

Analysis of behavior-related adverse experiences in clinical trials of montelukast

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Background: Frequencies of behavior-related adverse experiences (BRAEs) in controlled clinical studies of leukotriene modifier drugs have not been summarized.

Objective: We sought to compare the frequency of BRAEs in patients receiving montelukast or placebo in a retrospective analysis of Merck clinical trial data.

Methods: An adverse experience database was constructed to include all double-blind, placebo-controlled trials of montelukast meeting prespecified criteria. BRAEs (described using the Medical Dictionary for Regulatory Activities controlled vocabulary dictionary) were prespecified to include any term in the Psychiatric Disorders System Organ Class, selected terms related to general disorders, and terms related to akathisia. Frequencies of BRAEs (overall, leading to study discontinuation, and/or serious) were summarized. Analyses estimated the odds ratios (ORs) for montelukast versus placebo based on the frequency of patients with BRAEs in each study. **Results:** In total 35 adult and 11 pediatric placebo-controlled trials were included; 11,673 patients received montelukast, 8,827 received placebo, and 4,724 received active control. The frequency of patients with 1 or more BRAEs was 2.73% and 2.27% in the montelukast and placebo groups, respectively; the OR for montelukast versus placebo was 1.12 (95% CI, 0.93-1.36). The frequency of patients with a BRAE leading to study discontinuation was 0.07% and 0.11% in the montelukast and placebo groups, respectively (OR, 0.52; 95% CI, 0.17-1.51). The frequency of patients with a BRAE considered serious was 0.03% in both treatment groups.

Conclusion: Reports of BRAEs were infrequent in clinical trials of montelukast. Those leading to study discontinuation or considered serious were rare. Frequencies were similar regardless of treatment group. (*J Allergy Clin Immunol* 2009;124:699-706.)

Key words: Montelukast, placebo, clinical trial, behavior, psychiatric, adverse experiences, asthma, allergic rhinitis

Montelukast sodium (SINGULAIR; Merck Co. Inc, Whitehouse Station, NJ) is a leukotriene receptor antagonist

Abbreviations used

AE:	Adverse experience
Akath-PT:	Akathisia-related preferred term
BRAE:	Behavior-related adverse experience
CNS:	Central nervous system
CysLT ₁ :	Cysteinyl leukotriene type 1
CysLT:	Cysteinyl leukotriene
FDA:	US Food and Drug Administration
HLGT:	High-level Group Term
MedDRA:	Medical Dictionary for Regulatory Activities
OR:	Odds ratio
OtherSelect-PT:	Other selected behavior-related preferred term
PT:	Preferred Term
Psych-SOC:	Psychiatric Disorders System Organ Class
SMQ:	Standardized MedDRA query
SOC:	System Organ Class

indicated for the chronic treatment of asthma, prevention of exercise-induced bronchoconstriction, and relief of the symptoms of allergic rhinitis. Since market availability more than 11 years ago, postmarketing experience has included reports of adverse events across a variety of organ systems, prompting acknowledgement of such reports in product labeling,¹ including reports in the psychiatric system. Given that behavioral events do occur at increased background rates in populations who receive treatment with montelukast (eg, those with asthma),²⁻⁷ examining the incidence and nature of such events in randomized placebo-controlled trials can mitigate the potential confounding effects of these increased background rates, as well as other potential confounding factors. In an early communication issued on March 27, 2008, the US Food and Drug Administration (FDA) reported on their investigation of behavior/mood changes possibly associated with use of montelukast and other leukotriene modifiers,⁸ which they updated on January 13, 2009,⁹ and June 12, 2009.¹⁰ A retrospective analysis was conducted of randomized, double-blind, placebo-controlled clinical trials of montelukast that met criteria prespecified by an FDA request to address this issue. The objective was to determine the incidence of behavior-related adverse experiences (BRAEs; defined as any adverse experiences [AEs] within 3 prespecified categories of psychiatric and other BRAEs) that were reported by study investigators in patients receiving montelukast or placebo treatment. In this analysis, few BRAEs were reported, and frequencies were similar between the montelukast and placebo groups.

METHODS

A retrospective analysis was performed of BRAEs from clinical studies of montelukast conducted by Merck. Eligible studies, per the FDA's

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request, were randomized, double-blind, placebo-controlled trials; parallel-group or crossover trials; multiple-dose administrations; inclusive of 20 or more patients per treatment group of all ages (ie, patients aged ≥ 3 months); and completed by April 25, 2008 (see Table E1 in this article's Online Repository at www.jacionline.org). A single database was constructed in which all AE terms from the studies were included, and AE terms were coded by using the controlled vocabulary Medical Dictionary for Regulatory Activities (MedDRA, version 11.1), a dictionary specifically constructed to facilitate data analyses across multiple studies. MedDRA is organized with a tree structure to help organize and describe a wide variety of AEs, including the following hierarchy: System Organ Class (SOC), the High-level Group Term (HLGT), and the Preferred Term (PT). The level of PTs provides the specific descriptive term for an individual AE by using a standardized vocabulary. A verbatim term that is reported as an AE by a study investigator is mapped (or encoded) to the closest matching PT (by personnel blinded to treatment group); this approach enables standardized analyses of AEs reported across different studies. Serious AEs were prespecified by using regulatory criteria for "serious." The Methods section of this article's Online Repository at www.jacionline.org provides detailed descriptions of the methods used.

Definition of BRAEs

By using terms and groupings per the MedDRA dictionary and as agreed by the FDA, BRAEs were prespecified as investigator-identified AEs that were in at least 1 of the following three categories:

1. Psychiatric Disorders System Organ Class (Psych-SOC) of the MedDRA (see Table E2 in this article's Online Repository at www.jacionline.org for all of the Psych-SOC terms reported in the dataset);
2. Other selected behavior-related preferred terms (OtherSelect-PTs) in the "General Disorders and Administration Site Conditions" SOC of the MedDRA comprising the following 7 terms: "asthenia," "chronic fatigue syndrome," "fatigue," "feeling abnormal," "feeling jittery," "irritability," and "malaise"; and
3. Akathisia-related preferred terms (Akath-PTs) comprising the following 8 terms: "akathisia," "extrapyramidal disorder," "hyperkinesia," "hyperkinesia neonatal," "motor dysfunction," "movement disorder," "psychomotor hyperactivity," and "restlessness."

"Any BRAE" refers to an AE in any of the 3 categories; certain analyses pooled the first and second categories.

BRAE end points

The objective was to compare the incidence of BRAEs in patients receiving montelukast or placebo in double-blind, placebo-controlled clinical trials. Analyses were prespecified, as agreed with the FDA, to examine the frequencies of patients with the following:

- any BRAE (across all 3 categories);
- BRAEs in the Psych-SOC plus OtherSelect-PTs categories;
- BRAEs in the Akath-PTs category;
- any BRAE that led to study discontinuation (across all 3 categories);
- BRAEs that led to study discontinuation in the Psych-SOC plus OtherSelect-PTs categories; and
- BRAEs that led to study discontinuation in the Akath-PTs category.

Statistical methods

The prespecified primary analysis consisted of estimating the odds ratios (ORs) based on the frequency of patients with BRAEs to compare patient numbers in the montelukast and placebo groups for each of the 6 prespecified end points. The OR analysis used an exact method¹¹ to estimate a common OR (across the trials) incorporating event rates from the individual trials. This primary analysis was also supported by various sensitivity analyses.

One of the sensitivity analyses assessed the incidence of BRAEs over time: the number of patients with any BRAE was presented by using a categorized

distribution showing the total number of patients by treatment group based on treatment duration: less than 1 week, 1 to less than 2 weeks, 2 to less than 4 weeks, 4 to less than 12 weeks, and 12 weeks or longer. As a time-to-event analysis, BRAEs per 1,000 patient-weeks were calculated in each of these time intervals. A *post-hoc* sensitivity analysis was performed to describe and compare the distributions of the numbers of patients reporting 0, 1, 2, or more than 2 BRAEs; treatment-group comparisons used an exact Wilcoxon test stratified by trial. Other sensitivity analyses are described in the Methods section of this article's Online Repository.

Subgroup analyses were performed on the 3 BRAE end points of any BRAE, BRAEs in the Psych-SOC plus OtherSelect-PTs categories, and BRAEs in the Akath-PTs category for the following variables: age, sex, race, trial, location, and trial indication. The ORs and 95% CIs were estimated in each of these subgroups (provided the number of patients with BRAEs in a subgroup was ≥ 5) by using crude ORs.

