Association Between Leukotriene-Modifying Agents
and Suicide in Patients with Asthma

BY

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THESIS
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AAAAI</td>
<td>American Academy of Allergy, Asthma and Immunology</td>
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<tr>
<td>ACAAI</td>
<td>American College of Allergy, Asthma and Immunology</td>
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<tr>
<td>AERS</td>
<td>Adverse Events Reporting System</td>
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<tr>
<td>AED</td>
<td>Antiepileptic Drug</td>
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<td>CDC</td>
<td>Centers for Disease Control</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CMF</td>
<td>Compressed Mortality File</td>
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<tr>
<td>EB</td>
<td>Empirical Bayes</td>
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<td>ED</td>
<td>Emergency Department</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus/Acquired Immune Disease</td>
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<tr>
<td>IAC</td>
<td>Inhaled anticholinergic</td>
</tr>
<tr>
<td>ICD-9-CM</td>
<td>International Classification of Diseases Ninth Revision Clinical Modification</td>
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<tr>
<td>ICS</td>
<td>Inhaled corticosteroid</td>
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<tr>
<td>LABA</td>
<td>Long-Acting Beta-Agonist</td>
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<td>LTMA</td>
<td>Leukotriene-Modifying Agent</td>
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<tr>
<td>MMLE</td>
<td>Maximum Marginal Likelihood Estimate</td>
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<td>MPR</td>
<td>Medication Possession Ratio</td>
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<tr>
<td>NCHS</td>
<td>National Center for Health Statistics</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>SA</td>
<td>Suicide Attempt</td>
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<td>SABA</td>
<td>Short-Acting Beta-Agonist</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin-Reuptake Inhibitor</td>
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SUMMARY

This dissertation examines the association between leukotriene-modifying agents (LTMAs) and suicide. Based primarily on case reports, the United States Food and Drug Administration (FDA) issued safety alerts and required manufacturers of these agents to include suicide and neuropsychiatric events as a precaution in the drug label for LTMAs. Up to now there were no well-conducted observational studies of this association.

The LTMAs are effective drugs for the treatment of asthma and allergic rhinitis, and the presence of the FDA warning has the potential to result in these drugs being withheld from those who may benefit from them. More objective evidence to confirm or refute the association between LTMAs and suicide is needed so that clinicians and patients can make informed decisions about the balance of risks and benefits from their use. The purpose of this dissertation was to provide that evidence.

The null hypothesis was that there is no association between LTMAs and risk of suicide. Three studies were conducted to test this hypothesis. The first was an analysis of spontaneously reported suicides (completed suicides and suicide attempts) in the FDA Adverse Event Reporting System (AERS) using the Poisson method developed by Gibbons and others, which included a proxy denominator of LTMAs prescriptions dispensed in the United States. The second was an ecologic analysis of completed suicides and the prescribing rates of LTMAs at the county-level. The third was a patient-level case-control study using data from a national prescription and medical insurance-based claims database with suicide attempts as the outcome of interest.

The dissertation is comprised of five separate chapters. The first chapter serves as the background. It was published in the journal Drug Safety and titled “Association between
SUMMARY (continued)

Leukotriene-modifying agents and suicide: What is the evidence?"¹ It is both a review of the existing evidence examining the potential association between the LTMA and suicide behavior, and also a report of the findings of a descriptive analysis of spontaneous reports of suicide-related events attributed to LTMA that were submitted to the FDA.

The second chapter of the dissertation was published in the Drug Information Journal and titled “The association between leukotriene-modifying agents and spontaneously reported suicide.”² The purpose of this study was to examine the association between LTMA and completed suicide. Data from the FDA AERS from the period 1999 to 2009 were used to identify the number of completed suicides for each LTMA. Data from IMS Health were used to determine the number of prescriptions dispensed by drug in the same time period. The rate of completed suicides per million prescriptions for each drug was calculated, and Empirical Bayes (EB) rate multipliers and 95% confidence intervals (CI) were determined using a mixed-effects Poisson regression analysis. Selective serotonin-reuptake inhibitors (SSRIs) and short-acting beta-agonist (SABAs) were analyzed for comparison purposes.

The third chapter of the dissertation was published in the journal Drug, Healthcare and Patient Safety and titled “The relationship between leukotriene-modifying agent prescriptions dispensed and the rate of suicide deaths by county in the United States.”³ The objective of this study was to explore the relationship between LTMA and suicide deaths using data preceding the FDA warnings. A mixed-effects Poisson regression analysis of the association between LTMA prescriptions dispensed and suicide deaths at the county-level was conducted.

The fourth chapter of the dissertation was submitted to the Journal of Asthma and Clinical Immunology and is titled “Risk of suicide attempt in asthmatic children and young adults
SUMMARY (continued)

prescribed leukotriene-modifying agents.” A case-control study was conducted to determine the association between LTMAs and attempted suicide. Cases and controls were from a cohort of asthmatics age 5 to 24 years who were new users of LTMA or other asthma medications. Data were from an insurance claims database. Conditional logistic regression was used to determine the association between LTMA exposure and risk of attempted suicide adjusted for important covariates.

The final chapter provides a conclusion to the entire dissertation. The overall conclusion from this body of work is that LTMAs are not associated with suicide. This finding was generally consistent across the three studies that were conducted. While it is the responsibility of the FDA to alert the providers and the public in the event of suspected risk of pharmaceuticals, once evidence to the contrary becomes available then such warnings should be reconsidered. In the case of LTMAs, this dissertation and the papers associated with it provide evidence that these drugs are safe and not associated with suicide. Nevertheless, additional research on this subject can only be beneficial. Independent confirmation of these results would provide additional assurance about the safety of LTMAs.
1. ASSOCIATION BETWEEN LEUKOTRIENE-MODIFYING AGENTS AND SUICIDE: WHAT IS THE EVIDENCE?—BACKGROUND AND ANALYSIS OF SPONTANEOUS REPORTS

1.1 Preface

This chapter of the dissertation was published as article in the journal Drug Safety titled “Association between leukotriene-modifying agents and suicide: What is the evidence?” The full citation is provided in the reference section.1 Included here is the pre-publication version of the paper. Copyright permission for this use is described at http://adisonline.com/home/Documents/AuthorRights.pdf. The paper is both a review of the literature (i.e., Background) on the association between LTMA s and suicide, and a descriptive analysis of spontaneous reports from the FDA MedWatch system.

