

Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: A nested case-control study

Glen T. Schumock, PharmD, MBA, PhD,^a Leslie T. Stayner, PhD,^b Robert J. Valuck, PhD,^c Min J. Joo, MD, MPH,^d Robert D. Gibbons, PhD,^e and Todd A. Lee, PharmD, PhD^a *Chicago, Ill, and Aurora, Colo*

Background: The US Food and Drug Administration has issued safety alerts about leukotriene receptor-modifying agents and suicidality/suicide, but because these were based on case reports, there is controversy about the association.

Objective: We conducted a nested case-control study to determine the association between leukotriene-modifying agents (LTMA) and attempted suicide among asthmatic children and young adults.

Methods: Cases and control subjects were from a cohort of asthmatic patients aged 5 to 24 years who were new users of LTMA or other asthma medications. Data were from an insurance claims database. Cases were defined as those with a suicide attempt (SA) occurring after exposure to asthma medication. Control subjects were persons at risk and were selected by using incidence density sampling in a 10:1 match. Conditional logistic regression was used to determine the association between LTMA exposure and the risk of attempted suicide adjusted for important covariates.

Results: We identified 344 cases and 3438 matched control subjects. Cases were more likely than control subjects to have risk factors for suicide. We found that current use of any LTMA was not associated with increased risk of an SA; in fact, the direction of effect was the opposite (adjusted odd ratio, 0.70; 95% CI, 0.36-1.39).

Conclusion: In this analysis we found that use of LTMA was not associated with an increased risk of SAs in children, adolescents, and young adults with asthma. Further research needs to be conducted to more fully understand the association between LTMA and suicide, particularly in subpopulations. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Asthma, suicide, leukotriene-modifying agents, montelukast, drug safety

Abbreviations used

ED:	Emergency department
FDA:	US Food and Drug Administration
ICD-9-CM:	International Classification of Diseases–Ninth Revision–Clinical Modification
LTMA:	Leukotriene-modifying agent
MPR:	Medication possession ratio
OR:	Odds ratio
SA:	Suicide attempt

Asthma, one of the most common chronic conditions in the United States, is a respiratory disorder characterized by airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. The disease affects approximately 24 million Americans, including 7 million children.^{1,2} Asthma exacerbations can result in lost days of work and school, reduced quality of life, avoidable emergency department (ED) visits, hospitalizations, and death.

Treatment guidelines for asthma have been published by the National Heart, Lung, and Blood Institute that encourage stepwise therapy based on disease severity.³ Several classes of medication are available for long-term control of asthma. Although inhaled corticosteroids are often used first, leukotriene-modifying agents (LTMA) are an effective alternative.^{3,4} These drugs, which in the United States include montelukast (Singulair; Merck & Co, Inc, Whitehouse Station, NJ), zafirlukast (Accolate; AstraZeneca Pharmaceuticals, Wilmington, NC), and zileuton (Zyflo; Cornerstone Therapeutics, Inc, Cary, NC), are administered orally and therefore are particularly useful in children. LTMA work by preventing the inflammatory effects of leukotrienes, and all 3 are approved for asthma (montelukast is also approved for allergic rhinitis) and have been available in the United States since the late 1990s.⁵ Among the LTMA, montelukast is the most popular; in fact, the brand product, Singulair, has been among the top 10 best-selling drugs in the United States for several years.⁶ Until recently, the LTMA were considered to have minimal safety issues.

Beginning in 2008, when the US Food and Drug Administration (FDA) first issued a safety alert, there has been concern of a potential association between LTMA and increased risk of suicide.⁷ An FDA review of adverse event data from manufacturer-conducted placebo-controlled clinical trials found no association with suicide; nevertheless, subsequent communications by the FDA warned that “patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents.”⁸ In June 2009, the FDA requested that manufacturers include a precaution in the drug-prescribing information for all LTMA.⁹ Although the number of suicide-related events related to LTMA

From ^athe Center for Pharmacoeconomic Research and the Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago; ^bthe Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago; ^cthe Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Anschutz Medical Campus, Aurora; ^dthe Section of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, College of Medicine, University of Illinois at Chicago; and ^ethe Center for Health Statistics and the Departments of Medicine and Health Studies, Pritzker School of Medicine, University of Chicago.

Disclosure of potential conflict of interest: T. A. Lee is a consultant for Merck and Forest Pharmaceuticals and has received research support from Novartis. The rest of the authors declare they have no relevant conflicts of interest.

Received for publication January 31, 2012; revised April 24, 2012; accepted for publication April 25, 2012.

Corresponding author: Glen T. Schumock, PharmD, MBA, PhD, 833 S Wood St, MC 886, Chicago, IL 60612. E-mail: schumock@uic.edu. 0091-6749/\$36.00

© 2012 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2012.04.035

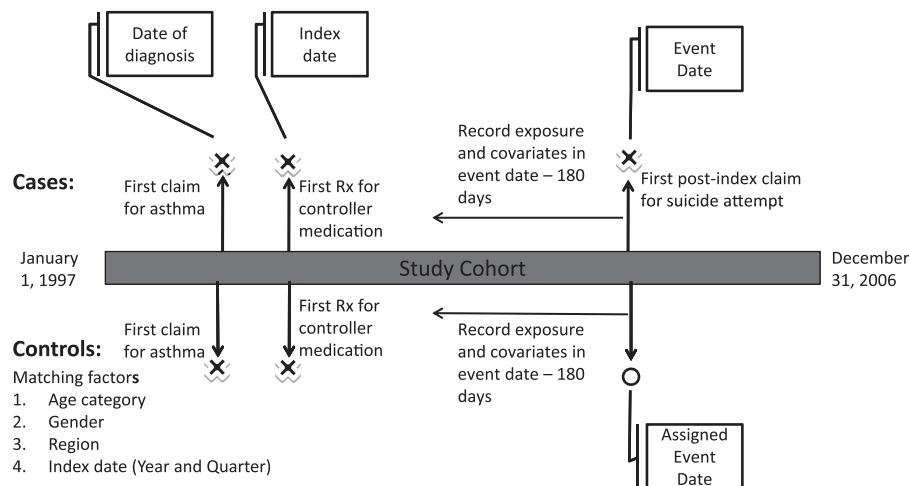


FIG 1. Nested case-control study design. Ten control subjects were matched with each case.