RESULTS

Studies included in BRAE analysis

The evaluation included 46 randomized, double-blind, placebo-controlled adult (age ≥ 15 years; 35 trials) and pediatric (age 3 months to 14 years; 11 trials) studies; some studies also had active-control arms (see Table E1). Forty-four were parallel-group studies, and 2 were crossover studies. Thirty studies were on asthma, 12 were on seasonal allergic rhinitis, 2 were on perennial allergic rhinitis, 1 was on respiratory syncytial virus-induced bronchiolitis, and 1 was on migraine headache. Across the 25,224 patients in these studies, 11,673 received montelukast, 8,827 received placebo, and 4,724 received active control. The total follow-up times were 1,854 patient-years for montelukast, 1,395 patient-years for placebo, and 516 patient-years for active control. The times exposed to montelukast versus placebo were proportionate to the patient numbers; hence the crude incidence rates reported in these groups will approximate the true incidence rates.

Patient demographics

Table I summarizes the demographics of patients by treatment group. Approximately 26% of the patients were aged less than 18 years, and 2% were aged 65 years or greater. In total, 56% of the patients were female, 68% were white, and 73% participated in a trial in North America. For the 20,500 patients assigned to montelukast or placebo, there were no statistically significant differences between the montelukast and placebo groups in patients' baseline characteristics. Patients were mainly enrolled in asthma (44%) and seasonal allergic rhinitis (38%) trials. The majority of patients in the active-control group were enrolled in seasonal allergic rhinitis studies.

BRAEs

The frequency of patients with at least 1 BRAE was 2.73% and 2.27% in the montelukast and placebo groups, respectively. The OR for montelukast versus placebo was 1.12 (95% CI, 0.93-1.36). The frequency of patients with at least 1 AE in the pooled Psych-SOC plus OtherSelect-PTs categories was 2.56% and 2.12% in the montelukast and placebo groups, respectively. The frequency of patients with at least 1 AE in the Akath-PTs category was 0.23% and 0.20% in the montelukast and placebo groups, respectively. The ORs for each end point have CIs that include 1.00 (Fig 1). The OR comparing the montelukast group

TABLE I. Patient demographics

	Montelukast (n = 11,673), no. (%)	Placebo (n = 8,827), no. (%)	Active control (n = 4,724), no. (%)	Total (n = 25,224), no. (%)
Age category				
<6 y	1,718 (14.7)	1,017 (11.5)	0 (0.0)	2,735 (10.8)
6–11 y	1,029 (8.8)	890 (10.1)	119 (2.5)	2,038 (8.1)
12–17 y	856 (7.3)	768 (8.7)	300 (6.4)	1,924 (7.6)
18–30 y	2,844 (24.4)	2,086 (23.6)	1,464 (31.0)	6,394 (25.3)
31–64 y	4,978 (42.6)	3,893 (44.1)	2,724 (57.7)	11,595 (46.0)
≥65 y	245 (2.1)	172 (1.9)	117 (2.5)	534 (2.1)
Missing information	3 (0.0)	1 (0.0)	0 (0.0)	4 (0.0)
Sex				
Female	6,381 (54.7)	4,924 (55.8)	2,877 (60.9)	14,182 (56.2)
Male	5,291 (45.3)	3,902 (44.2)	1,847 (39.1)	11,040 (43.8)
Missing information	1 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)
Race				
White	7,588 (65.0)	5,926 (67.1)	3,654 (77.3)	17,168 (68.1)
Black	798 (6.8)	648 (7.3)	266 (5.6)	1,712 (6.8)
Hispanic	1,367 (11.7)	918 (10.4)	613 (13.0)	2,898 (11.5)
Asian	1,301 (11.1)	775 (8.8)	132 (2.8)	2,208 (8.8)
Other	186 (1.6)	132 (1.5)	59 (1.2)	377 (1.5)
Missing information	433 (3.7)	428 (4.8)	0 (0.0)	861 (3.4)
Location of trial				
North America	8,028 (68.8)	6,449 (73.1)	3,972 (84.1)	18,449 (73.1)
Non–North America	3,645 (31.2)	2,378 (26.9)	752 (15.9)	6,775 (26.9)

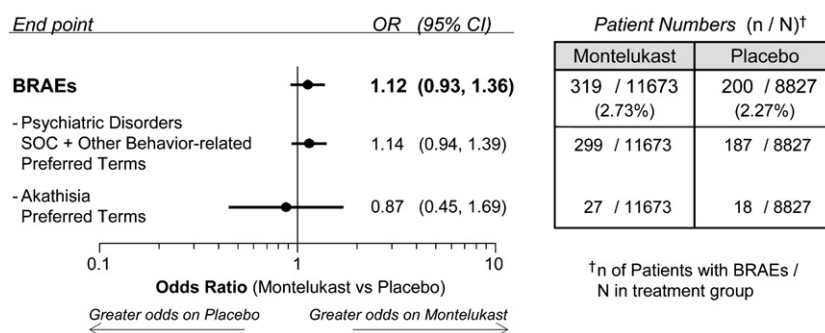


FIG 1. Patients with BRAEs. Plot showing the ORs and 95% CIs for all BRAEs, Psych-SOC plus OtherSelectPTs, and Akath-PTs.

with the placebo group for Akath-PTs was 0.87; the crude OR (ie, pooling all patients as if data were obtained in a single trial) was 1.13.

Overall, the reporting of individual BRAEs was infrequent in each treatment group. The most commonly reported BRAE in both the montelukast and placebo groups was insomnia. Frequencies of individual BRAEs ranged up to 0.70% in the montelukast group and up to 0.52% in the placebo group (ie, the frequency of insomnia reported in each group); all other BRAEs in these treatment groups occurred at an incidence no greater than 0.35%. MedDRA HLGTS provide a higher-level view of the BRAE reports. Of the 16 HLGTS that had reports within the Psych-SOC, only 4 HLGTS (each having a frequency of $\geq 0.10\%$ in ≥ 1 treatment group) contained the majority of these reports (Table II). The individual BRAEs that occurred with a frequency of 0.10% or greater in any treatment group are shown in Table III. As shown in both Tables II and III, the frequencies reported were low, and for many terms, frequencies were similar among the treatment groups. For other terms, there was variation in which group

(montelukast, placebo, or active control) showed slightly higher frequencies. A complete tabular presentation of all the BRAEs reported in the 46 studies is shown in Table E2. Because of its clinical interest, a summary of the depression AEs, which were reported in 30 of 25,224 patients in the study database, is shown in Table E3 (available in this article's Online Repository at www.jacionline.org); most of the 18 patients in the montelukast group reported depression of mild-to-moderate intensity and did not receive other therapy for the depression, which is similar to findings for the other treatment groups, and only 2 of the 18 patients discontinued the study drug because of the depression AE.

The time-to-event sensitivity analysis showed that the BRAEs per patient-week of drug exposure were generally similar between the montelukast and placebo groups for each of the time intervals and that they were more common early after treatment initiation for both groups (Table IV). The percentages of patients with 0, 1, 2, and more than 2 BRAEs were 97.3%, 2.2%, 0.4%, and 0.1% and 97.7%, 2.0%, 0.2%, and 0.1% in the montelukast and placebo groups, respectively. Results of the sensitivity analyses were

TABLE II. Patients with BRAE terms listed by HLGTS within the Psych-SOC

Reports listed under HLGTS	Montelukast (n = 11,673), no. (%)		Placebo (n = 8,827), no. (%)		Active control (n = 4,724), no. (%)	
Total across all HLGTS in the Psych-SOC	174	1.49	117	1.33	66	1.40
Anxiety disorders and symptoms	30	0.26	22	0.25	14	0.30
Changes in physical activity	2	0.02	1	0.01	0	0.00
Cognitive and attention disorders and disturbances	1	0.01	3	0.03	2	0.04
Deliria (including confusion)	0	0.00	1	0.01	0	0.00
Depressed mood disorders and disturbances	19	0.16	8	0.09	4	0.08
Disturbances in thinking and perception	1	0.01	0	0.00	0	0.00
Eating disorders and disturbances	0	0.00	1	0.01	1	0.02
Impulse control disorders NEC	0	0.00	2	0.02	0	0.00
Manic and bipolar mood disorders and disturbances	0	0.00	1	0.01	0	0.00
Mood disorders and disturbances NEC	9	0.08	11	0.12	1	0.02
Personality disorders and disturbances in behavior	3	0.03	5	0.06	1	0.02
Psychiatric and behavioral symptoms NEC	4	0.03	2	0.02	0	0.00
Schizophrenia and other psychotic disorders	1	0.01	0	0.00	0	0.00
Sexual dysfunctions, disturbances, and gender identity disorders	3*	0.03	1	0.01	2	0.04
Sleep disorders and disturbances	112	0.96	61	0.69	45	0.95
Suicidal and self-injurious behaviors NEC	0	0.00	1†	0.01	0	0.00

Boldface italic text shows the percentages for the 4 HLGTS containing reports with a frequency of 0.10% or greater in any treatment group. Although a patient might have had 2 or more AEs, the patient is counted only once with a category. The same patient can appear in different categories.