1.2 Introduction

Suicide is a significant public health issue. In the United States there were 33,300 people who died from suicide in 2006 making it the 11th leading cause of death, while approximately one million people die worldwide from suicide each year.4, 5 The United States and global age-adjusted rates of death from suicide are 10 and 16 per 100,000 respectively.4, 6

Males are at nearly 4 times greater risk for completed suicide compared to females, with white males having the highest rate at 19.8 per 100,000.4 Suicide occurs both in adolescents and adults, with rates increasing until middle age, declining around age 50 to 70, and then increasing again late in life, as shown in Figure 1.6 Lost productivity associated with suicides in the United States has been estimated at $636,406 for each completed suicide, or approximately $21.2 billion total in 2006.7

While there are many reported risk factors, more than 90% of suicides in the United
States are associated with psychiatric illness. The most common type of psychiatric illness is affective disorders, which are present in more than half of all suicides, followed by substance abuse, and schizophrenia.\textsuperscript{8} Studies have reported suicide in 4\% to 15\% of people with depression,\textsuperscript{9} bipolar disorder,\textsuperscript{10} and schizophrenia.\textsuperscript{11} Increased risk of suicide has also been reported among those with dementia,\textsuperscript{12} eating disorders,\textsuperscript{13, 14} anxiety\textsuperscript{15} and panic disorders, attention deficit disorder,\textsuperscript{16} personality disorders,\textsuperscript{17} and body dysmorphic disorder.\textsuperscript{18, 19}

Figure 1. Rate of suicide by age in the United States.

Over the past five years there has been an increasing recognition of the potential for certain prescription medications to increase the risk of suicide.\textsuperscript{20} Based primarily on spontaneous adverse drug event reports (e.g., via the MedWatch system), the FDA has issued warnings about psychiatric symptoms and suicidality for whole classes of medications, including SSRIs\textsuperscript{21-24} which was expanded to all antidepressants,\textsuperscript{21, 25} antiepileptic drugs (AEDs),\textsuperscript{26} and more recently LTMAs.\textsuperscript{27-29}
The LTMA s are effective drugs for the treatment of asthma and allergic rhinitis, see Table I. Among these montelukast is the most popular. In 2008, Singulair, the brand product of montelukast, was ranked number seven among the top selling prescription drugs in the United States, with $2.9 Billion in sales,\textsuperscript{30} while world-wide sales of Singulair were $3.6 Billion (2006).\textsuperscript{31} The widespread use of LTMA s heightens the concern about the potential association with suicide. At the same time, excessive caution could mean that effective therapies are withheld from patients who could benefit from them.

In this article we review the evidence for the potential association between LTMA s and suicide, and we make recommendations for current practice and future research. We are aware of only one previous review on this subject,\textsuperscript{32} which we expand and update here.

**TABLE I**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Food and Drug Administration Approved Indication (Date)</th>
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<tr>
<td>Montelukast</td>
<td>Singulair</td>
<td>Merck and Co. Inc.</td>
<td>Asthma (2/20/98) Allergic rhinitis (12/31/02)</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Accolate</td>
<td>AstraZeneca Pharmaceuticals</td>
<td>Asthma (9/26/96)</td>
</tr>
<tr>
<td>Zileuton</td>
<td>Zyflo and Zyflo-CR</td>
<td>Cornerstone Therapeutics Inc.</td>
<td>Asthma (12/9/96)</td>
</tr>
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1.3. **Suicide and Respiratory Diseases**

Because LTMA s are used for both asthma and allergic rhinitis, it is important to recognize the underlying risk for suicide in these populations. Recent evidence has established
a clear link between common respiratory diseases and suicidal behavior, although the potential for such an association was identified as early as the mid-1960s. Asthma and allergic rhinitis have each been independently linked to suicide, and these are also often co-morbid conditions, making the potential relationship to suicide even more complex.

1.3.1 Asthma

Asthma is a chronic respiratory disease that affects about 22.2 million Americans (or 1 in every 15 people) in 2005. While asthma occurs in people of all ages it is the most common chronic condition among children. Adults with asthma are more likely to be female, whereas in children asthma more commonly affects males.

People with asthma have been found to be at increased risk for a variety of mental disorders. Goodwin and others found that lifetime severe asthma was associated with the increased likelihood of anxiety disorder (OR 2.09, 95% CI 1.3–3.36), panic disorder (OR 2.61, 95% CI 1.29–5.25), panic attacks (OR 2.84, 95% CI 1.66–4.89), social phobia (OR 3.28, 95% CI 1.42–7.59), specific phobia (OR 2.93, 95% CI 1.71–5.0), generalized anxiety disorder (OR 5.51, 95% CI 2.29–13.22), and bipolar disorder (OR 5.64, 95% CI 1.95–16.35). Associations were even stronger in the time period during or immediately following an asthma exacerbation.

Asthma has also been associated with suicidal ideation, with odds ratios ranging from 1.9 in adults to 3.25 in youths (compared to those without asthma). Asthma has been associated with a more than 4-fold (OR 4.34, p < 0.001) increase in the likelihood of a suicide attempt. A recent study by Clarke and others suggested that people with asthma are more likely to have suicidal ideation and attempt suicide, rather than suicidal ideation without attempts. This would indicate that asthma is associated with the more severe form of suicide behavior (i.e., suicide attempts) rather than just ideation.
The reasons why those with asthma are more likely to commit suicide is unclear. A study by Harwood and others found that physical health problems were present in 82% of successful suicides in older adults. “Breathlessness,” along with pain and functional limitation, were the most frequent symptoms of health problems contributing to suicide in those with asthma. Concern about the symptoms of asthma may contribute to the various mental disorders (anxiety, panic, depression) that have been associated with the disease. Thus, it seems likely that depression or these other mental disorders are intermediate variables in the pathway between asthma and suicide, as shown in Figure 2.

| Asthma and/or Allergic Rhinitis | Depression or other Mental Disorders | Suicidal Ideation | Suicide Attempt |

Figure 2. Potential causal pathway.

1.3.2 **Allergic Rhinitis**

Allergic rhinitis is a very common condition. Approximately 40 million people in United States, or about 10% to 30% of adults and 40% of children, have allergic rhinitis. The disease typically presents in early school age and is characterized by sneezing, running nose, and nasal congestion. It is primarily caused by an allergic reaction to pollen or other allergens. Allergic rhinitis has traditionally been categorized as seasonal (now called “intermittent”) or perennial (now called “persistent”)—based on the allergens being present either seasonally (or intermittently) or all the time (persistence). Seasonal allergic rhinitis is the more common type, though the prevalence of each is increasing worldwide because of increased exposure to

Allergic rhinitis results in 3.5 million lost workdays and 2 million lost school days annually, and has a negative impact on quality of life. The association between suicidality and allergies is not as clear cut as that with asthma. The link was first considered because of the observation that, contrary to what one might expect, suicides are more common in Spring rather than Fall or Winter. This observation was made in both hemispheres. Of course allergies too are more common in the Spring. Subsequent studies found seasonal variation in suicides rates in those with allergic disorders, with higher rate corresponding to peaks in disease. The reasons for the seasonal correlation between allergies and suicidality are not well understood, though a logical hypothesis is that Spring time increases in pollen result in the onset of symptoms of the disease which leads to worsening mood or depression—the most common risk factor for suicide. Allergic conditions have also been associated with other mental illnesses—including anxiety, depression, hostility/aggression, and sleep disturbances—all of which may also be related to suicide. Thus, like asthma, it seems likely that depression or these other mental disorders may be intermediate variables in the pathway between allergic rhinitis and suicide, as shown in Figure 1.