reported to the FDA have increased since 2008, it is unclear whether such reports are a result of the FDA warning or represent a true association.¹⁰ Ecologic studies have failed to find an association,^{11,12} and the only observational study that has been conducted was limited by small sample size and failure to include a comparison group.¹³ Nevertheless, prescribing of LTMA has decreased by 8.9% from 2007 to 2009.¹¹

More objective information is needed about the potential association between LTMA and suicide, particularly in children in whom LTMA might be a preferential treatment option because of difficulty using inhalers. The purpose of this study was to assess the association between LTMA and suicide attempts (SAs) in children, adolescents, and young adults with asthma.

METHODS

We conducted a case-control study of the association between the LTMA and attempted suicides. Cases and control subjects were nested within a cohort of asthmatic children and young adults identified in a commercial health insurance claims database who were new users of LTMA or other asthma medications, as shown in Fig 1.

Data source and cohort

The data for this study were obtained from the LifeLink Health Plan Claims Database (IMS Health, Inc, Danbury, Conn). The LifeLink Health Plan Database includes adjudicated medical and pharmaceutical claims along with demographic information (eg, age, sex, and geographic region) and dates of enrollment for more than 60 million unique anonymous patients from more than 90 health plans across the United States and is representative of the national commercially insured population on a variety of demographic measures. The data extract contained claims for patients with a diagnosis of asthma based on International Classification of Diseases–Ninth Revision–Clinical Modification (ICD-9-CM) codes of 493.XX whose age was between 5 and 24 years on at least 1 claim. Our analysis was restricted to patients with claims adjudicated between January 1, 1997, and December 31, 2006. This end date was selected to limit the potential for confounding by indication. Although the first FDA warnings about a potential association between LTMA and suicide occurred in 2008, the package insert for Singular was changed to include a warning about suicidal thinking a year earlier and could have influenced prescribing thereafter.⁷

The cohort was limited to those patients with at least 1 prescription claim for an asthma controller medication, which included inhaled corticosteroids,

LTMA, long-acting β -agonists, methylxanthines, immunomodulators, mast cell stabilizers, and inhaled anticholinergics, and the date of the first claim for an asthma controller medication was defined as the index date. Because LTMA are used for indications other than asthma, such as allergic rhinitis, or for off-label indications, patients were excluded if the index date occurred more than 30 days before the asthma diagnosis date. This was done to ensure homogeneity within the cohort with respect to suicide risk because asthmatic patients have a higher baseline risk of suicide. Patients were also excluded if they were less than 5 or greater than 24 years old on their index date or if their last enrollment date (ie, enrollment in the health plan) was on or before their index date. The latter was considered necessary for accurate assessment of exposure. Finally, subjects were excluded if they were not continuously enrolled for at least 6 months before the index prescription date or if they had significant gaps in enrollment in either the preindex or follow-up periods. Significant gaps were defined as 2 or more months of continuous disenrollment and 20% or more of total months.

Patients were followed until (1) an SA occurred, (2) disenrollment from the database, or (3) the end of the follow-up period (December 31, 2006).

Cases and control subjects

Cases were defined as those with an SA occurring after (at least 1 day) the index date. The ICD-9-CM codes used to identify SAs were E950 to E959, with subcategories of E950 to E952 (self-inflicted poisoning), E953 (self-inflicted injury by hanging), E954 (drowning), E955 (self-inflicted injury by firearms), E956 (self-inflicted injury by cutting), E957 (self-inflicted injury by jumping from high places), E958 (other/unspecified self-inflicted injury), and E959 (late effects of self-inflicted injury).

Potential control subjects were persons at risk for an event on the date of an event in a corresponding case. The study was planned to randomly select 10 control subjects from the at-risk population after matching to each case on (1) age (within groups 5-11, 12-18, and 19-24 years), (2) sex, (3) geographic region of the country (East, Midwest, South, and West), and (4) cohort entry quarter and year by using the incidence density sampling approach (without replacement) and assigned the “event” date of the case. Cases could serve as control subjects for other cases in the time period before the event. The choice of a 10:1 match was based on previous evidence that suggests that matching beyond 10 control subjects does not significantly increase statistical power.¹⁴

Exposure

LTMA exposure was determined in the 180 days before the event date (ie, date of SA in cases and corresponding date in control subjects). We first determined the exposed period for each prescription based on the prescription fill date and the number of days supplied as recorded in prescription claims.

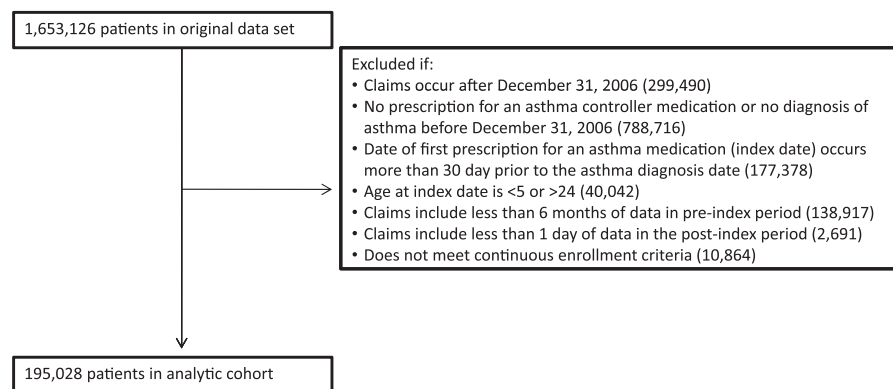


FIG 2. Study cohort entry. The number of patients excluded and the reasons for exclusion are shown.