NEC, Not elsewhere classified.

*For 1 patient, the AE verbatim term was “dripping of urine” after surgery (orchiopexy) in a 2-year-old patient.

†The AE verbatim term was “bite in mouth” in a 4-year-old patient.

TABLE III. Patients with BRAEs listed by preferred terms reported with a frequency of 0.10% or greater in any treatment group*

Individual BRAEs: PTs	Montelukast (n = 11,673), no. (%)		Placebo (n = 8,827), no. (%)		Active control (n = 4,724), no. (%)	
Anxiety	16	(0.14)	11	(0.12)	5	(0.11)
Asthenia	37	(0.32)	25	(0.28)	44	(0.93)
Depression	18	(0.15)	8	(0.09)	4	(0.08)
Fatigue	41	(0.35)	22	(0.25)	7	(0.15)
Insomnia	82	(0.70)	46	(0.52)	39	(0.83)
Irritability	32	(0.27)	19	(0.22)	6	(0.13)
Malaise	25	(0.21)	11	(0.12)	6	(0.13)
Nervousness	8	(0.07)	5	(0.06)	7	(0.15)
Nightmare	14	(0.12)	4	(0.05)	5	(0.11)
Psychomotor hyperactivity	7	(0.06)	9	(0.10)	0	(0.00)
Restlessness	13	(0.11)	7	(0.08)	0	(0.00)
Sleep disorder	14	(0.12)	6	(0.07)	2	(0.04)

Although a patient might have had 2 or more AEs, the patient is counted only once with a category. The same patient might appear in different categories.

*The full list of behavior-related adverse events can be found in Table E2.

generally supportive of the primary analyses (data are shown in the Results section of this article's Online Repository at www.jacionline.org).

Analysis of the frequency of BRAEs by age subgroup (Table V) showed the age group with the highest frequency of BRAEs overall was less than 6 years. The ORs comparing montelukast versus placebo were numerically higher in patients in the 12- to 17-year age range and in patients aged 65 years and older; however, the numbers of patients with BRAEs in each of these 2 subgroups were relatively small to draw firm conclusions. Results of the other subgroup analyses are shown in Table E4 (available in this article's Online Repository at www.jacionline.org).

Discontinuations because of BRAEs

The percentages of patients who discontinued because of an AE in any of the behavior-related categories were small and were

numerically lower, with an OR of 0.52 (95% CI, 0.17-1.51; montelukast versus placebo) for any BRAE and Psych-SOC plus OtherSelect-PTs (Table VI). Time to discontinuation was similar for the 2 groups (Fig E1). A summary of the patients with BRAEs leading to study discontinuation is provided in Table VII.

BRAEs considered serious AEs

Serious BRAEs were reported for 6 patients. Three were in the montelukast group (anxiety disorder, depression, and schizoaffective disorder), resulting in a frequency of 0.03%, and all were in adults. Three were in the placebo group (bipolar disorder, irritability, and mood swings), resulting in a frequency of 0.03%, and all were in children. The 3 events in the montelukast group were considered by the investigator as probably not related to study treatment, and 2 of these patients (with depression and schizoaffective disorder, respectively)

TABLE IV. Patients reporting AEs per time of exposure to treatment (time-to-event sensitivity analysis)

Weeks	Montelukast			Placebo		
	AEs	Patients exposed	AEs per patient-time*	AEs	Patients exposed	AEs per patient-time
<1	101	11,595	8.71	53	8,763	6.05
1-2	59	11,059	2.67	41	8,319	2.46
2-4	62	8,899	3.48	43	6,573	3.27
4-12	77	4,866	1.98	48	3,480	1.72
≥12	20	1,291	0.39	15	887	0.42

The number of patients is estimated at the midpoint of the interval.

*AEs per patient-time is expressed as the hazard, which is calculated as AEs reported per 1,000 patient-weeks.

TABLE V. Patients with BRAEs by age subgroups

Age	Montelukast		Placebo		Montelukast vs placebo OR (95% CI)
	n/N	Percent	n/N	Percent	
<6 y	74/1,718	4.31	51/1,017	5.01	0.85 (0.58-1.25)
6-11 y	21/1,029	2.04	13/890	1.46	1.41 (0.67-3.07)
12-17 y	12/856	1.40	5/768	0.65	2.17 (0.71-7.89)
18-30 y	67/2,844	2.36	40/2,086	1.92	1.23 (0.82-1.88)
31-64 y	139/4,978	2.79	89/3,893	2.29	1.23 (0.93-1.63)
≥65 y	6/245	2.45	2/172	1.16	2.13 (0.38-21.83)

discontinued the study. In the placebo group bipolar disorder was not thought to be related to study therapy, and the patient discontinued from the study. The other 2 events were thought to be possibly related to study therapy, and the patient with mood swings discontinued from the study. Case narratives for the patients with serious BRAEs are provided in Table E5 (available in this article's Online Repository at www.jacionline.org).

DISCUSSION

As part of their investigations of potential safety signals in various classes of marketed medications,¹² the FDA requested that companies that market drugs active in the leukotriene pathway examine their clinical trial data to determine the frequency of reports of BRAEs in active-drug and placebo groups.^{8,9} Analyses of data from montelukast clinical trials performed by Merck, as presented in this article, showed that reports of BRAEs were infrequent in any treatment group, and the frequency was similar between the montelukast and placebo groups. When reported, these experiences were relatively mild (because they only rarely led to study discontinuations) and were generally without important clinical sequelae (because they only rarely met the prespecified definition of a serious AE).

Assessing data in controlled clinical trials, especially with a placebo control group, is particularly important because behavior and mood disorders are often comorbid with asthma, as with other chronic diseases.² A number of studies have demonstrated a higher prevalence of psychiatric disorders in patients with asthma compared with that seen in the general population. Data generated from the World Mental Health Survey showed that, after adjusting for age and sex, those adults with asthma were more likely to have depressive and anxiety disorders (depression, OR, 1.6 [95% CI, 1.4-1.8]; anxiety, OR, 1.5 [95% CI, 1.4-1.7]) than those in the general population.³ Similar associations were found in 2 separate analyses of the Behavioral Risk Factor Surveillance System in the United States,^{4,5} including an analysis of data from 355,710 subjects who participated in the 2006 Behavioral Risk Factor

Surveillance System survey, in which the prevalence of asthma was 6.2% among respondents reporting no mental health issues, 8.7% among those reporting 1 to 7 days of poor mental health, and increasing to 10.0%, 12.8%, and 21.6% for those reporting 8 to 14 days, 15 to 21 days, and 22 or more days of poor mental health, respectively.⁴ Studies specific to children and youths have also shown these patterns. Data from the National Survey of Children's Health showed significantly higher ORs for developmental or behavioral problems in children with asthma and more so with greater asthma severity (eg, for depression/anxiety: mild asthma, OR, 1.82 [99% CI, 1.43-2.33]; severe asthma, OR, 4.47 [99% CI, 2.27-8.80]).⁶ Similarly, a telephone interview of a population of youths (11-17 years) enrolled in a health maintenance organization found that those with asthma were nearly twice as likely to have comorbid *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, anxiety disorders, depressive disorders, or both than youths without asthma.⁷ These associations with behavior disorders in patients with asthma might also be present in patients with allergic rhinitis. Postolache et al¹³ found a positive association between changes in allergy symptoms and changes in depression scores. Others also have found an association between atopy and depression,¹⁴⁻¹⁶ particularly in women.¹⁷⁻¹⁹

Based on the known association between asthma and mood and anxiety disorders, it could be expected that BRAEs would be reported in postmarketing safety surveillance of any asthma medication, including montelukast. A number of asthma medications list behavioral AEs in the postmarketing section of their prescribing information.²⁰⁻²² Similarly, montelukast's prescribing information has been updated periodically since marketing approval to reflect postmarketing reports of various behavior and mood-related events.¹ Postmarketing surveillance is an important mechanism for monitoring drug safety after product approval (and for reporting this experience in product labeling) because it has the ability to encompass a treated population that is broader than the study populations enrolled in clinical trials.