Many asthmatics also have allergic rhinitis. Given the increased risk of suicide in those with allergic rhinitis, studies of the relationship between asthma and suicide clearly need to control for concomitant allergic rhinitis.

1.4 Food and Drug Administration Alerts About Potential Association Between Leukotriene-Modifying Agents and Suicide

The FDA first issued a safety alert for Singulair in March 2008. In that communication the FDA indicated that the manufacturer, Merck and Co. Inc., had “updated the prescribing
information and patient information for Singulair to include the following post-marketing adverse events: tremor (March 2007), depression (April 2007), suicidality (suicidal thinking and behavior) (October 2007), and anxiousness (February 2008). The FDA was apparently first alerted to the possible link between montelukast and suicide as a result of a media report of a 15-year-old in New York who killed himself 17 days after starting to take the drug for allergies.65

Subsequent to its initial communication (March 2008), the FDA requested the manufacturers of all three LTMAs, including montelukast, (Singulair, Merck and Co.), zafirlukast (Accolate, Astra Zeneca), zileuton (Zyflo and Zyflo CR, Cornerstone Therapeutics), to submit data on suicidality adverse events, as well as mood and behavioral-related adverse events, from all available placebo-controlled clinical trials. According to the FDA,29 Merck reported one case of suicidal ideation but no completed suicides out of 9,929 montelukast-treated patients across 41 placebo-controlled trials. There were no events among 7,780 placebo patients. Astra Zeneca reported no cases of suicidal ideation or completed suicide among 7,540 zafirlukast-treated patients in 45 placebo-controlled clinical trials. However, there were two patients in the placebo group (out of 4,659 = 0.04%) that had suicidality (one suicide attempt and one suicidal ideation). Cornerstone Therapeutics report no cases of suicidal ideation or completed suicides in 1,745 zileuton treated or 1,063 placebo-treated patients in 11 clinical trials. FDA’s conclusion from this analysis was that, while these data do not suggest that montelukast, zafirlukast, or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events. A separate review of placebo-controlled pediatric studies of montelukast found similar results.66 Among 2,751 pediatric patients in four multicenter placebo-controlled studies there were no neuropsychiatric adverse events.

In the same communication, the FDA provided information on post-market reports of neuropsychiatric events associated with the LTMAs. According to the FDA, “most of the reports
of neuropsychiatric events are associated with montelukast, [but] the paucity of reports involving zafirlukast and zileuton make assessment of drug–induced effects with these limited."

Nevertheless, the FDA warned that “patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents.”

The most recent communication from FDA, dated June 2009, stated that post-market reports of patients on these medications included “cases of neuropsychiatric events, [some of which] included clinical details consistent with a drug-induced effect.” Finally, the FDA indicated that it had requested that manufacturers include a precaution in the drug prescribing information (drug labeling) for all three drugs.

1.5. **Spontaneous Adverse Event Reports**

A January 15, 2009 report from the Institute for Safe Medication Practices (Horsham, Pennsylvania) provided a summary of adverse drug events related to montelukast reported to FDA’s MedWatch Safety Information and Adverse Event Reporting Program. The report identified a surge in “aggressive and suicidal behavior in children and adults” taking montelukast, with 644 cases identifying montelukast as the principal suspect drug in the second quarter of 2008 alone. The surge in cases was attributed to the FDA public alert in 2008—which presumably caused clinicians to become more aware of and report such events. According to the Institute for Safe Medication Practices report, a total of 712 montelukast-related adverse event cases were received by the FDA in the 13 weeks after the initial FDA notice, whereas just 206 reports were filed in the 116 weeks prior to the notice. Among those cases listing “psychiatric side effects”, just 24 (4%) were received by the FDA prior to the initial safety notice, whereas 602 (96%) after the warning.

In order to better quantify LTMA-related suicide event reports in the FDA AERS we
analyzed reports associated with all three LTMAs available on the United States market for the period 1998-2009 (1998 being the earliest data available and 2009 the most recent). Reports were included where one of the three LTMAs of interest was listed as a primary or secondary suspected drug cause. Only initial reports were counted and duplicate cases were eliminated. Reports were identified where the terms “suicide” or “suicidal” were part of the Medical Dictionary for Regulatory Activities preferred term used by AERS for the reaction description. Where more than one suicide-related reaction was listed for a single case we used the higher order term in the following manner: completed suicide > suicide attempt > suicidal ideation > suicide behavior > depression suicidal.

In total we identified 838 LTMA-associated cases, with the majority (96.1%) occurring in 2008 or 2009. As shown in Table II, suicidal ideation was the most common type of event, followed by suicide attempt, and completed suicide. As shown in Table III, montelukast was the suspected drug cause in all but five events (zileuton was the suspected cause in the other five, while there were no cases for zafirlukast). Among the 838 cases, an equal proportion were males (391, 46.7%) versus females (384, 45.8%), and the average age was 25.1 years [standard deviation (SD) 19.6).

Spontaneous reporting data such as these have a number of important limitations that have been reviewed elsewhere, not the least of which is lack of denominator data necessary to calculate a rate.\textsuperscript{68} Clearly other, more rigorous methods are necessary to further elucidate the potential association between LTMAs and suicide-related events.

1.6 **Other Evidence of Leukotriene-Modifying Agent-Suicide Association**

The literature contains little other evidence to support the FDA precaution on LTMAs. After the initial FDA alert was issued, Holbrook and Harik-Kan published an analysis of the
association between montelukast and depression based on data from three previously published randomized controlled clinical trials involving 504 patients exposed to montelukast.\textsuperscript{69} Using emotional well-being as a marker for depression they reported no evidence of a negative effect from montelukast. In fact, to the contrary there was some evidence of short-time improvement in quality-of-life measures of emotional well-being compared to placebo. They also reported no cases of psychiatric disturbances, suicide, or depressive episodes in any of the patients who received montelukast in these trials. These data are limited by the small number of patients enrolled, the indirect measure of depression used, exclusion of patients with previous psychiatric disorders, and short-term follow-up.

The potential association between montelukast and neuropsychiatric events was first raised in 2001 when Biswas and others had reported 36 cases of insomnia and 5 cases of depression among 15,612 patients treated with montelukast.\textsuperscript{70} Other adverse event case report-based data have been reported. A May 2007 report by the Netherlands Pharmacovigulance Centre summarized four cases of apparent montelukast-induced depression. Three of the four cases were in patients who did not suffer depressive symptoms prior to starting montelukast.\textsuperscript{71} Depressive symptoms started soon after initiation of montelukast and ended with discontinuation of the drug.