We then classified exposure as current, immediate past, past, or never based on the relation between medication dispensings and the event date. Current exposure was assigned when the exposed period overlapped the event date. *Immediate past exposure* was assigned if the exposed period ended within 30 days before the event date, whereas *past exposure* was assigned when the exposed period ended from greater than 30 days and 180 days or less before the event date. Patients with no claims for LTMA in the 180 days before the event date were classified as *never exposed*. We also created a category of *ever exposed* that was the combination of current, immediate past, and past exposure.

To examine any dose-response relationship that might exist, we also created an exposure variable based on the cumulative dose of LTMA received. To do this, we converted milligrams of LTMA received per day into LTMA equivalents in the same manner done previously by Heaton et al,¹⁵ in which 1 LMTA equivalent is 10 mg of montelukast, 40 mg of zafirlukast, or 2400 mg of zileuton. We then examined the total cumulative dose (during the past 180 days) in ever users of LTMA. As a final measure of exposure, we calculated the medication possession ratio (MPR) for those exposed to LTMA, which was defined as the total days' supply from dispensed prescriptions divided by the number of days from the first prescription.

Covariates

Patients' characteristics and demographic data were assessed during the 6 months preceding the event date. In addition to the variables used to match cases and control subjects, we assessed comorbidities (through ICD-9-CM codes) that could have been associated with a higher risk of SAs, including substance abuse disorders, bipolar disorder, depression, schizophrenia, other mental disorders, HIV/AIDS, malignant neoplasm/cancer, epilepsy, irritable bowel disease, migraine headaches, multiple sclerosis, renal disease, lupus, chronic pain, and allergic rhinitis.¹⁶⁻³² We also identified both previous SAs and previous psychological counseling (≥ 2 visits based on Current Procedural Terminology 4 codes). Because certain medications have been associated with increased risk of suicide, we also assigned these as covariates based on pharmacy claims and associated National Drug Codes based on current or past use. These included anticonvulsants, antidepressants, antipsychotics, hypnotics, anxiolytics, and isotretinoin.³³⁻³⁵

Asthma itself can be associated with suicide, and those with higher asthma severity might be at even higher risk.³⁶⁻³⁸ Therefore we assigned several covariates designed to assess asthma severity, and again, all were based on the 180 days before the event.^{39,40} These included (1) ED visits with a diagnosis of asthma, (2) number of short-acting β -agonist canisters dispensed, (3) number of oral corticosteroid prescriptions, and (4) number of asthma exacerbations.³⁹ Asthma exacerbations were defined by a prescription for oral corticosteroids filled within 7 days of an outpatient encounter for asthma.⁴⁰

Statistical analysis

Descriptive statistics were used to characterize the cases and control subjects. Conditional logistic regression was used to compare the

demographic and clinical characteristics of cases and control subjects (univariate) and to determine crude and adjusted odds ratios (ORs) and 95% CIs for the association between LTMA exposure and SAs. In the adjusted analyses a stepwise approach to model building was used in which each covariate and possible interactions were examined, and variables were retained only if considered clinically significant (based on previous literature) or if they modified the risk estimate by greater than 10%.⁴¹ The best-fitting multivariable model included bipolar disease, depression, other mental disorders, substance abuse, and ED visits. For the final adjusted model, we also included previous psychological counseling and previous SAs because both have been found to have strong associations with SAs.^{42,43} Statistical analyses were performed in STATA version 11 software (StataCorp, College Station, Tex). The study was approved by the University of Illinois at Chicago's Institutional Review Board.

Sensitivity analysis

In addition to examining the potential association based on current, immediate past, and past exposure and the effect of dose and MPR, we conducted several stratified analyses to examine the association within subgroups by age and sex. Sample size calculations were conducted on the main analysis and predicted sufficient power (>0.85) with approximately 100 cases, which we predicted to be easily obtained with the dataset. In addition, estimates provided by IMS Health, Inc, of the number of subjects in the Lifelink database exposed to LTMA in our age range of interest suggested that we should not have issues with insufficient exposure. However, we were unclear whether we would have a sufficient number of cases among the subgroups assessed in stratified analyses.⁴⁴ Nevertheless, we believed these analyses could be important for exploratory purposes.

RESULTS

Limiting the dataset based on exclusion criteria described above (as shown in Fig 2) resulted in an analytic cohort of 195,028 patients from which cases and control subjects were drawn. There were 344 cases, and all except 1 were able to be matched with 10 control subjects; 1 case was matched with 8 control subjects, for a total of 3,438 control subjects.