Interpretation of postmarketing experience with any medication, however, poses challenges. Because the medication use is

TABLE VI. Patients with BRAEs leading to study discontinuation expressed as ORs and 95% CIs

Treatment	n/N	Percent	Montelukast vs placebo	
			OR*	95% CI
All BRAEs			0.52	0.17-1.51
Montelukast	8/11,673	0.07		
Placebo	10†/8,827	0.11		
Active control	2/4,724	0.04		
Psych-SOC + OtherSelect-PTs			0.52	0.17-1.51
Montelukast	8/11,673	0.07		
Placebo	10†/8,827	0.11		
Active control	2/4,724	0.04		
Akath-PTs			0.00	0.00-38.53
Montelukast	0/11,673	0.00		
Placebo	1†/8,827	0.01		
Active control	0/4,724	0.00		

Psych-SOC + OtherSelect-PTs, preferred terms in the Psychiatric System Organ Class plus OtherSelect-PTs.

*OR analysis using the exact method stratified by trial.

†One patient discontinued because of AEs of both sleep disorder (in Psych-SOC) and restlessness (in Akath-PTs).

open label and uncontrolled (and the reports are usually anecdotal), the reporting of a postmarketing AE does not necessarily lead to a conclusion that the event was caused by the medication of interest. Also, the number of patients who actually have been treated with a broadly marketed medication cannot be determined accurately. Furthermore, it is not known how many patients possibly experienced the AE overall, other than those spontaneous reports that are received, and these AEs are generally acknowledged to be underreported.^{23,24} It does appear that this underreporting can be modulated by greater public awareness. For instance, after the Web site posting of the FDA's Early Communication in March 2008⁸ and associated lay-media coverage, there was a prompt increase in the number of postmarketing reports for montelukast received directly by the FDA through the MedWatch system, as well as reports received directly by Merck (that Merck then submits to the FDA). This spike in reporting, which was likely stimulated by greater awareness among the general public and health care providers, was captured in the FDA Adverse Event Reporting System database²⁵ and has been reported by others.²⁴ Thus, related to the generally uncontrolled nature of postmarketing reporting, information from postmarketing surveillance must be interpreted with care and expertise. Nevertheless, despite challenges in collection and interpretation of the data, information from postmarketing surveillance remains an important aspect of drug safety monitoring, and it is prudent for prescribers to be alert for events consistent with behavior-related changes and to carefully evaluate the risks and benefits of continuing treatment if such events occur, which is consistent with the FDA's updated information on leukotriene modifiers.¹⁰

Because it is not possible to estimate reliably the frequency of AEs reported in postmarketing experience (because of the inherent limitations in these data), it can be instructive to examine the reporting frequencies of AEs in controlled clinical trial data once a possible "signal" has been noted in postmarketing experience, whether reported to the manufacturer (and then acknowledged in product labeling), reported to the FDA (and then available through the Adverse Event Reporting System database), or reported in other databases.²⁶ Controlled clinical trials can provide insight regarding whether the use of a drug might be causally related to certain AEs.

In assessing the montelukast clinical trial data for AE reports related to behavior, we found that reports of BRAEs were infrequent and generally mild. Study discontinuations because of BRAEs were rare (and numerically more were reported in the placebo group), and even the BRAEs that led to discontinuation from the study were generally reported as mild to moderate in intensity. Serious BRAEs were even more rare (and similar to that seen with placebo). Subgroup analyses by age also showed no clear association between montelukast and BRAEs by age because the CIs for ORs versus placebo for each age group included 1.00.

As noted above, interpretation of postmarketing experience poses challenges because of some inherent limitations in postmarketing data. Interpretation of psychiatric AEs reported during clinical trials, especially nonpsychiatric trials, also poses challenges, particularly because of problems in ascertainment. Understanding what a reporter (typically not a psychiatrist or other mental health professional) was describing in his or her use of a particular term, which often has both informal, commonly understood meanings and more precise medical definitions, is difficult. These studies of montelukast were generally designed as clinical trials of asthma and allergic rhinitis and were not designed to determine the incidence of BRAEs with montelukast treatment. By design, the AEs in these trials were captured generally as any unfavorable and unintended change in structure, function, or chemistry of the body, as reported by the patient/caregiver, ascertained by the investigator, or both and temporally associated with the use of active study drug or placebo. Consistent with the absence of preclinical data or emerging clinical trial data to suggest a risk of BRAEs with montelukast, these trials were designed without specific prompting to report such AEs and without providing criteria to investigators for reporting BRAEs as psychiatric diagnoses. For example, a report of "depression" as an AE does not mean it meets the diagnostic criteria for a depressive disorder (eg, consistent with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria). In fact, the individual BRAEs reported in the dataset appear more consistent with reporting of isolated psychiatric symptoms, noting also that very few patients in either treatment group had more than 1 BRAE.

This presentation of BRAEs as isolated symptoms, along with the generally infrequent and mild nature of the BRAEs, supports that these events, when reported, were not associated with an important overall effect of montelukast on emotional well-being. Consistent with these results, Holbrook and Harik-Khan²⁷ reported that their assessment of measures of quality of life that included scales of emotional well-being from 3 montelukast clinical trials (which included 1,469 patients and were conducted by the American Lung Association Asthma Clinical Research Centers) showed no evidence of any deterioration of emotional well-being in either adults or children taking montelukast. There were no AE reports of psychiatric disturbances, depressive episodes, or suicide with montelukast use in any of the 3 trials.²⁸

In the preclinical and clinical literature, there is a paucity of data describing a role for cysteinyl leukotrienes (CysLTs) or the cysteinyl leukotriene type 1 (CysLT₁) receptor in the central nervous system (CNS) related to behavior. A recently published literature review surveyed possible biologic pathways that might be involved in common between asthma and depressive disorders; evidence was cited for several drug mechanisms, including those involving glucocorticoid signaling, but no evidence was cited for mechanisms directly associated with CysLTs.²⁸ Montelukast's mechanism of action is through selective antagonism of the

TABLE VII. Listing of patients with BRAEs leading to study discontinuations

AE		Onset RelDay*	AE duration	Intensity	Serious†
Montelukast treatment group, n/N = 8/11,673 (0.07%)					
37-y-old woman	Anxiety	54	21 d	Mild (17 d), Moderate (4 d)	No
46-y-old man	Depression	23	23 d	Mild (6 d), Moderate (7 d), Mild (10 d)	No
45-y-old woman	Depression	2	2 d	Severe	Yes
7-y-old girl	Insomnia	7	10 d	Mild	No
6-mo-old girl	Irritability	11	4 d¶	Moderate	No
36-y-old woman	Paranoia	1	2 d	Severe	No
32-y-old man	Schizoaffective disorder	22	23 d	NA	Yes
8-y-old girl	Sleep disorder	1	36 d¶	Moderate	No
Placebo treatment group, n/N = 10/8,827 (0.11%)					
3-y-old boy	Abnormal behavior	9	24 d	Mild	No
4-y-old boy	Bipolar disorder	9	56 d	Moderate	Yes
59-y-old woman	Depression	4	26 d	Moderate	No
3-y-old girl	Disturbance in social behavior	117	6 d	Mild	No
25-y-old man	Insomnia	−10	36 d	Moderate	No
42-y-old woman	Insomnia	3	18 d	Moderate	No
43-y-old woman	Mood swings	32	29 d	Severe	No
4-y-old girl	Mood swings	4	18 d	Mild	Yes
6-mo-old boy	Sleep disorder	11	25 d	NA	No
42-y-old woman	Sleep disorder; Restlessness	16; 16	8 d¶; 13 d	Moderate; Moderate	No; No
Active treatment‡ group, n/N = 2/4,724 (0.04%)					
44-y-old man	Insomnia	1	10 d	Moderate	No
39-y-old woman	Nervousness	3	3 d	Moderate	No

NA, Not available.

*RelDay is defined as the day of onset relative to the first day of randomized therapy.

†Defined by using regulatory criteria (see the [Methods](#) section in this article's Online Repository); patients with serious AEs are described in [Table E5](#).

‡Both patients received loratadine, 10 mg once daily.