In March 2008 Brunlof and others, using the Swedish Adverse Drug Reaction Database, reported a high number of safety events for montelukast used in children.\textsuperscript{72} Many of the adverse effects reported were neuropsychiatric in origin, including nightmares, sleep disorders, aggressiveness, and anxiety. A follow-up study, using the same database was published in June 2009 and used Bayesian Confidence Propagation Neural Network methods to confirm the signal.\textsuperscript{73} A total of 48 reports of psychiatric disorders in children during treatment with
TABLE II

LEUKOTRIENE-MODIFYING AGENT SUICIDE-RELATED EVENTS REPORTED TO THE UNITED STATES FOOD AND DRUG ADMINISTRATION BY YEAR AND TYPE OF EVENT

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Number of events (% of total for major categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1998 to 2007</td>
</tr>
<tr>
<td>Completed suicide</td>
<td>4</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>10</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>18</td>
</tr>
<tr>
<td>Suicidal behaviour</td>
<td>1</td>
</tr>
<tr>
<td>Depression suicidal</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33 (3.9)</td>
</tr>
</tbody>
</table>

TABLE III

LEUKOTRIENE-MODIFYING AGENT SUICIDE-RELATED EVENTS REPORTED TO THE UNITED STATES FOOD AND DRUG ADMINISTRATION BY YEAR AND DRUG

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of events (% of total for major categories)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1998 to 2007</td>
</tr>
<tr>
<td>Montelukast</td>
<td>33</td>
</tr>
<tr>
<td>Zileuton</td>
<td>0</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>33 (3.9)</td>
</tr>
</tbody>
</table>

montelukast were identified. Psychiatric disorders reported more than once included nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity, and personality disorder; but not suicide. In most cases, time from exposure to adverse event was less than one week. The authors reported that a positive statistical signal for psychiatric disorders was identified by the fourth quarter of 1998, and that the signal was even more significant by the fourth quarter of 2007. The authors concluded that psychiatric ADRs occurred during montelukast treatment in children more often than expected. Like other numerator-based analyses of spontaneous event reports, this study lacked...
consideration of the population at risk.

Only one retrospective cohort study on the association between montelukast and suicide has been published. Jick and others conducted a population based cohort study using data from the United Kingdom General Practice Research Database. The investigators identified 23,500 patients exposed to one or more prescription for montelukast from February 1998 to March 2007, representing 21,050 person-years at risk. Only one case of suicide was identified, but this was in a woman who had been prescribed a single 28-day course of montelukast approximately 2 years prior to her death. The case was therefore ruled-out and the author reported a suicide rate of zero. This study was limited by the relatively small sample size (especially given the low rate of suicide), and failure to include a comparison group.

1.7 **Biologic Plausibility of Leukotriene-Modifying Agent-Suicide Association**

In addition to the limited evidence of an association between LTMAs and suicide behavior, there is also no clear pharmacologic mechanism through which montelukast or other leukotriene inhibitors might cause suicide or neuropsychiatric effects. Montelukast and zafirlukast are leukotriene antagonists, which bind and block the CysLT₁ receptor in the cell membrane. By blocking these receptors the drugs prevent the effects of cysteinyl leukotrienes (leukotriene C₄, leukotriene D₄, and leukotriene E₄), which act to recruit inflammatory cells, alter vascular permeability, hinder ciliary function, and promote bronchoconstriction. Zileuton works further upstream by inhibiting 5-lipoxygenase and thus the production of leukotriene A₄ which is eventually converted into the cysteinyl leukotrienes.

Leukotrienes do exist in the brain and central nervous system, but their exact role there is unclear. Like elsewhere, brain leukotrienes are involved in inflammation. Brain astrocytes and microglial cells generate several inflammatory mediators, including leukotrienes. These
mediators and the components of the complement cascade play an important role in the etiology of most of the neuroinflammatory disorders.\textsuperscript{77} It is also known that leukotrienes are involved in pain response.\textsuperscript{76} At the same time montelukast and other LTMAs penetrate the blood brain barrier and can be found in significant concentrations in brain tissue.\textsuperscript{78} In fact, montelukast has even been studied as a neuroprotective agent in traumatic brain injury,\textsuperscript{79} and for treatment of focal cerebral ischemia,\textsuperscript{80} and migraine headaches.\textsuperscript{81}

It has been suggested that inhibition of leukotriene receptors in the brain could be responsible for the neuropsychiatric adverse effects reported, though it is not clear why.\textsuperscript{82} Another theory is that when montelukast binds to the CysLT-1 receptor it produces nitric oxide which is toxic to brain tissue.\textsuperscript{83} However, there appears to be no objective evidence to support this mechanism.

1.8 **Recommendations**

1.8.1 **Recommendations for Research**

There remains a lack of definitive data supporting the association between montelukast or other LTMAs and suicide.\textsuperscript{84} As described above, the FDA stance is that “the clinical details of some adverse event reports involving montelukast are consistent with a drug-induced effect”, and has issued a precaution for the entire class. To the contrary, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have issued a joint statement stating that “there are no data from well-designed studies to indicate a link between Singulair and suicide [and] it is unknown whether there is an increased incidence of suicide in patients receiving Singulair.”\textsuperscript{84}

In our opinion the AAAAI/ACAAI statement about lack of well-designed studies is correct. As stated above, the only cohort study conducted to date had an insufficient sample
size and no control group for comparison. Even considering the elevated baseline rate of suicide in those with asthma, the sample of exposed patients would likely need to be an order of magnitude larger to observe an effect from montelukast if one exists. In fact, our preliminary estimates are that a sample in the tens of thousands would be necessary. Because of this, only a retrospective cohort analysis using existing data, such as a prescription and medical insurance-based claims or electronic medical record data, may be practical.

However, such a study may be limited by lack of availability of the outcome of interest. While completed suicides may be the primary outcomes of interest, only related measures, such as suicide attempts, suicide ideation, or suicide behavior (generally considered an umbrella term) may be available. In medical claims data the most commonly available suicide-related outcome is suicide attempt. Suicide attempts are recorded in these data as event codes (e-codes) and likely suffer from under-reporting, though there is not good information on the validity of suicide data for research purposes. Linking exposure (to LTMAs) information from prescription claims to data on cause of death (e.g., from the National Death Index) or other sources of compete suicides would be more reliable but perhaps cost prohibitive.

1.8.2 **Recommendations for Practice**

Regardless of whether a true association exists between LTMAs and neuropsychiatric events, the presence of the FDA precaution and subsequent media attention has the potential to reduce utilization of these drugs in a manner similar to that which occurred in the case of antidepressants following their FDA warning. The FDA warnings on antidepressants had a profound effect of reducing utilization of medications that are beneficial and necessary for people with serious disease. This resulted in a paradoxical effect of increased suicides because effective treatment was being withheld from patients who needed it. In addition,
good observational studies have now been conducted that show convincingly that the risk of suicide is lower, not higher, with exposure to the antidepressants. The same may be true for AEDs, where recent data show that there may be no association with suicide attempts. The case of antidepressants and AEDs highlights the importance of weighing the benefits of early disclosure of potential but unconfirmed safety issues against the risks that may be incurred should those warnings result in the withholding of necessary treatment.

Given the current lack of evidence regarding the association between LTMAs and suicide, what are clinicians to do? Clearly one should not completely ignore the fact that such an association may exist. Nevertheless, given the effectiveness of LTMAs, these drugs should not be withheld in patients who might benefit from them. For now, taking extra precaution in those who may be at elevated risk for suicide, and monitoring more carefully for neuropsychiatric effects is warranted.