Demographic and clinical characteristics of the cases and control subjects are shown in Table I. Cases were more likely than control subjects to have had previous SAs and to have previously received psychological counseling. Cases were also more likely to have been given a diagnosis of substance abuse, bipolar disease, depression, schizophrenia, other mental disorders, epilepsy, HIV/AIDS, and migraine headaches and to have been treated with anticonvulsants, antidepressants, antipsychotics, anxiolytics, and hypnotic medications. Cases also had more ED

TABLE I. Demographic and clinical characteristics of cases and control subjects

Characteristic	Cases, no. (%) or mean (SD)	Control subjects, no. (%) or mean (SD)	P value
No.	344	3438	
Demographic characteristics			
Age (y)*	16.5 (3.21)	15.9 (3.67)	NA
5-11	15 (4.36%)	150 (4.36%)	NA
12-18	256 (74.42%)	2558 (74.40%)	NA
19-24	73 (21.22%)	730 (21.23%)	NA
Female sex*	245 (71.22%)	2448 (71.20%)	NA
Risk factors for suicide			
Previous SA†	22 (6.40%)	11 (0.32%)	<.001
Previous psychological counseling	139 (40.41%)	197 (5.73%)	<.001
Mental health disorders			
Substance abuse	105 (30.52%)	82 (2.39%)	<.001
Bipolar disorder	48 (13.95%)	32 (0.93%)	<.001
Depression	231 (67.15%)	192 (5.58%)	<.001
Schizophrenia	11 (3.20%)	1 (0.03%)	<.001
Other mental disorders	172 (50.00%)	215 (6.25%)	<.001
Other comorbidities			
Allergic rhinitis	68 (19.77%)	666 (19.37%)	.853
Cancer	1 (0.29%)	8 (0.23%)	.832
Chronic pain	0 (0%)	0 (0%)	NA
Epilepsy	7 (2.03%)	7 (0.20%)	<.001
HIV/AIDS	2 (0.58%)	2 (0.06%)	.021
Irritable bowel syndrome	4 (1.16%)	17 (0.49%)	.118
Lupus	0 (0%)	3 (0.09%)	1.000
Migraine	20 (5.81%)	68 (1.98%)	<.001
Multiple sclerosis	0 (0%)	1 (0.03%)	1.000
Renal disease	0 (0%)	2 (0.06%)	1.000
Use of medications associated with suicide			
Anticonvulsants	50 (14.53%)	55 (1.60%)	<.001
Antidepressants	150 (43.60%)	293 (8.52%)	<.001
Antipsychotics	50 (14.53%)	47 (1.37%)	<.001
Anxiolytics	30 (8.72%)	87 (2.53%)	<.001
Hypnotics	17 (4.94%)	21 (0.61%)	<.001
Isotretinoin	1 (0.29%)	12 (0.35%)	.861
Varenicline	0 (0%)	0 (0%)	NA
Asthma severity and treatment characteristics			
Use of short-acting β -agonist inhalers (no. of inhalers dispensed in past 6 mo)	2.12 (1.31)	1.79 (2.13)	.297
0	213 (61.92%)	2169 (63.09%)	.643
1	54 (15.70%)	630 (18.32%)	.213
2	25 (7.27%)	272 (7.91%)	.669
≥ 3	36 (10.47%)	255 (7.42%)	.041
Missing	16 (4.65%)	112 (3.26%)	NA
ED visits for asthma (no. in past 6 mo)	0.36 (0.96)	0.11 (0.56)	<.001
0	285 (82.85%)	3245 (94.39%)	<.001
1	24 (6.98%)	87 (2.53%)	<.001
2	18 (5.23%)	71 (2.07%)	<.001
≥ 3	17 (4.94%)	35 (1.02%)	<.001
Asthma exacerbations (no. in past 6 mo)	0.60 (2.97)	0.43 (2.27)	.202
0	306 (88.95%)	3112 (90.52%)	.340
1	11 (3.20%)	90 (2.62%)	.522
2	5 (1.45%)	66 (1.92%)	.546
≥ 3	22 (6.40%)	170 (4.94%)	.239

(Continued)

TABLE I. (Continued)

Characteristic	Cases, no. (%) or mean (SD)	Control subjects, no. (%) or mean (SD)	P value
Use of oral corticosteroids (no. of prescription in past 6 mo)	0.22 (0.55)	0.19 (0.56)	.452
0	289 (84.01%)	2954 (85.92%)	.327
1	39 (11.34%)	369 (10.73%)	.725
2	13 (3.78%)	84 (2.44%)	.136
≥ 3	3 (0.87%)	31 (0.90%)	.957
Use of other asthma controller medications in past 6 mo			
Inhaled corticosteroids	109 (31.69%)	1085 (31.56%)	.957
Long-acting β -agonists	80 (23.26%)	635 (18.47%)	.026
Inhaled anticholinergics	9 (2.62)	48 (1.40%)	.079
Mast cell stabilizers	5 (1.45%)	43 (1.25%)	.742
Methylxanthines	1 (0.29%)	4 (0.12%)	.412
Immunomodulators	0 (0.00%)	1 (0.03%)	1.000

The original dataset used to create this table was obtained under license from the following IMS Health, Inc, information service: LifeLink Health Plan Claims Database, January 1997–August 2010, IMS Health, Inc.

NA, Not applicable.

*Matching variable.

†Measured in the preindex period.

visits with a diagnosis of asthma and were more likely to have had a prescription for an inhaled long-acting β -agonist in the past 6 months but were otherwise similar to control subjects with respect to asthma severity and use of other asthma controller medications.

Among cases, 19 (5.52%) were using LTMA at the time of the SA compared with 224 (6.52%) control subjects (unadjusted OR, 0.80; 95% CI, 0.49–1.31), as shown in Table II. All 19 cases and 219 control subjects received montelukast, whereas 5 control subjects received zafirlukast, and no cases or control subjects received zileuton. When adjusted for other important covariates, we found that current use of any LTMA was not associated with increased risk for SAs. In fact, although not statistically significant, the adjusted OR of 0.70 (95% CI, 0.36–1.39) is suggestive of a reduction (by 30%) in the odds of SAs in those using LTMA. Also shown in Table II are adjusted ORs for immediate past, past, and ever exposure. Past and ever exposure were similar to current exposure, whereas immediate past exposure was closer to the null, but in all cases the CIs included 1.0.