¶AE stop date was missing or unknown. To calculate AE duration, a stop date was assigned equal to the last day of study therapy in the treatment period.

CysLT₁ receptor²⁹ (although it cannot be excluded that potential effects might occur as a result of off-target activity). In animal studies, intravenous radiolabeled montelukast showed minimal ability to cross the blood-brain barrier.¹ Expression of the CysLT₁ receptor is also relatively restricted. In Northern blot analysis of normal human tissues, expression of the CysLT₁ receptor was highest in spleen and peripheral blood leukocytes (which is consistent with its role in mediating inflammation), lower in other tissues (eg, the lung), and minimal in the brain.³⁰ In some animal models, CysLT₁ receptor expression can be upregulated in the CNS after ischemic brain injury³¹; other data in rodent models have suggested that a putative role for CysLTs could relate to an inflammatory response to CNS injury, against which inhibition of the leukotriene pathway might be protective.^{32,33} The only published animal model data for leukotriene pathway involvement in behavior is associated with the 5-lipoxygenase enzyme, which is critical in forming leukotriene B₄ and the CysLTs³⁴: either genetic knockout or pharmacologic inhibition of 5-lipoxygenase reduced the anxiety-related behavior of mice.^{35,36} This enzyme has been reported to be upregulated in postmortem studies of brains obtained after suicide.³⁷

Several factors limit the interpretation of the BRAE analyses presented here. One limitation is that AEs were gathered by asking general, open-ended questions; this accepted methodology, by not actively soliciting specific AE information on some preselected symptoms, could have allowed underreporting of some events. For instance, patients who do not connect the study drug with an experience might not report that experience, or patients who are embarrassed or ashamed of a certain symptom

might not offer information unless questioned specifically. Thus we cannot conclude definitively that all BRAEs were reported, and we cannot exclude definitively that BRAEs were more frequent in one of the treatment groups. However, it seems likely that if use of unsolicited reports has obscured an effect, it would probably be a relatively modest one because underreporting is likely more relevant to events that were relatively less troubling or impactful.

Another limitation relates to the fact that montelukast is more efficacious than placebo as a treatment for asthma and allergic rhinitis. Conceivably, drug-related BRAEs could occur only to be counterbalanced by improvements in mood, anxiety, or other behavioral symptoms as the primary respiratory disorder improved with montelukast. The overall rarity of events in either group, however, suggests that such effects either did not occur or had only minimal effects. Also, these studies, which were mostly clinical trials of asthma and allergic rhinitis, were generally of short duration (providing <2 months of follow-up per patient, on average, in the dataset); therefore conclusions related to long-term use are limited. Finally, patients in these trials were selected based on specific entry criteria that might affect the generalizability of these findings; for example, patients with clinically significant psychiatric illnesses at baseline were excluded because of concerns about the risk for noncompliance with study procedures. However, these criteria might also have excluded a group of patients at higher risk for BRAEs; hence these clinical trial data do not address questions about montelukast specifically in such high-risk populations.

In summary, this large database of montelukast clinical trials provides systematically collected data on BRAEs reported by study investigators, with AE terms for analysis that were prespecified (and agreed to by the FDA). In the face of the increased incidence of psychiatric disorders in patients with asthma and allergic disease compared with the general population, availability of controlled data leverages the advantages of a randomized trial to address known and unknown confounding factors and provides additional information after the postmarketing observations that have been made regarding montelukast and behavior and mood changes. Although the trials were not prospectively designed to evaluate BRAEs, results show that BRAEs were reported infrequently in these controlled clinical trials and, when reported, were relatively mild and without important/serious clinical sequelae. Prospectively specified analyses showed that BRAEs leading to study discontinuation were rare and frequencies were similar, regardless of treatment group.

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Clinical implications: Although these studies were not designed specifically to examine BRAEs, these events were infrequent with montelukast in Merck clinical trials and were similar between the montelukast and placebo groups.

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METHODS

A retrospective analysis of BRAEs from the montelukast program was performed on Merck randomized, double-blind, placebo-controlled, parallel-group, multiple-dose studies meeting criteria specified by the FDA and completed by April 25, 2008 (Table E1). The selected studies, per the FDA's request, had at least 20 patients per treatment group. Because BRAEs could potentially occur in patients of essentially all ages, it was considered appropriate (and prespecified) to include studies with patients as young as age 3 months. Also included were completed placebo-controlled, multiple-dose crossover studies that enrolled patients aged 3 months or older with at least 20 patients per treatment group for the first active treatment period after randomization (Table E1). All studies were placebo controlled; some studies also had a positive control arm (or arms). Active controls in asthma studies included inhaled/nebulized corticosteroids, salmeterol, and inhaled/nebulized cromolyn. Active controls in allergic rhinitis studies included loratadine, montelukast plus loratadine, and cetirizine. The active control in the migraine study was rofecoxib.

Objectives

The primary objective was to compare the incidence of BRAEs in patients receiving montelukast versus those receiving placebo in double-blind, placebo-controlled clinical trials.

Identification of BRAEs used for the database query

All AE terms from the montelukast studies were re-encoded to the MedDRA dictionary (version 11.1). MedDRA is a "controlled vocabulary" dictionary that provides a single standardized vernacular for description of AEs. MedDRA was developed by the International Conference on Harmonization as a single pragmatic and medically valid dictionary for use worldwide by regulatory authorities and the regulated biopharmaceutical industry (<http://www.meddrasso.com/MSSOWeb/index.htm>).

- To help organize and describe a wide variety of AEs, the MedDRA is organized with a tree structure and different levels of hierarchies. These hierarchies include the SOC, the HLGT, the High-Level Term, and the PT.
- The level of PT provides the specific descriptive term for an individual AE using a standardized vocabulary. A verbatim term that is reported as an AE by a study investigator is mapped (or encoded) to the closest matching PT; this enables standardized analyses of AEs across different studies reported across different countries. Coding was done by trained experts using validated methods in accordance with the International Conference on Harmonization's "Points to consider for MedDRA coding." More specifically, the personnel responsible for the MedDRA mapping were trained on their use of the encoding guidance documents (which are based on the International Conference on Harmonization's guidance). For creation of this dataset, Merck required that all manual-encoding personnel be certified at a 98% confidence level for accuracy and consistency in following the standard operating procedure for manual encoding.
- The MedDRA dictionary also provides a method to assess for medically related AEs. A standardized MedDRA query (SMQ) is a query that is applied against an AE database of MedDRA-encoded terms. An SMQ is defined by a set of AE dictionary terms that fit within a specified medical/safety concept of interest; the same AE dictionary terms can be found in different SMQs if the SMQs are related to similar medical concepts.

The BRAEs analyzed (as prespecified, in agreement with the FDA) were PTs in at least one of the following 3 categories:

1. Psych-SOC of the MedDRA: All PTs in the Psych-SOC of the MedDRA dictionary were searched in the dataset. All of the 53 PTs that were actually reported in the dataset are presented in Table E2.
2. OtherSelect-PTs prospectively defined from the General Disorders and Administration Site Conditions SOC: 7 PTs were searched—"asthenia," "chronic fatigue syndrome," "fatigue," "feeling abnormal," "feeling jittery," "irritability," and "malaise."
3. PTs included among the Akath-PTs: 8 PTs were searched—"akathisia," "extrapyramidal disorder," "hyperkinesia," "hyperkinesia neonatal,"

"motor dysfunction," "movement disorder," "psychomotor hyperactivity," and "restlessness."

As specified by the FDA, only BRAEs that occurred during the double-blind phase of treatment or within 1 day of stopping randomized treatment in parallel-group studies and during the first double-blind active treatment period or within 1 day of stopping randomized treatment in crossover studies were included in the data analysis.

BRAE end points

A full statistical analysis plan was written and agreed on with the FDA before the construction of the AE database for analysis was completed. The analyses were thus prespecified to examine the frequencies of patients with the following:

- any BRAE (defined as PTs reported in ≥ 1 of the 3 categories);
- BRAEs in the Psych-SOC plus OtherSelect-PTs (defined as PTs in the initial 2 categories pooled);
- BRAEs in the Akath-PTs (defined as PTs in the Akathisia SMQ);
- any BRAE that led to study discontinuation;
- BRAEs in the Psych-SOC plus OtherSelect-PTs that led to study discontinuation; and
- BRAEs in the Akath-PTs that led to study discontinuation.