1.9 **Conclusions**

While the FDA has issued alerts about the potential association between LTMAs and suicide, there are no well-conducted, comparative, observational studies of this association. Until such studies are conducted (which we recommend) clinicians should consider the potential when prescribing LTMAs, and should monitor patients who may be at elevated risk of suicide carefully.
2. THE ASSOCIATION BETWEEN LEUKOTRIENE-MODIFYING AGENTS AND SPONTANEOUSLY REPORTED SUICIDE—AN ECOLOGIC STUDY USING FDA DATA

2.1 Preface

This chapter of the dissertation was published as article in the Drug Information Journal and titled “The association between leukotriene-modifying agents and spontaneously reported suicide.” The full citation is provided in the reference section. Included here is the pre-publication version. Copyright permission for this use is described at http://www.sagepub.com/authors/journal/permissions.sp#3. This paper describes the first of the three studies that comprise the dissertation research.

2.2 Introduction

Suicide is a significant public health issue both in the United States, where it is the 11th leading cause of death, and worldwide. While there are many causes and risk factors for suicide, over the past 5 years there has been an increasing recognition of the potential association between use of certain prescription medications and suicide. The United States FDA has issued warnings about psychiatric symptoms and suicidality for entire classes of medications, including antidepressants, AEDs, and more recently LTMAs.

The LTMAs, which in the United States include montelukast (Singulair, Merck and Co. Inc.), zafirlukast (Accolate, AstraZeneca Pharmaceuticals), and zileuton (Zyflo, Cornerstone Therapeutics Inc.), are an important class of medications used in the treatment of both asthma and allergic rhinitis. These drugs are particularly useful in children because of side effects associated with other options and for asthma because they are available in an oral dosage form. In fact, Singulair is among the top 10 best selling drugs in the United States.
The presence of an FDA precaution has the potential to drastically reduce utilization of LTMAs, in a manner similar to that which occurred in the case of antidepressants. Limiting utilization of LTMAs could have negative health consequences for patients who would otherwise benefit from these agents. For this reason it is important to ascertain whether an association between LTMAs and suicide exists. The FDA warnings were based on case reports, and experts have called for more research to be conducted in order to confirm or refute the presumed association. In this study we attempt to provide additional insight by examining the potential association between LTMAs and spontaneous reports of completed suicide.

2.3 Methods

We conducted a mixed-effects Poisson regression analysis of the association between the LTMAs agents—montelukast, zafirlukast, and zileuton—and completed suicides using data from the FDA and from IMS Health Incorporated.

Data from the FDA AERS from 1999 to 2009 (most recent available) were used to determine the number of reports of completed suicides associated with a LTMA. In the FDA AERS such reports are submitted by health care providers (usually physicians, pharmacists, or nurses), pharmaceutical companies, or rarely the patient/caregiver. Only initial reports of completed suicides were included in this analysis. Other types of suicide-related events (i.e., suicide attempts), and follow-up reports of the same event, were not included. We also excluded reports of events occurring outside of the United States. Reports were included only if the generic or brand name of a LTMA—montelukast (Singulair), zafirlukast (Accolate), or zileuton (Zyflo)—was listed as the primary suspected drug, secondary suspected drug, or concomitant drug. For comparison purposes we also examined reports involving SSRIs—including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. SSRIs are a class
of antidepressants that have been the focus of numerous FDA warnings about increased risk of suicide, and in this analysis were included as a “positive” control. For a potential “negative” control we included reports of completed suicides involving SABAs. To the best of our knowledge SABAs have not been previously associated with suicide, but like LTMA these drugs are used for the treatment of asthma, so any underlying risk of suicide in the patient population could be anticipated to be similar.

The Xponent™ Database from IMS Health Incorporated, was used to determine counts of dispensed prescriptions for each drug identified above for the time period January 1999 to December 2009. These data were based on total dispensed prescriptions from retail (chain, independent, food stores, and mass merchandisers) pharmacies in the United States. The data do not provide information on whether the prescriptions were taken by patients. Nevertheless, these data are commonly used for measuring prescription dispensations and are a reliable representation of total prescriptions dispensed in the United States.

We used the mixed effects Poisson regression analysis approach described by Gibbons and others to analyze these data. This method, which specifically includes denominators adjusting for drug usage, is a more robust alternative to commonly used “numerator-only” methods, such as the Proportional Reporting Ratio, Bayesian Confidence Propagation Neural Network, and Empirical Bayes Screening. This method requires an exact denominator or a proxy denominator. We used the proxy denominator of number of prescriptions dispensed described above because no such denominator is available from the FDA AERS data.

We first determined the rate of completed suicides per million prescriptions for each drug class (LTMA, SNRI, and SABA) by year (1999 to 2009). Next we calculated the aggregated rate of completed suicide per million prescriptions for each individual drug. We also did this for two time periods, 1999 to 2007 and 2008 to 2009, in order to examine changes in reporting that
might have occurred as a result of the FDA warning issued in 2008.

Next we determined the EB estimate and associated rate multiplier for each drug. The rate multiplier describes the deviation of the rate of suicide for a target drug from the overall rate for all drugs in the analysis as a whole. We conducted this analysis first with a model that included LTMA and SSRIs and then for a model that include LTMA and SABAs. Each of these analyses were conducted for the entire dataset (1999 to 2009), and then separately for each of the two time periods of interest (1999 to 2007 and 2008 to 2009). A description of the mixed effects Poisson regression model used is described in detail by Gibbons and others elsewhere. A rate multiplier of 1.0 indicates that the drug has the same rate as the average for the other drugs in the analysis (i.e., SSRIs in the first analysis, and SABAs in the second analysis), a multiplier of 2.0 is twice the average rate, and a multiplier of 0.5 is one-half the average rate. Statistical inference was made by calculating large sample confidence (posterior) intervals for the rate multipliers.

2.4 **Results**

Table IV shows the number of completed suicides reported to the FDA each year from 1999 to 2009 for each of the LTMA. Also shown is the number of prescriptions (in thousands) dispensed in the United States for each LTMA. Last, the calculated rate of suicide per million prescriptions per year is provided. Similar tables were created for the SSRIs and SABAs (not shown).

