticosteroid (ICS) in the nested matched cohort

	Montelukast		ICS		Final model[#]
	Patients	Incidence (95% CI)	Patients	Incidence (95% CI)	Relative risk (95% CI)
Patients n	84		84		
ADR reported by parents	12	14 (8–25)	1	1 (0–8)	12.0 (1.6–90.2)
ADR confirmed by the adjudication committee[¶]	9	11 (6–21)	1	1 (0–8)	9.00 (1.2–69.5)

[#]: none of the potential confounders (age, sex, ethnicity, phenotype, asthma control, overall personal predisposing condition, overall predisposing condition in first-degree relatives, delay between interview and drug initiation and co-intervention with ICS) or covariates reflecting potential baseline group imbalances (atopy, child anxiety, any family predisposing conditions and sleep disorder in family) were statistically significant determinants in the multivariable logistic model; [¶]: ascertained as definitely (⩾9; n=0) or probably (5–8; n=9) related to the drug on the Naranjo causality scale. Of note, the causality assessment was identical whether the adjudicator assumed that the ADR was related to ICS or to montelukast.

anxiety is to be expected. Similar to diverging findings observed between efficacy *versus* effectiveness trials [9, 10], it is thus likely that the exclusion criteria used in clinical trials to increase internal validity may have introduced a bias in the assessment of the safety profile, resulting in lower generalisability to that observed in the real-world setting [18].

Importantly, the 12-fold higher risk of neuropsychiatric ADR-related drug cessation between children treated with montelukast *versus* ICS is notable. It remained large, at six-fold, when replicated in several *post hoc* analyses exploring the potential impact of cohort selection and co-interventions, due to a doubling of events to 2% in the larger ICS group, in the face of stable incidence in the montelukast group. The observed risk is consistent with the disproportionally high proportion (60%) of neuropsychiatric ADRs reported with montelukast compared to ICS (7%) or β_2-agonists (7%) in several pharmacovigilance databases [17, 18, 31]. In montelukast-associated ADR reports, children were markedly overrepresented compared to adults, with more reports of depressive and psychotic symptoms, sleep disorders and suicidal behaviour, suggesting increased susceptibility compared to adults [17]. In our study, where 75% of children were aged $\leqslant$8 years, the most frequent ADRs were irritability, aggressiveness and sleep disturbances, in line with pharmacovigilance reports, where the main symptoms in toddlers were sleep disorders, in those aged 2–11 years the main symptoms were anxiety and depression, and in adolescents the main symptoms were suicidal behaviour, depression and anxiety [16–18].

Most (75%) symptoms developed within 14 days of initiation, concordant with prior pharmacovigilance reports of montelukast-related ADRs occurring within a week in 80% of cases [31, 32]. Other paediatric studies reported a delay ranging from 3 days to 4 months [16, 33]. The time to ADR occurrence may be contingent on specific neuropsychiatric ADRs, with sleep disorders, agitation, nervousness and psychotic disorders developing within hours to a few days, whereas depression and suicidal behaviour occurred within months or years of treatment [17].

Most ADRs were assessed as probably related to the medication (none were definitively related). The absence of direct observation of ADR by a healthcare professional, the inability to obtain blood levels to prove toxicity and the fixed dosage preventing the assessment of a potential variation in ADR severity with dosage change, resulted in the automatic loss of three out of 12 points on the Naranjo scale, making it difficult to conclude to a "definite" imputability [20]. The adjudication committee assessed most ADRs as mild or very mild; none required intervention or hospitalisation. Neuropsychiatric ADRs regressed rapidly, usually within 3.5 days of cessation, concordant with the 48 h reported for visual hallucinations [34]. In pharmacovigilance studies, most nonsuicidal cases recovered, but the delay until remission of ADR was seldom specified [17]. Whether duration of symptoms after discontinuation depends on the type of ADR remains to be clarified.

With regards to determinants, the increased risk of neuropsychiatric ADR when montelukast was combined with ICS/LABA suggests a synergistic interaction, because ICS and ICS/LABA alone have infrequently been associated with neuropsychiatric ADRs [17]; alternatively, the poorer asthma control in children requiring adjunct therapy may be associated with greater parental anxiety and less tolerance to ADRs. Of note, the stability of the effect when repeated in patients in whom the ADR was ascertained as possibly or probably related to montelukast underscores the robustness of findings. In this sensitivity analysis, the strong association with non-Caucasian ethnicity suggests either a cultural variation in tolerance to ADR or genetic variation. Although no significant association between polymorphisms of CYP2C8*3 and *SLCO2B1* with ADRs was observed, the low prevalence of specific polymorphisms precludes firm conclusions [25]. In contrast to prior pharmacovigilance reports, sex and prior mood and behaviour problems were not significantly associated with neuropsychiatric ADRs [12, 17, 18, 33] nor was the weight-adjusted dose. Yet, given the small number of events, the power was insufficient to firmly exclude these determinants. To our knowledge, cotherapy and ethnicity have not previously been identified as potential determinants of neuropsychiatric ADRs with montelukast [17].

Limitations

We recognise that the documentation of ADRs may be subject to selection, interview, recall and awareness biases, as well as confounding. The large proportion of nonparticipants may have introduced a selection bias, with perhaps more children at risk of ADR agreeing to participate. Yet conservative sensitivity analyses that increased the denominator by assuming no drug cessation due to ADR among nonparticipants and lowered the numerator by restricting to only ADRs with higher imputability confirmed the high incidence and relative risk of ADR, attesting to the robustness of findings. Non-leading standardised parental interviews minimised the possibility of overreporting due to interview bias, with the adjudication committee minimising ascertainment bias, but reporting may have been influenced by drug labels [35]. The focus on neuropsychiatric ADRs leading to drug cessation as the primary outcome lessened the risk of recall bias and appeared as a memorable event, despite a median delay of 3 years

between drug initiation and interview. We recognise the possibility of confounding due to prior drug exposure, confounding by indication, asthma *per se* and drug adherence. As our interest was in the incidence rather than the prevalence of ADR-related drug cessation, we specifically excluded children who were already on maintenance montelukast (or ICS in the matched cohort); this served to eliminate those who had "tolerated" the medication of interest and thus prevented an underestimation of the incidence of ADRs. Children initiated on ICS were less well controlled than those on montelukast; this group difference should have lessened the observed group difference, as asthma severity is usually associated with greater anxiety and depression [29, 30]. Rescue or controller medications may cause neuropsychiatric ADRs, but the risk appears to be smaller than with montelukast [17, 36]. Most ADRs occurred within the first 2 weeks, at a time of an expected reasonably good adherence. We acknowledge that, similar to post-marketing surveillance studies, the classification of neuropsychiatric symptoms was based on patient-reported outcomes, without formal validation of symptoms or comorbidity with validated scales.

Generalisability

The fair participation rate, with a higher proportion of non-Caucasians among nonparticipants, raise the possibility of a selection bias. The findings apply primarily to children aged 1–17 years with significant previous asthma morbidity and a high prevalence of neurobehavioural comorbidities; the results may not be generalisable to other or older populations.

Interpretation

In conclusion, in our real-life practice, >10% of children initiated on montelukast developed neuropsychiatric symptoms leading to drug cessation by parents. Risk factors predisposing to neuropsychiatric ADRs remain to be clarified.

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