Although a patient might have had BRAEs that exist in more than 1 category (eg, Psych-SOC plus OtherSelect-PTs and Akath-PTs), the patient is counted only once within a category (eg, any BRAE). The same patient might appear in different categories. The preferred term "restlessness" is in both the Psych-SOC and the Akath-PTs. Patients with the AE restlessness were counted in the Akath-PTs category and not in the Psych-SOC category to avoid reporting duplicate records.

BRAEs considered serious AEs

Serious AEs were determined by using a definition of serious based on regulatory criteria. A serious AE is any AE that results in death; is life-threatening (places the patient, in the view of the investigator, at immediate risk of death from the experience as it occurred); results in a persistent or significant disability/incapacity; results in or prolongs an existing inpatient hospitalization; is a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis); is a cancer; or is an overdose (whether accidental or intentional). Other important medical events that might not result in death, not be life-threatening, or not require hospitalization can be considered serious AEs when, based on appropriate medical judgment, the event might jeopardize the patient and might require medical or surgical intervention to prevent one of the outcomes listed previously.

Statistical methods

Following the prespecified statistical analysis plan, all analyses were performed with an all-patients-as-treated population, which includes all patients who received at least 1 dose of active treatment in the period of interest. The prespecified primary analysis consisted of estimating the OR for each AE end point for patients in the montelukast group compared with patients in the placebo group based on the frequency of patients with BRAEs. An exact analysis across the individual trials was performed; the Zelen test was used to test the assumption of a common OR across the trials for the 6 end points.

Sensitivity analyses were performed for the 3 BRAE end points of any BRAE, BRAEs in the Psych-SOC plus OtherSelect-PTs categories, and BRAEs in the AkathPTs category. No sensitivity analyses were performed for BRAEs that led to study discontinuation because few BRAEs were detected.

Sensitivity analyses were as follows:

- Incidence of primary end point over time: To explore the incidence of the primary end point over time since the start of therapy, the number of patients with any BRAE was presented by using a categorized distribution showing the total number of patients by treatment group based

on treatment duration (using the life-table approach) in disjointed time intervals: less than 1 week, 1 to less than 2 weeks, 2 to less than 4 weeks, 4 to less than 12 weeks, and at least 12 weeks (because of the low number of AEs observed after 12 weeks of treatment, this interval was not further divided). As a time-to-event analysis, the hazard was calculated in each of these time intervals and expressed as BRAEs per 1000 patient-weeks.

- Cochran-Mantel-Haenszel risk difference: The stratified analysis of risk difference (Cochran-Mantel-Haenszel risk difference and associated CI) is a weighted average of the individual-trial risk differences, with the weights being proportional to the sample size of the trial. This analysis was performed to incorporate the influence of trials that had zero BRAEs in the 2 treatment groups because these trials cannot be reflected in an OR analysis using the exact method.
- An exact method based on patient-years of therapy: This analysis was performed similarly to the primary method but based on person-time (rather than based on patients as the unit of analysis) to examine possible consequences of differences in treatment duration between treatment groups. The BRAEs in each study were assumed to follow a Poisson distribution.
- Distribution of patients with more than 1 BRAE: A *post-hoc* analysis comparing the distribution of patients with 0, 1, 2, and more than 2 BRAEs in the montelukast and placebo groups was performed by using an exact Wilcoxon test stratified by trial.

Subgroup analyses

The 3 BRAE end points of any BRAE, BRAEs in the Psych-SOC plus OtherSelect-PTs categories, and BRAEs in the Akath-PTs category are presented by subgroup for the following variables: age, sex, race (note that some trials did not have the variable race collected; these trials were not included in this subgroup analysis), location, and trial indication. The ORs

with 95% CIs were estimated in each of these subgroups (provided the number of patients with BRAEs in a subgroup was ≥ 5) using crude ORs.

RESULTS

The percentage of patients who discontinued from treatment for any reason was 8% in the montelukast group and 9% in the placebo group; this difference between the 2 treatment groups was small yet nominally statistically significant because of the large sample sizes. The time to discontinuation was similar for the 2 groups (Fig E1). Overall treatment duration in the trial (as the least-square mean data) was 60 days in the montelukast group and 59 days in the placebo group; this difference was small but nominally statistically significant.

The sensitivity analysis using an exact method based on patient-years to examine possible consequences of differences in treatment duration between treatment groups and the analysis assessing the difference in risk between the 2 treatment groups led to the same conclusions as the main analysis (rate ratio [montelukast vs placebo], 1.10; 95% CI, 0.92-1.33). The risk difference (Cochran-Mantel-Haenszel risk difference) was 0.27% (95% CI, -0.16 to 0.70) for the BRAEs category, 0.31% (95% CI, -0.11 to 0.72) for the Psychiatric Disorders/Behavior-Related Preferred Terms category and -0.03% (95% CI, -0.16 to 0.10) for the Akathisia-related terms category, supporting the results from the OR analysis. The *post-hoc* sensitivity analysis comparing the distributions of the numbers of patients reporting 0, 1, 2, or more than 2 BRAEs in the montelukast and placebo groups showed no significant difference ($P = .211$), supporting the same conclusions as the main analysis.

TABLE E1. Studies included in analysis for BRAEs

Protocol no.	Study design	Citation
Adult studies		
009	Double-blind, placebo-controlled, parallel-group	Altman LC, et al. J Allergy Clin Immunol 1998;102:50-6
012	Double-blind, placebo-controlled, parallel-group in healthy volunteers	Malmstrom K, et al. Am J Ther 1998;5:189-95
015	Double-blind, placebo-controlled, parallel-group	Dahlen SE, et al. Am J Respir Crit Care Med 2002;165:9-14
017	Double-blind, placebo- and active-controlled, parallel-group pilot to determine safety and tolerability of montelukast (capsule formulation) in patients with allergic rhinitis	Data on file
020	Double-blind, placebo- and active-controlled, parallel-group	Malmstrom K, et al. Ann Intern Med 1999;130:487-95
025	Double-blind, placebo-controlled, parallel-group	Noonan MJ, et al. Eur Respir J 1998;11:1232-9
029	Double-blind, placebo-controlled (in US only), active-controlled, parallel-group, additivity removal	Laviolette M, et al. Am J Respir Crit Care Med 1999;160:1862-9
031	Double-blind, placebo-controlled, parallel-group	Reiss TF, et al. Arch Intern Med 1998;158:1213-20
042	Double-blind, placebo-controlled, parallel-group	Leff JA, et al. N Engl J Med 1998;339:147-52
046	Double-blind, placebo-controlled, parallel-group	Löfdahl CG, et al. BMJ 1999;19:87-90
059	Double-blind, placebo-controlled, parallel-group	Ramsay CF, et al. Respir Med 2009;103:995-1003
068	Double blind, placebo- and active-controlled, parallel-group	Meltzer EO, et al. J Allergy Clin Immunol 2000;105:917-22
069	Double-blind, placebo- and active-controlled, parallel-group	Baumgartner RA, et al. Eur Respir J 2003;21:123-8
070	Double-blind, placebo- and active-controlled, parallel-group	Israel E, et al. J Allergy Clin Immunol 2002;110:847-54
073	Double-blind, placebo-controlled, parallel-group safety study in patients with chronic asthma (needed for a single country-specific registration)	Data on file
075	Double-blind, placebo-controlled, parallel-group	Vaquerizo MJ, et al. Thorax 2003;58:204-10
077	Double-blind, placebo- and active-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888.
087	Double-blind, placebo-controlled, parallel-group	Montelukast Net. J Tuberc Respir Dis 2002;25:180-1
102	Double-blind, active- and placebo-controlled, parallel-group	Philip G, et al. Eur Respir J 2004;24(suppl 48):P888
113	Double-blind, active- and placebo-controlled, parallel-group	Storms W, et al. Respir Med 2004;98:1051-62
116	Double-blind, placebo-controlled, parallel-group	Camargo CA Jr, et al. Am J Respir Crit Care Med 2003;167:528-33
117	Double-blind, placebo- and active-controlled, parallel-group	Nayak AS, et al. Ann Allergy Asthma Immunol 2002;88:592-600
Rofecoxib PN 125	Double-blind, placebo- and active-controlled, parallel-group	Brandes JL, et al. Headache 2004;44:581-6
162	Double-blind, placebo- and active-controlled, parallel-group	Philip G, et al. Clin Exp Allergy 2002;32:1020-8
192	Double-blind, active- and placebo-controlled, parallel-group	Chervinsky P, et al. Ann Allergy Asthma Immunol 2004;92:367-73
202	Double-blind, placebo-controlled, parallel-group	Miyamoto T, et al. J Clin Therap Med 2001;17:493-517
235	Double-blind, active- and placebo-controlled, parallel-group	van Adelsberg J, et al. Ann Allergy Asthma Immunol 2003;90:214-22
240	Double-blind, active- and placebo-controlled, parallel-group	van Adelsberg J, et al. Allergy 2003;58:1268-76
246	Double-blind, active- and placebo-controlled, parallel-group	Philip G, et al. Allergy Asthma Proc 2007;28:296-304
256	Double-blind, placebo-controlled, crossover	Perry TT, et al. Ann Allergy Asthma Immunol 2004;93:431-8
265	Double-blind, placebo-controlled, parallel-group	Patel P, et al. Ann Allergy Asthma Immunol 2005;95:551-7
269	Double-blind, placebo-controlled, parallel-group	Philip G, et al. Curr Med Res Opin 2004;20:1549-58
289	Double-blind, placebo-controlled, parallel-group	Busse WW, et al. Ann Allergy Asthma Immunol 2006;96:60-8
378	Double-blind, placebo-controlled, parallel-group	Okubo K, et al. Allergol Int 2008;57:247-55
402	Double-blind, placebo-controlled, parallel-group	Tohda Y, et al. Clin Exp Allergy 2002;32:1180-6
Pediatric studies		
049	Double-blind, placebo-controlled, parallel-group	Knorr B, et al. JAMA 1998;279:1181-6
072	Double-blind, placebo-controlled, parallel-group	Knorr B, et al. Pediatrics 2001;108:e48 (1-10)
097	Double-blind, active- and placebo-controlled, parallel-group	Becker AB, et al. Ann Allergy Asthma Immunol 2006;96:800-7
165	Double-blind, placebo-controlled, parallel-group	Robertson CF, et al. Am J Respir Crit Care Med 2007;175:323-9
176	Double-blind, placebo-controlled, parallel-group	van Adelsberg J, et al. Curr Med Res Opin 2005;21:971-9
219	Double-blind, placebo-controlled, parallel-group	Bisgaard H, et al. Pediatr Pulmonol 2009;44:568-79
272	Double-blind, placebo-controlled, parallel-group	Bisgaard H, et al. Am J Respir Crit Care Med 2008;178:854-60
336	Double-blind, placebo-controlled, parallel-group	Papadopoulos N, et al. J Asthma 2009;46:413-20
340	Double-blind, placebo-controlled, parallel-group	Weiss KB, et al. Presented at the European Academy of Allergology and Clinical Immunology and European Respiratory Society Pediatrics Joint meeting, Lisbon, Portugal, October 20-23, 2007
906	Double-blind, 2-period, crossover	Simons FER, et al. J Pediatr 2001;138:694-8
907	Double blind, placebo-controlled, parallel-group	Bisgaard H, et al. Am J Respir Crit Care Med 2005;171:315-22