In total there were 101 completed suicides where montelukast was implicated, and all but nine occurred in 2008 or 2009. Over the entire time period analyzed, only three suicides were reported for zafirlukast and just one for zileuton. The number of prescriptions for zileuton was very low relative to the other two LTMA, therefore the single suicide (in 2009) has a
### TABLE IV

NUMBER OF COMPLETED SUICIDES, PRESCRIPTIONS DISPENSED, AND SUICIDE RATE FOR LEUKOTRIENE-MODIFYING AGENTS BY YEAR IN THE UNITED STATES

<table>
<thead>
<tr>
<th>Drug</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed Suicides</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>62</td>
<td>30</td>
<td>101</td>
</tr>
<tr>
<td>Prescriptions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4,610</td>
<td>7,754</td>
<td>10,565</td>
<td>12,631</td>
<td>16,627</td>
<td>19,734</td>
<td>21,821</td>
<td>24,890</td>
<td>27,306</td>
<td>25,333</td>
<td>24,948</td>
<td>196,217</td>
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<tr>
<td>Suicide Rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.22</td>
<td>0.00</td>
<td>0.00</td>
<td>0.08</td>
<td>0.12</td>
<td>0.10</td>
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<td>0.11</td>
<td>2.45</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed Suicides</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td></td>
<td></td>
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<td>1</td>
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<tr>
<td>Prescriptions&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2</td>
<td>2</td>
<td>25</td>
<td>32</td>
<td>49</td>
<td>48</td>
<td>245</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
<tr>
<td>Completed Suicides</td>
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<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>62</td>
<td>31</td>
<td>105</td>
</tr>
<tr>
<td>Prescriptions&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>12,421</td>
<td>14,088</td>
<td>17,772</td>
<td>20,632</td>
<td>22,538</td>
<td>25,517</td>
<td>27,841</td>
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<td>0.14</td>
<td>0.11</td>
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<td>0.00</td>
<td>0.11</td>
<td>2.40</td>
<td>1.22</td>
<td>0.50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Expressed in thousands

<sup>b</sup> Expressed per million prescriptions
disproportionate influence on the suicide rate for that drug. The aggregated suicide rate over all the years assessed was 0.51 (95% CI 0.42–0.62), 0.24 (95% CI 0.02–0.38), and 4.09 (95% CI 0.05–22.71) per million prescriptions for montelukast, zafirlukast, and zileuton.

In Figure 3 we show rates of completed suicide for LTMAs as a class compared to SSRIs and SABAs. Suicide rates for SSRIs were generally quite high, with an aggregate rate over the entire time period of 2.79 completed suicides per million prescriptions (95% CI 2.69–2.90). The rate for SSRIs appeared to peak in 2005 (at 4.49 completed suicides per million prescriptions), declined until 2007, and then rose again dramatically in 2008. The suicide rate for LTMAs remained near zero until 2008 when the FDA issued the first warning for this class of drugs.64 Prior to the warning, the LTMAs as a class never exceed 0.28 completed suicides per million prescriptions, but in 2008 the rate was 2.40, which is not dissimilar to the rate for SSRIs. The rate for LTMAs aggregated over the entire time period was 0.50 (95% CI 0.41–0.61). This class suicide rate is primarily driven by montelukast because this drug accounts for 94% of all prescriptions for LTMAs. As expected, the rate of completed suicides for SABAs remained near zero (aggregate rate 0.17, 95% CI 0.14–0.21) throughout the time period analyzed.

In Figure 4 we compare the rate of completed suicides per million prescriptions by individual drug for LTMAs, SSRIs, and SABAs. In the 1999 to 2007 period the suicide rate was 0.06 (95% CI 0.03–0.12) and 0.26 (95% CI 0.05–0.75) for montelukast and zafirlukast, respectively (no reported suicides for zileuton in this period), and 0.06 (95% CI 0.03–0.10) for the class. In the 2008-2009 period the suicide rate was 1.83 (95% CI 1.47–2.24) and 10.34 (95% CI 0.13–57.54) per million prescriptions for montelukast and zileuton respectively (no reported suicides for zafirlukast in this time period), and 1.82 (95% CI 1.47–2.23) for the class. Similar data for SSRIs and SABAs are also presented in Figure 4.
Table V provides the EB rate multipliers and their 95% confidence limits derived from the mixed effects Poisson regression analyses that included LTMA and SSRIs. In the table the results are shown separately for each time period and also for the entire period. Figure 5 displays these results graphically for the full time period. In this analysis montelukast and zafirlukast had rate multipliers and upper bounds of the confidence limit less than 1.0. This held true for both time periods (and for the entire period), with the only exception being 2008 to 2009 where zafirlukast had an upper confidence limit greater than 1.0. Zileton had a rate multiplier near 1.0 and CI that included 1.0 regardless of the time period. In contrast, the SSRIs all had EB rate multipliers and lower bounds of their confidence limits greater than 1.0.
Table VI provides the EB rate multipliers and their 95% confidence limits for the analyses that included LTMAs and SABAs, again shown separately for each time period, while Figure 6 displays these results graphically for the full time period. In this case we found that in the early time period (1997 to 2008) there were no significant differences between drugs—that is the LTMAs and SABA all had confidence limits that included 1.0. However, in the 2008 to 2009 time period montelukast had a EB rate multiplier of 5.61 (95% CI 4.46–6.89). This effect also held when the analysis was conducted over the entire time period, as can been seen in Figure 6. Among the SABAs, albuterol and levalbuterol had EB rate multipliers and confidence
limits less than 1.0. The other SABAs, like zileuton, had relatively sparse data (because of low prescription volume) thus wide confidence limits that include 1.0.

2.5 Discussion

In this study we combined counts by year of spontaneously reported completed suicides for which a LTMA was implicated, with a denominator of prescriptions dispensed for the same drug—the later coming data from pharmacies across the United States. We found very few (9 total) completed suicides for these drugs reported prior to 2008. In 2008 there were 62 events reported, and 31 in 2009.

In March of 2008 the FDA first issued a safety alert for LTMA's. In that communication the FDA indicated that the manufacturer of montelukast, Merck and Co. Inc., had “updated the prescribing information and patient information for Singulair to include the following post-marketing adverse events: tremor (March 2007), depression (April 2007), suicidality (suicidal thinking and behavior) (October 2007), and anxiousness (February 2008).” A subsequent review by FDA of clinical trials data found no cases of completed suicide, and only one case of suicidal ideation in over 19,000 patients treated with LTMA's. Nevertheless, the warning was continued and FDA issued a statement to the effect that while these data do not suggest that montelukast, zafirlukast, or zileuton are associated with suicide or suicidal behavior, these clinical trials were not designed specifically to examine neuropsychiatric events.