We found no association between the cumulative dose of LTMA and SAs. The cumulative dose over the past 180 days was also very similar (mean, 57.44 and 63.96 mg of LTMA equivalent in cases and control subjects, respectively). Categories of cumulative dose were also assessed (≤ 60 LTMA equivalents vs > 60 LTMA equivalents) compared with never use, and although the adjusted ORs again suggested a protective effect (0.64 and 0.54, respectively), the CIs for each included 1 (ie, not statistically significant), as shown in Table II. Adherence to LTMA, expressed as the MPR, was the same in cases and control subjects (mean, 0.63% and 0.67%, respectively), as shown in Table II.

We conducted several stratified analyses to determine whether the relationship between LTMA use and SAs varied within subgroups, as shown in Table III. All analyses shown in Table III compared current use of LTMA with never use (reference,

TABLE II. Exposure to LTMA and risk of an SA

Exposure	Cases, no. (%) or mean (SD)	Control subjects, no. (%) or mean (SD)	Crude OR (95% CI)	Adjusted OR (95% CI)
Exposure associations				
Never use of LTMA	305 (88.66%)	2903 (84.44%)	Reference	Reference
Current use of LTMA	19 (5.52%)	224 (6.52%)	0.80 (0.49-1.31)	0.70 (0.36-1.39)
Immediate past use of LTMA	8 (2.33%)	100 (2.91%)	0.75 (0.36-1.57)	0.95 (0.36-2.50)
Past use of LTMA	12 (3.49%)	211 (6.14%)	0.54 (0.30-0.98)	0.69 (0.32-1.50)
Ever use of LTMA	39 (11.34%)	535 (15.56%)	0.69 (0.49-0.98)	0.74 (0.46-1.20)
Dose-response associations				
Continuous analyses				
Cumulative LTMA equivalent dose among ever users*	57.44 (46.46)	63.96 (83.02)	1.00 (0.99-1.01)	0.99 (0.96-1.01)
MPR (%) among LTMA current users	0.63 (0.28)	0.67 (0.37)	0.51 (0.08-3.43)	1.03 (0.02-50.98)
Categorical analyses				
Never users	305 (88.66%)	2903 (84.44%)	Reference	Reference
≤60 LTMA equivalents	16 (4.65%)	277 (8.06%)	0.55 (0.32-0.92)	0.64 (0.32-1.28)
>60 LTMA equivalents	12 (3.49%)	166 (4.83%)	0.67 (0.37-1.23)	0.54 (0.23-1.30)
Missing	11 (3.02%)	92 (2.68%)	NA	NA

The original dataset used to create this table was obtained under license from the following IMS Health, Inc, information service: LifeLink Health Plan Claims Database, January 1997–August 2010, IMS Health, Inc.

NA, Not applicable.

*One LTMA equivalent dose equals 10 mg of montelukast, 40 mg of zafirlukast, or 2400 mg of zileuton.

TABLE III. Stratified analyses

Exposure	Cases,* no. (%)	Control subjects,* no. (%)	Crude OR (95% CI)†	Adjusted OR (95% CI)†
Association within age groups				
5-11 y	1 (6.67%)	13 (8.67%)	0.75 (0.09-6.19)	0.78 (0.03-18.09)
12-18 y	12 (4.69%)	179 (7.00%)	0.65 (0.36-1.19)	0.47 (0.20-1.09)
19-24 y	6 (8.22%)	32 (4.38%)	2.01 (0.79-5.09)	5.15 (1.16-22.86)
Association within sex groups				
Female	11 (4.49%)	168 (6.86%)	0.63 (0.34-1.19)	0.65 (0.27-1.59)
Male	8 (8.08%)	56 (5.66%)	1.47 (0.68-3.18)	0.71 (0.23-2.16)

The original dataset used to create this table was obtained under license from the following IMS Health, Inc, information service: LifeLink Health Plan Claims Database, January 1997–August 2010, IMS Health, Inc.

*Values shown in cells are the numbers (percentages) of subjects exposed (current users) to LTMA. The total number of cases and control subjects in each stratum is shown in Table I.

†Crude and adjusted ORs are for current users of LTMA compared with never users.

data not shown); however, we also conducted the analyses comparing ever use with never use and had similar results (not shown). We examined the effect in male and female subjects and found results similar to those of the full dataset.

Next, we examined the potential association between LTMA use and SAs within different age groups (5-11, 12-18, and 19-24 years). The adjusted OR in the 5- to 11-year and 12- to 18-year age groups was not much different from that in the full dataset. However, in the 19- to 24-year age group, we found a statistically significantly increased risk (adjusted OR, 5.15; 95% CI, 1.16-22.86). Because of the apparent effect, we further examined the demographic and clinical characteristics in this group. Compared with the full sample, patients in the 19- to 24-year age group had overall higher prevalence of risk factors for suicide, including previous SAs, psychiatric disorders and other diseases associated with suicide, greater exposure to medications known to increase suicide risk, and more severe asthma. To account for the potential effect of these differences on our analysis, we then reassessed the covariates included in our adjusted model and revised the model accordingly, adding previous exposure to both other asthma medications and other drugs associated with suicide. Using this revised model resulted in an adjusted OR of 5.64, but it was no longer statistically significant (95% CI, 0.87-36.66).