TABLE E2. Numbers of patients with BRAEs by HLGTS and PTs

	Montelukast, n = 11,673		Placebo, n = 8,827		Active control, n = 4,724	
	No.	Percent	No.	Percent	No.	Percent
Psych-SOC: total	174	1.49	117	1.33	66	1.40
Anxiety disorders and symptoms	30	0.26	22	0.25	14	0.30
Anxiety disorder	1	0.01	0	0.00	0	0.00
Obsessive-compulsive disorder	1	0.01	0	0.00	0	0.00
Agitation	1	0.01	3	0.03	1	0.02
Anxiety	16	0.14	11	0.12	5	0.11
Nervousness	8	0.07	5	0.06	7	0.15
Stress	2	0.02	2	0.02	1	0.02
Tension	2	0.02	0	0.00	0	0.00
Panic disorder	0	0.00	1	0.01	0	0.00
Panic attack	0	0.00	1	0.01	0	0.00
Changes in physical activity	2	0.02	1	0.01	0	0.00
Decreased activity	1	0.01	1	0.01	0	0.00
Bruxism	1	0.01	0	0.00	0	0.00
Cognitive and attention disorders and disturbances	1	0.01	3	0.03	2	0.04
Attention deficit/hyperactivity disorder	1	0.01	3	0.03	2	0.04
Deliria (including confusion)	0	0.00	1	0.01	0	0.00
Confusional state	0	0.00	1	0.01	0	0.00
Depressed mood disorders and disturbances	19	0.16	8	0.09	4	0.08
Depression	18	0.15	8	0.09	4	0.08
Psychomotor retardation	1	0.01	0	0.00	0	0.00
Disturbances in thinking and perception	1	0.01	0	0.00	0	0.00
Hallucination	1	0.01	0	0.00	0	0.00
Eating disorders and disturbances	0	0.00	1	0.01	1	0.02
Eating disorder	0	0.00	1	0.01	1	0.02
Impulse control disorders NEC	0	0.00	2	0.02	0	0.00
Compulsive lip biting	0	0.00	1	0.01	0	0.00
Trichotillomania	0	0.00	1	0.01	0	0.00
Manic and bipolar mood disorders and disturbances	0	0.00	1	0.01	0	0.00
Bipolar disorder	0	0.00	1	0.01	0	0.00
Mood disorders and disturbances NEC	9	0.08	11	0.12	1	0.02
Affect lability	0	0.00	1	0.01	0	0.00
Crying	1	0.01	2	0.02	0	0.00
Euphoric mood	1	0.01	0	0.00	0	0.00
Mood altered	1	0.01	1	0.01	0	0.00
Mood swings	5	0.04	7	0.08	1	0.02
Affective disorder	1	0.01	0	0.00	0	0.00
Personality disorders and disturbances in behavior	3	0.03	5	0.06	1	0.02
Aggression	1	0.01	3	0.03	0	0.00
Disturbance in social behavior	1	0.01	1	0.01	1	0.02
Paranoia	1	0.01	0	0.00	0	0.00
Personality change	0	0.00	1	0.01	0	0.00
Psychiatric and behavioral symptoms NEC	4	0.03	2	0.02	0	0.00
Abnormal behavior	4	0.03	2	0.02	0	0.00
Schizophrenia and other psychotic disorders	1	0.01	0	0.00	0	0.00
Schizoaffective disorder	1	0.01	0	0.00	0	0.00
Sexual dysfunctions, disturbances, and gender identity disorders	3	0.03	1	0.01	2	0.04
Libido decreased	2	0.02	1	0.01	2	0.04
Paraphilia*	1	0.01	0	0.00	0	0.00
Sleep disorders and disturbances	112	0.96	61	0.69	45	0.95
Initial insomnia	1	0.01	0	0.00	0	0.00
Insomnia	82	0.70	46	0.52	39	0.83
Middle insomnia	0	0.00	1	0.01	0	0.00
Abnormal dreams	4	0.03	5	0.06	0	0.00
Nightmare	14	0.12	4	0.05	5	0.11
Sleep terror	0	0.00	1	0.01	0	0.00
Somnambulism	1	0.01	0	0.00	0	0.00
Sleep disorder	14	0.12	6	0.07	2	0.04
Suicidal and self-injurious behaviors NEC	0	0	1	0.01	0	0.00
Intentional self-injury†	0	0.00	1	0.01	0	0.00

(Continued)

TABLE E2. (Continued)

	Montelukast, n = 11,673		Placebo, n = 8,827		Active control, n = 4,724	
	No.	Percent	No.	Percent	No.	Percent
Other behavior-related PTs: total	134	1.15	77	0.87	63	1.33
Asthenia	37	0.32	25	0.28	44	0.93
Fatigue	41	0.35	22	0.25	7	0.15
Malaise	25	0.21	11	0.12	6	0.13
Feeling abnormal	1	0.01	0	0.00	1	0.02
Feeling jittery	2	0.02	0	0.00	0	0.00
Irritability	32	0.27	19	0.22	6	0.13
Akathisia-related PTs: total	27	0.23	18	0.20	3	0.06
Akathisia	6	0.05	2	0.02	3	0.06
Hyperkinesia	1	0.01	0	0.00	0	0.00
Psychomotor hyperactivity	7	0.06	9	0.10	0	0.00
Restlessness	13	0.11	7	0.08	0	0.00

Although a patient might have had 2 or more AEs, the patient is counted only once within a category. The same patient might appear in different categories.

NEC, Not elsewhere classified.

*Verbatim term: “dripping of urine” after surgery (orchiopexy) in a 2-year-old patient

†Verbatim term: “bite in mouth” in a 4-year-old patient.