The dramatic increase in reporting of suicides that we observed following the FDA warning is not surprising. This reporting bias has been a frequently cited limitation of spontaneous event reporting system. While it is likely that these events would not have been reported had the FDA warnings not been issued, we can’t say with the same certainty that the association between the drugs and the events does not exist. Clearly spontaneous reporting
<table>
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<th>Drug</th>
<th>Class</th>
<th>1999 to 2007</th>
<th>2008 to 2009</th>
<th>Entire Period</th>
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<tr>
<td></td>
<td></td>
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<td>Mean 95% CI</td>
<td>Mean 95% CI</td>
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<td></td>
<td>(lower) upper</td>
<td>(lower) upper</td>
<td>(lower) upper</td>
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<td>0.27 0.2207 0.3244</td>
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<td>LTMA</td>
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<td>LTMA</td>
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<td>1.06 0.6168 1.8049</td>
<td>1.20 0.3187 4.5426</td>
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<td>SSRI</td>
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<td>0.99 0.8306 1.1774</td>
<td>1.88 1.7271 2.0469</td>
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<tr>
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<td>1.09 1.0003 1.1795</td>
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## TABLE VI

EMPIRICAL BAYES RATE MULTIPLIER ESTIMATES AND CONFIDENCE INTERVALS BY DRUG FOR LEUKOTRIENE-MODIFYING AGENTS AND SHORT-ACTING BETA-AGONISTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>1999 to 2007</th>
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<th>2008 to 2009</th>
<th></th>
<th>Entire Period</th>
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<td>95% CI (lower)</td>
<td>Mean</td>
<td>95% CI (upper)</td>
<td>Mean</td>
<td>95% CI (lower)</td>
<td>Mean</td>
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<td>2.2788</td>
<td>0.50</td>
<td>0.0317</td>
<td>7.7522</td>
</tr>
</tbody>
</table>
systems are not designed to prove causality. Nevertheless, the apparently direct link between the FDA warnings and the reporting of completed suicides is somewhat disconcerting. Furthermore, we see the same pattern of apparent reporting bias with the SSRIs in Figure 1, where the timing of FDA warnings about SSRIs and suicides in 2003 and 2004 coincides directly with increase reporting of suicides. Reporting then appears to wane for a period before being stimulated again by additional and expanded FDA alerts in 2007.21-25, 96

Despite the issues of reporting bias, the reporting of these events suggests an important signal for further investigation. We used an EB method to test if the rate of reported suicides for LTMA was different than that of SSRIs—a class of drugs known to be associated with suicides.
We also compared LTMA to SABA—a class of drugs that is also used to treat asthma but has not been associated with suicides. In the analysis that included SABA, montelukast clearly demonstrated an elevated rate in the time period after the FDA warnings. However, compared to SSRIs, even in the time period after FDA warnings, montelukast and zafirlukast both had rate multipliers that were significantly lower than those drugs, while the results for zileuton across all analyses were null and likely influenced by sparse data (only a single reported suicide and low prescription volume).

While the reporting of completed suicides clearly seems to have been influenced by the
FDA warnings about suicidality and LTMA, what is unclear from this analysis is the degree to which this represents either underreporting in the early time period (before the warnings), or over-reporting in the later time period (after the warning). It could be that suicides were occurring throughout the time that montelukast was on the market, but that these events were just never recognized until it was brought to the attention of the public. On the other hand, the FDA warnings may have prompted individuals to report suicides in patients taking montelukast even when there was no real link between the two.

Our result should be interpreted with an understanding of the limitations that may exist with the data and associations observed. The numerator used to calculate suicide rates in our analysis was from reports submitted to the FDA AERS. Besides the reporting bias we have already mentioned, there are other problems inherent in spontaneously reported adverse effects data, including under-reporting of events, and problems with reporting quality (missing data and inability to validate). Additionally, besides heightened awareness and reporting secondary to FDA warnings, reporting bias can be related to the length of time the suspected medication has been on the market (i.e., newer products are more likely to be reported), the reporting environment (i.e., reporting is encourage in some hospitals or health care settings but not others), or the severity of the event (i.e., more severe events are more likely to be reported).

A major limitation of the FDA AERs data is the mechanism but which drugs are entered in the database. Drug names are listed as a text field only, and are recorded exactly as reported to the FDA on the adverse event form—meaning that both generic and brand names may be used, and that spelling errors are common. This makes searching the database for drugs of interest difficult, and as a result the accuracy of the counts of events by drug may suffer. We used several different search strategies to capture the greatest number of potentially relevant reports.
A related issue with the FDA AERS data is the way that drugs are categorized in the database. Reporters are instructed to identify up to two suspected products (“primary suspect product” and “secondary suspect product”) along with any concomitant drugs. In our analysis we considered completed suicides where the drug of interest was listed in any one of these fields. However, as a sensitivity analysis we limited the events to include only those where the drug of interest was reported as the primary suspect product, and separately when the drug was either the primary or secondary suspect product. While the number of events changed and subsequently our calculated suicide rates changed, the conclusions of our analyses did not.

The denominator used to calculate suicide rates in our analysis was based on retail prescriptions dispensed in the US. While the retail distribution channel likely captures a majority of the use of these drugs, some utilization occurs in hospitals or other settings that is not captured in these data. Further, prescriptions dispensed are not necessarily the same as exposure because of the inability to measure patient adherence. However, there is substantial literature validating the use of prescriptions claims as a measure of drug exposure.

Some of the drugs we examined had relatively low prescription volume, including zileuton. The EB rate multipliers that we estimated are considered a “shrinkage estimators” because when there are sparse data the estimators will regress towards the overall mean—in this case 1.0. We observed this for zileuton and some of the SABAs as indicated by the wide confidence intervals.

2.6 Conclusions

In summary, we found that rates of reported completed suicides associated with montelukast increased substantially following warnings issued by the FDA. Using a mixed effects Poisson regression model, we found these rates were statistically greater than those of
SABAs, but were lower than SSRIs. While these findings are informative, because of potential biases for the observed associations, it is important to evaluate the association between LTMAss and suicide using more robust study designs and data of higher quality.
3. THE RELATIONSHIP BETWEEN LEUKOTRIENE-MODIFYING AGENT PRESCRIPTIONS DISPENSED AND THE RATE OF SUICIDE DEATHS BY COUNTY IN THE UNITED STATES—AN ECOLOGIC STUDY USING CDC MORTALITY DATA

3.1 Preface

This chapter of the dissertation was published as article in the journal *Drug, Healthcare and Patient Safety* and titled “The relationship between leukotriene-modifying agent prescriptions dispensed and the rate of suicide deaths by county in the United States.” The full citation is provided in the reference section.3 Included here is the pre-publication version. Copyright permission for this use is described at http://www.dovepress.com/author_guidelines.php?content_id=696. This paper describes the second of the three studies that comprise the dissertation research.

3.2 Introduction

In 2008 the United States FDA issued a warning about a potential link between montelukast (Singulair, Merck and Co., Inc., Whitehouse Station, New Jersey, USA) and suicide.64 Later the warning was expanded to all LTMAs.28, 29 These warnings were based primarily on information from case reports. Subsequently, several retrospective evaluations of clinical trials data were conducted, but these found no elevated risk of suicide or other behavior-related adverse events in those treated with LTMAs compared to placebo.29, 66, 108, 109 As a result there was, and remains, controversy about the proposed association.84

Following the initial FDA warning there was a sharp increase in the number of suicide-related events reported to the FDA’s AERS where LTMAs were considered the suspect drug.1, 68 Over 800 such events were reported in 2008 and 2009, while only 33 were reported during the
10 years prior to the FDA warnings. The timing of these “spontaneous reports” in relation to FDA warnings makes it difficult to make conclusions about the association using these data.