DISCUSSION

In this nested case-control study we found no statistically significant association between use of LTMA and SAs in the general population of patients aged 5 to 24 years. This finding is consistent with previous research on the association between LTMA and suicide, including a retrospective review of LTMA clinical trials conducted by the FDA.⁸

After the FDA warning, Jick et al¹³ conducted a population-based cohort study to examine the potential association. The investigators identified 23,500 patients exposed to 1 or more prescriptions for montelukast from 1998 to 2007, representing 21,050 person-years at risk. Only 1 case of suicide was identified, but that was ruled out because montelukast had been prescribed as a single 28-day course 2 years before her death. The authors reported a suicide rate of zero and no association with montelukast. However, this study was limited by the relatively small sample size (especially given the low rate of suicide) and failure to include a comparison group.

We previously conducted 2 related ecologic studies. In the first we examined the association between the number of prescriptions for LTMA dispensed in the United States from 1999 to 2009 (obtained from IMS Health, Inc) and the number of completed suicides reported by the FDA's Adverse Event Reporting System

over the same time period.¹¹ There were 105 completed suicides reported in which an LTMA was implicated, most of which involved montelukast, and all but 9 occurred in 2008 to 2009 after an FDA warning. The number of prescriptions for LTMA increased from 6.9 million in 1999 to 27.8 million in 2007 and then decreased to 25.8 million in 2008 and 25.4 million in 2009. Aggregated suicide rates over the 1999-2009 period were 0.51, 0.24, and 4.09 per million prescriptions for montelukast, zafirlukast, and zileuton, respectively. The suicide rate as a class was 0.06 per million prescriptions in the prewarning period and 1.82 per million prescriptions in the postwarning period.

We also examined the association between LTMA and completed suicides on a county level by using data from the Centers for Disease Control and Prevention.¹² In this mixed-effects Poisson regression analysis, counts of suicide-related deaths in each US county (stratified by race, age group, sex, and year) were compared with counts of LTMA prescriptions dispensed in each US county. We found a negative within-county association between the rate of total LTMA prescriptions dispensed and the suicide rate by county. This association was primarily driven by montelukast.

In the current study we found an adjusted OR of 0.70 (95% CI, 0.36-1.39) across all age groups (full dataset) for the association between current use of LTMA and SA. Although not statistically significant, if anything, this suggests an overall reduction in risk by LTMA. It is not clear why risk might be reduced except that LTMA might result in better control of asthma. Asthma itself has been associated with a more than 4-fold (OR, 4.34; $P < .001$) increase in the likelihood of an SA.^{36,45} Furthermore, a study by Harwood et al⁴⁶ found that respiratory symptoms, including "breathlessness," along with pain and functional limitation, were the most frequent symptoms of health problems contributing to suicide in those with asthma. By controlling asthma symptoms and improving asthma control, LTMA could reduce the risk of suicide. However, we are not aware of any evidence for LTMA or other asthma medications that would support this. In our own data we investigated this and were not able to find this protective effect with other asthma controller medications. Clearly, more investigation of this is necessary.

Our study provides exploratory results that suggest that the effect of LTMA on the risk of SAs might vary by age. We observed an adjusted OR of 5.64 (95% CI, 0.87-36.66) after revising our model for the 19- to 24-year age group. Although not statistically significant, this finding suggests the need for further investigation. We present this as exploratory because we were limited by small sample sizes within age subgroups. Furthermore, there is a possibility that our results for the 19- to 24-year age group suffer from confounding. Patients in this age group are generally at higher baseline risk for suicide than those 18 years or younger.⁴⁷ Although measured confounders were controlled for in our analysis, it is possible that other unmeasured confounders are present and affected the results. For example, it is possible that the effect observed in the 19- to 24-year group was caused by a selection bias associated with the fact that our data were from a commercially insured population. Subjects in this age group typically leave their parents' insurance unless they have health problems (including psychiatric disorders) that prevent them from doing so, and this could result in selection of a more at-risk group in our data. LTMA could also be used preferentially in those with psychiatric disorders because of difficulty administering inhalers, resulting in confounding by indication. Given these findings, we believe that the effect of age on the risk of suicide in those exposed to LTMA requires further

investigation to fully understand whether there are differences across age groups. Although prescribing of LTMA in young adult should not change until more is known, prescribers should always be cognizant of signs of suicidal behavior in these and other patients.

There are several limitations to our study in addition to those already identified that need to be considered when interpreting the results. The source of data for this study was an insurance claims database. Such data are not designed for research purposes and, as a consequence, might suffer from various potential problems described below. Nevertheless, these databases are commonly used for retrospective research and have the advantages of large sample sizes and long follow-up time. However, because the source of data was an insured population, the results might not be generalizable to those without commercial insurance. In fact, previous studies suggest that those without insurance might be at greater risk for suicide.⁴⁸

One potential limitation in these data is the inability to measure true exposure. We defined exposure of LTMA based on prescription fills recorded in the claims data. Prescriptions dispensed are not necessarily the same as exposure because of the inability to measure patient adherence. Because our definitions of exposure (current, immediate past, and past) were based on the prescription fill dates and days' supply, as recorded in the claim; if patients did not take the medications as directed, then we might have misclassified exposure. Indeed, when we measured adherence based on the MPR, we found it to be less than 100%. Nevertheless, there is substantial literature validating the use of prescriptions claims as a measure of drug exposure, and our findings were relatively consistent across the categories of exposure.^{49,50} Furthermore, misclassification of exposure in this way would bias our result toward the null and therefore leads to a more conservative estimate.

The number of subjects exposed to LTMA was relatively low in our data: approximately 6% in the current exposure group and 11% to 16% in the ever exposed group. Although unlikely, it is possible that subjects were exposed but not classified as such, and small changes in the number of exposed cases could result in large changes in our effect estimate. However, there is no reason to believe that misclassification such as this occurred, and if it did, it would typically be nondifferential and thus bias our results toward the null. Furthermore, our results were consistent across different definitions of exposure.