TABLE E3. Summary of the depression AEs reported in 30 of 25,224 patients in the study database

Patient age	Previous history*	AE onset RelDay	AE duration in treatment period	AE intensity	Received therapy for depression†	AE resolved during study therapy
Montelukast, n/N = 18/11,673 (0.15%)						
Mean 34.7 y	Five of 18 patients	Mean 50.6	Mean 26.1 d	Mild n = 7	Six of 18 patients	Seven of 18 patients
Median 35.5 y		Median 29.0	Median 12.5 d	Moderate n = 6		
Range 7–70 y		Range 2–311	Range 2–97 d	Severe n = 1		
				Other n = 4‡		
Placebo, n/N = 8/8,827 (0.09%)						
Mean 48.9 y	Two of 8 patients	Mean 30.8	Mean 37.5 d	Mild n = 3	Four of 8 patients	Four of 8 patients
Median 49.5 y		Median 28.5	Median 34.0 d	Moderate n = 4		
Range 34–64 y		Range 2–89	Range 26–56 d	Severe n = 0		
				Other n = 1§		
Active control, n/N = 4/4,724 (0.08%)						
Mean 43.3 y	One of 4 patients	Mean 13.5	Mean 34.0 d	Mild n = 3	Two of 4 patients	One of 4 patients
Median 46.0 y		Median 6.0	Median 24.0 d	Moderate n = 1		
Range 21–60 y		Range 5–37	Range 6–82 d	Severe n = 0		

RelDay is defined as the day of onset relative to the first day of randomized therapy

*History of a condition from the Psych-SOC before randomization, as follows: montelukast—3 patients with depression, 1 patient with depression and anxiety, and 1 patient with attention deficit disorder; placebo—2 patients with depression; active control—1 patient with AE of depression before randomization.

†Received therapy to treat depression during the study treatment period.

‡One patient: intensity changed from mild to moderate to mild (see also Table VI); 2 patients: intensity changed from moderate to mild; 1 patient: unknown intensity.

§One patient: unknown intensity.

TABLE E4. Patients with BRAEs by subgroup

Subgroup	Montelukast		Placebo		Montelukast vs placebo OR (95% CI)
	n/N	Percent	n/N	Percent	
Sex					
Female	177/6,381	2.77	124/4,924	2.52	1.10 (0.87-1.41)
Male	142/5,291	2.68	76/3,902	1.95	1.39 (1.04-1.87)
Race					
White	221/7,588	2.91	143/5,926	2.41	1.21 (0.98-1.51)
Black	21/798	2.63	10/648	1.54	1.72 (0.77-4.13)
Asian	19/1,301	1.46	6/775	0.77	1.90 (0.73-5.84)
Hispanic	33/1,367	2.41	24/918	2.61	0.92 (0.52-1.64)
Other	6/186	3.23	5/132	3.79	0.85 (0.21-3.59)
Location					
North America	211/8,028	2.63	129/6,449	2.00	1.32 (1.05-1.66)
Non-North America	108/3,645	2.96	71/2,378	2.99	0.99 (0.73-1.36)
Trial indication					
Asthma	187/5,701	3.28	97/3,905	2.48	1.33 (1.03-1.73)
Migraine	5/93	5.38	5/84	5.95	0.90 (0.20-4.06)
Perennial allergic rhinitis	34/1,632	2.08	40/1,603	2.50	0.83 (0.51-1.35)
Seasonal allergic rhinitis	63/3,613	1.74	41/2,917	1.41	1.24 (0.82-1.90)
Respiratory syncytial virus-induced bronchiolitis	30/634	4.73	17/318	5.35	0.88 (0.46-1.73)

TABLE E5. Description of serious* BRAEs reported in 6 of 25,224 patients in the study database

Patient	AE	Onset RelDay†	AE duration	Intensity	Discontinued study and/or study drug because of AE
Montelukast treatment group (n = 3)					
72-y-old woman	Anxiety disorder	6	3 d	Moderate	No
The patient (with history of insomnia and anxiety) was hospitalized on RelDay 6 to rule out a myocardial infarction; results of all tests were negative. Study drug was not taken on RelDays 6 and 7. The patient recovered on RelDay 8 and was discharged from the hospital with a diagnosis of anxiety and exhaustion. Study drug was resumed on RelDay 8.					
45-y-old woman	Depression	2	2 d	Severe	Yes
The patient (with a history of depression [approximately 10 years before the study], bipolar disorder, and hospitalization for hallucinations [approximately 2 years before the study]) had a serious AE of depression and hospitalization with hallucinations on RelDay 2. On RelDay 3, the patient was discharged from the hospital after resolution and returned to baseline status of "mild depression." Study drug was discontinued on RelDay 7.					
32-y-old man	Schizoaffective disorder	22	23 d	NA	Yes
Patient (with a history of narcissistic personality disorder [approximately 15 years before the study]) was given a diagnosis of schizoaffective disorder on RelDay 22 after reporting anxiety and increased stress starting on RelDay 17 and stopping on RelDay 22. Study drug was stopped on RelDay 23. The patient was hospitalized on RelDay 24 with an initial diagnosis of acute schizophrenia; the patient was judged to be paranoid-psychotic and suicidal. The patient was treated and recovered and was discharged on RelDay 44 with a final diagnosis of schizoaffective disorder.					
Placebo treatment group (n = 3)					
4-y-old boy	Bipolar disorder	9	56 d	Moderate	Yes
The patient (with a history of hyperkinesia, behavioral problem, and hyperactivity since age 1.5 years treated with diphenhydramine, 12.5 mg at bedtime as needed) had a serious AE of bipolar disorder that started on RelDay 9 and stopped on RelDay 64. Hyperactivity worsened 4 months before the study and worsened again 2 months before the study. The patient underwent psychiatric examinations on RelDays -20 and -6. On RelDay 6, therapy with lithium and thioridazine began. On RelDay 8, the patient discontinued the study drug. On RelDay 9, the patient experienced bipolar/manic stage and was hospitalized until RelDay 17. The patient was discharged from the hospital on RelDay 21.					
13-mo-old girl	Irritability	165	1 d	Mild	No
The patient had a serious AE of irritability on RelDay 165, when she was given 2 doses of study drug (considered an overdose). The patient was irritable for 3 to 4 hours and then recovered. The study drug was not interrupted.					
4-y-old girl	Mood swings	4	18 d	Mild	Yes
The patient experienced mood swings, which started on RelDay 4 and stopped on RelDay 21. On RelDay 4, the patient exhibited aggressive behavior, was uncooperative, and had mood swings after 3 doses of study drug. Therapy with the study drug was interrupted on RelDay 18. After missing 2 doses (RelDays 19 and 20), the aggressive behavior diminished. The study drug was not reinitiated. On RelDay 21, the parent informed the investigator (by telephone) that the child's behavior had returned to normal.					

*Defined by using regulatory criteria.

†RelDay is defined as the day of onset relative to first day of randomized therapy.

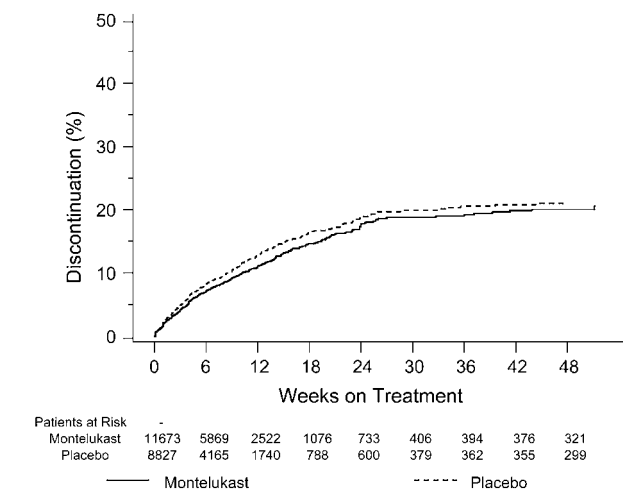


FIG E1. Time to discontinuation: Kaplan-Meier cumulative incidence of discontinuation for any reason for patients included in the analysis of BRAEs.

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Correction

With regard to the October 2009 article entitled “Analysis of behavior-related adverse experiences in clinical trials of montelukast” (*J Allergy Clin Immunol* 2009;124:699-706), two protocol numbers in Table E1 are incorrect as given. Under “Adult Studies,” protocol number “202” should read “A202,” and protocol number “402” should read “A402.”