Another limitation is in identification of SAs. In this study we used ICD-9-CM codes in medical claims to identify SAs. This method might underreport the true number of SAs if health care providers fail to accurately record such events in the medical record. However, ICD-9-CM coding has been reported to have a positive predictive value of 86% for identification of SAs in one study.⁵¹ It should also be noted that our outcome of interest in this study was SAs rather than completed suicides or suicidal ideation, neither of which were available in the administrative data.

Similar to the above, because we used medical claims data, we were limited in our ability to measure certain clinical outcomes, such as asthma symptoms and asthma severity. Asthma severity might be a potential confounder in the association between LTMA and suicide. We did adjust for proxy measures of asthma severity, such as ED visits with a diagnostic code of asthma, short-acting β -agonist canisters dispensed, and number of acute asthma exacerbations, based in part on a previously validated asthma severity index.^{39,40} However, because a claim for an ED visit in the database used might have included up to 4 associated

diagnostic codes, we could not be sure that all the ED visits were for asthma. In fact, because ED visits outnumbered asthma exacerbations, it is likely that some were for reasons other than asthma.

Finally, although we did our best to identify covariates in our database that could be potential confounders in the relationship between LTMA and suicide, it is possible that there are important unmeasured confounders that we could not measure. For example, we did not have access to information on race, socioeconomic class, sexual or physical abuse, family history of suicide, family relationships, access to firearms, or criminal/legal issues, all of which have previously been associated with suicide in children and young adults.⁵²

Our study was restricted to patients aged 5 to 24 years, and for this reason, the results cannot be generalized to other age groups. Our focus on children and adolescents was based on both the fact that LTMA is easier to administer than inhalers and thus more important in children and that in older age groups there tend to be a greater number of risk factors for an SA that are not measurable in administrative data. Examples of these were mentioned above. In fact, this latter rationale likely explains the results we observed in 19- to 24-year-old group.

Again, the stratified analyses that we conducted should be considered exploratory. Some of the subgroups in these analyses lacked sufficient statistical power because of low sample size. Furthermore, we did not adjust our statistical approach for the multiple comparisons made in these analyses.

In conclusion, in this analysis we found that use of LTMA was not associated with an increased risk of SAs in children, adolescents, and young adults with asthma. In fact, we observed a trend for a protective effect of LTMA, although this was not statistically significant. However, we did find exploratory evidence that the association between LTMA and SAs might vary by age group, with potentially increased risk in those 19 to 24 years of age. Further research needs to be conducted to more fully understand the association between LTMA and suicide, particularly in subgroups by age (including adults). Ideally, future research studies would also include information on covariates that might be important confounders but are not available in the type of data we used for this study. Although suicides are rare, future studies might benefit from richer clinical information that could be captured in prospective registries or other similar designs.

The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health, Inc, information service: LifeLink Health Plan Claims Database, January 1997–August 2010, IMS Health, Inc. All Rights Reserved. Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health, Inc, or any of its affiliated or subsidiary entities.

We thank Sruthi Adimadhyam for her assistance in creating the analytic dataset.

Key messages

- In this study LTMA were not associated with an increased risk of SAs in children, adolescents, and young adults with asthma.
- Further research needs to be conducted in those 19 to 24 years of age.

REFERENCES

1. ACCAAI/AAAAI. Joint statement on FDA investigation of Singulair from the ACCAAI and AAAAI. *Eur Ann Allergy Clin Immunol* 2008;40:64.
2. Centers for Disease Control and Prevention. Asthma at a glance. Atlanta: CDC National Center for Health Statistics—Centers for Disease Control and Prevention; 2010.
3. National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. Bethesda: National Heart, Lung, and Blood Institute; 2007.
4. Riccioni G, Bucciarelli T, Mancini B, Di Ilio C, D'Orazio N. Antileukotriene drugs: clinical application, effectiveness and safety. *Curr Med Chem* 2007;14:1966-77.
5. Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004;20:1549-58.
6. Top 200 drugs for 2010 by sales. Available at: <http://drugs.com/top200.html>. Accessed May 11, 2012.
7. US Food and Drug Administration. Early communication about an ongoing safety review of montelukast (Singulair), 3/23/2009. Postmarket drug safety information for patients and providers. Rockville (MD): US Food and Drug Administration; 2008.
8. US Food and Drug Administration. Follow-up to the March 27, 2008, communication about the ongoing safety review of montelukast (Singulair), 1/13/2009. Postmarket drug safety information for patients and providers. Rockville (MD): US Food and Drug Administration; 2009.
9. US Food and Drug Administration. Updated information on leukotriene inhibitors: montelukast (marketed as Singulair), zafirlukast marketed as Accolate), and zileuton (marketed as Zflo and Zflo CR), 8/28/2009. Postmarket drug safety information for patients and providers. Rockville (MD): US Food and Drug Administration; 2009.
10. Schumock GT, Lee TA, Joo MJ, Valuck RJ, Stayner LT, Gibbons RD. Association between leukotriene-modifying agents and suicide: what is the evidence? *Drug Saf* 2011;34:533-44.
11. Schumock GT, Gibbons RD, Lee TA, Joo MJ, Stayner LT, Valuck RJ. The association between leukotriene-modifying agents and spontaneously reported suicide. *Drug Information J* 2012;46:99-106.
12. Schumock GT, Gibbons RD, Lee TA, Joo MJ, Valuck RJ, Stayner LT. Relationship between leukotriene-modifying agent prescriptions dispensed and rate of suicide deaths by county in the US. *Drug Healthcare Patient Saf* 2011;3:47-52.
13. Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. *Pharmacotherapy* 2009;29:165-6.
14. Jewell N. Assessing significance in a 2 × 2 table. In: *Statistics in epidemiology*. Boca Raton (FL): Chapman & Hall/CRC; 2004. p. 69.
15. Heaton PC, Guo JJ, Hornung RW, Johnston JA, Jang R, Moomaw CJ, et al. Analysis of the effectiveness and cost benefit of leukotriene modifiers in adults with asthma in the Ohio Medicaid population. *J Manag Care Pharm* 2006;12:33-42.
16. Coryell W, Young EA. Clinical predictors of suicide in primary major depressive disorder. *J Clin Psychiatry* 2005;66:412-7.
17. Jolin EM, Weller EB, Weller RA. Suicide risk factors in children and adolescents with bipolar disorder. *Curr Psychiatry Rep* 2007;9:122-8.
18. Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 2005;62:247-53.
19. Haw C, Harwood D, Hawton K. Dementia and suicidal behavior: a review of the literature. *Int Psychogeriatr* 2009;21:440-53.
20. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. *J Affect Disord* 2002;68:183-90.
21. Paris J. The development of impulsivity and suicidality in borderline personality disorder. *Dev Psychopathol* 2005;17:1091-104.
22. Robinson D, Renshaw C, Okello C, Moller H, Davies EA. Suicide in cancer patients in South East England from 1996 to 2005: a population-based study. *Br J Cancer* 2009;101:198-201.
23. Hitiris N, Mohanraj R, Norrie J, Brodie MJ. Mortality in epilepsy. *Epilepsy Behav* 2007;10:363-76.
24. Komiti A, Judd F, Grech P, Mijch A, Hoy J, Lloyd JH, et al. Suicidal behaviour in people with HIV/AIDS: a review. *Aust N Z J Psychiatry* 2001;35:747-57.
25. Robins Wahlin TB. To know or not to know: a review of behaviour and suicidal ideation in preclinical Huntington's disease. *Patient Educ Couns* 2007;65:279-87.
26. Spiegel B, Schoenfeld P, Naliboff B. Systematic review: the prevalence of suicidal behaviour in patients with chronic abdominal pain and irritable bowel syndrome. *Aliment Pharmacol Ther* 2007;26:183-93.
27. Wang SJ. Migraine and suicide. *Expert Rev Neurother* 2007;7:1069-71.
28. Bronnum-Hansen H, Stenager E, Nylev Stenager E, Koch-Henriksen N. Suicide among Danes with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2005;76:1457-9.
29. Soykan A, Arapassan B, Kumbasar H. Suicidal behavior, satisfaction with life, and perceived social support in end-stage renal disease. *Transplant Proc* 2003;35:1290-1.

30. Karassa FB, Magliano M, Isenberg DA. Suicide attempts in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003;62:58-60.
31. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychol Med* 2006;36:575-86.
32. Goodwin RD, Kroenke K, Hoven CW, Spitzer RL. Major depression, physical illness, and suicidal ideation in primary care. *Psychosom Med* 2003;65:501-5.
33. US Food and Drug Administration. Suicidality in children and adolescents being treated with antidepressant medications. Rockville (MD): Food and Drug Administration; 2004.
34. US Food and Drug Administration. Suicidal thoughts and behavior antiepileptic drugs. Rockville (MD): Food and Drug Administration; 2008.
35. US Food and Drug Administration. Early communication about an ongoing safety review of varenicline (marketed as Chantix). Rockville (MD): US Food and Drug Administration; 2008.
36. Goodwin RD, Eaton WW. Asthma, suicidal ideation, and suicide attempts: findings from the Baltimore epidemiologic catchment area follow-up. *Am J Public Health* 2005;95:717-22.
37. Goodwin RD, Jacobi F, Thfeld W. Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003;60:1125-30.
38. Goodwin RD, Marusic A. Asthma and suicidal ideation among youth in the community. *Crisis* 2004;25:99-102.
39. Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care* 2004;10:25-32.
40. Schatz M, Zeiger RS, Yang SJ, Chen W, Crawford WW, Sajjan SG, et al. Relationship of asthma control to asthma exacerbations using surrogate markers within a managed care database. *Am J Manag Care* 2010;16:327-33.
41. Greenland KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.
42. Brent DA. Risk factors for adolescent suicide and suicidal behavior: mental and substance abuse disorders, family environmental factors, and life stress. *Suicide Life Threat Behav* 1995;25(suppl):52-63.
43. Beautrais AL. Risk factors for suicide and attempted suicide among young people. *Aust N Z J Psychiatry* 2000;34:420-36.
44. Pang D. A relative power table for nested matched case-control studies. *Occup Environ Med* 1999;56:67-9.
45. Druss B, Pincus H. Suicidal ideation and suicide attempts in general medical illnesses. *Arch Intern Med* 2000;160:1522-6.
46. Harwood DM, Hawton K, Hope T, Harriss L, Jacoby R. Life problems and physical illness as risk factors for suicide in older people: a descriptive and case-control study. *Psychol Med* 2006;36:1265-74.
47. Heron MP, Hoyert DL, Murphy SL, Xu JQ, Kochanek KD, Tejada-Vera B. Deaths: final data for 2006. *National vital statistics reports*; Vol 57, No. 14. Hyattsville (MD): National Center for Health Statistics; 2009.
48. Lang M. The impact of mental health insurance laws on state suicide rates. *Health Econ* 2011[Epub ahead of print].
49. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol* 1997;50:619-25.
50. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;50:105-16.
51. Iribarren C, Sidney S, Jacobs DR Jr, Weisner C. Hospitalization for suicide attempt and completed suicide: epidemiological features in a managed care population. *Soc Psychiatry Psychiatr Epidemiol* 2000;35:288-96.
52. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. *J Child Psychol Psychiatry* 2006;47:372-94.