In the case of suicides, other sources of data are available that may be used to investigate drug-event associations, while avoiding the limitations associated with spontaneously reported adverse events data. Gibbons and others used data from the NCHS, a division of the Centers for Disease Control (CDC) of the United States Department of Health and Human Services, to obtain the number of suicides deaths by county in the United States. These data were combined with prescription rates for antidepressants to examine the association between antidepressants and suicides. Here we apply the same methodology to explore further the potential association between LTMAs and suicide.

### 3.3 Methods

We conducted a mixed-effects Poisson regression analysis of the association between LTMA prescriptions dispensed and suicides at the county-level (i.e., county was the clustering variable). Annual counts of suicide deaths occurring in each county of the United States were obtained from the Compressed Mortality File (CMF) available from the NCHS for the period January 1, 1999 to December 31, 2006 (most recent available). Mortality data in the CMF are based on information from all death certificates filed in the 50 States and the District of Columbia, excluding deaths of nonresidents (e.g. deaths of nonresident aliens, nationals residing abroad, and residents of Puerto Rico, the Virgin Islands, Guam, and other territories of the United States) and fetal deaths. The suicide counts we obtained for each county were stratified by race (black or non-black), age group (5 to 14, 15 to 24, 25 to 44, 45 to 64, and 65 years and older), sex, and year. The population of each county for these same subgroups was also obtained from the NCHS.
We obtained counts of the number of LTMA prescriptions dispensed in each county of the United States from the Xponent™ database, from IMS Health Incorporated, for the same time period. These data were based on total dispensed prescriptions from retail (chain, independent, food stores, and mass merchandisers) pharmacies in the United States. These data were not available for the demographic subgroups as were the CDC data. Further, these data did not provide information on whether the prescriptions were taken by patients, nor did they provide information on the number of patients taking the medications. Nevertheless, these data are commonly used for measuring prescription dispensations and are a reliable representation of total prescriptions dispensed in the United States. Because antidepressant use has been associated with suicides, we also obtained counts of antidepressant prescriptions dispensed by county from the IMS Health database to use as a covariate in our analysis.

To relate LTMA prescription use to suicide rate, adjusting for county-specific socio-demographic characteristics we used a mixed-effects Poisson regression model in a manner similar to that of Gibbons et al.\textsuperscript{92, 93} The model estimated the overall suicide rate conditional on age, sex, race, year, and LTMA use. We also included antidepressant drug prescriptions dispensed as a covariate. In one model LTMAAs were combined into a single variable, and in another each LTMA (montelukast, zafirlukast, and zileuton) was included separately to examine individual drug effects. To account for differential population sizes across counties, counts of LTMA and antidepressant prescription dispensed were divided by the population of each county in each year. To decompose the overall relationship between suicides and LTMA prescriptions dispensed into intra-county and inter-county components, we included in the models variables representing the county mean drug prescriptions and a yearly deviation from the mean for each LTMA. In the models, age, sex, race, year, antidepressant prescriptions dispensed, and LTMA prescriptions dispensed were considered fixed effects, while the intercept (i.e., county) was
treated as a random effect.

3.4 Results

There were 249,872 suicides in the United States between 1999 and 2006 (inclusive). As shown in Table VII, the annual suicide rate for the entire population ranged from 11.17 per 100,000 (in 2000) to 11.92 per 100,000 (in 2006), with an average of 11.61 per 100,000 for the entire time period. The rate varied widely by age group, race, and sex—with non-black males having the highest rates (20.18 per 1,000) and black females the lowest (1.80 per 1,000). We also calculated suicide rates at the county level. These varied widely with an average county-level suicide rate over the entire time period of 11.42 per 100,000 (95% CI 11.40–11.45).

There were 118.63, 11.68, and 0.12 million prescriptions dispensed for montelukast, zafirlukast, and zileuton respectively between 1999 and 2006. Adjusted for the population, the rate of prescriptions was 55.10, 5.19, and 0.05 per 1,000, as shown in Table VIII. These rates varied by year. The mean LTMA prescription dispensing rate by county was 42.91 per 1,000 (95% CI 42.78–43.04) for montelukast, 4.82 per 1,000 (95% CI 4.81–4.84) for zafirlukast, and 0.05 (95% CI 0.053–0.054) per 1,000 population for zileuton.

Adjusting for county-specific socio-demographic characteristics and antidepressant use, we found a negative within-county association between the rate of total LTMA prescriptions
<table>
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<th>2001</th>
<th>2002</th>
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</tr>
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<td>2.44</td>
<td>1.90</td>
<td>2.19</td>
</tr>
<tr>
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<td>6.70</td>
<td>7.14</td>
<td>7.30</td>
<td>7.55</td>
<td>8.30</td>
<td>7.80</td>
<td>8.52</td>
<td>7.52</td>
</tr>
<tr>
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<td>22.54</td>
<td>23.90</td>
<td>25.10</td>
<td>25.19</td>
<td>25.23</td>
<td>25.65</td>
<td>26.46</td>
<td>24.61</td>
</tr>
<tr>
<td>Total</td>
<td>13.22</td>
<td>13.52</td>
<td>14.32</td>
<td>14.88</td>
<td>15.02</td>
<td>15.42</td>
<td>15.35</td>
<td>16.01</td>
<td>14.78</td>
</tr>
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<td>&gt;65</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1.29</td>
<td>1.59</td>
<td>1.14</td>
<td>1.39</td>
<td>0.74</td>
<td>1.45</td>
<td>0.71</td>
<td>1.21</td>
</tr>
<tr>
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<td>4.29</td>
<td>4.10</td>
<td>4.38</td>
<td>4.02</td>
<td>4.08</td>
<td>4.24</td>
<td>4.17</td>
<td>4.23</td>
</tr>
<tr>
<td>Non-black males</td>
<td>33.80</td>
<td>32.69</td>
<td>33.02</td>
<td>33.42</td>
<td>31.44</td>
<td>30.45</td>
<td>31.13</td>
<td>30.01</td>
<td>31.96</td>
</tr>
<tr>
<td>All ages</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black females</td>
<td>1.71</td>
<td>1.85</td>
<td>1.83</td>
<td>1.69</td>
<td>1.94</td>
<td>1.96</td>
<td>1.97</td>
<td>1.49</td>
<td>1.80</td>
</tr>
<tr>
<td>Non-black females</td>
<td>4.71</td>
<td>4.64</td>
<td>4.76</td>
<td>4.99</td>
<td>4.94</td>
<td>5.38</td>
<td>5.21</td>
<td>5.45</td>
<td>5.02</td>
</tr>
<tr>
<td>Non-black males</td>
<td>19.55</td>
<td>19.52</td>
<td>20.14</td>
<td>20.58</td>
<td>20.27</td>
<td>20.32</td>
<td>20.46</td>
<td>20.54</td>
<td>20.18</td>
</tr>
<tr>
<td>Total</td>
<td>11.22</td>
<td>11.17</td>
<td>11.48</td>
<td>11.76</td>
<td>11.60</td>
<td>11.84</td>
<td>11.81</td>
<td>11.92</td>
<td>11.61</td>
</tr>
</tbody>
</table>

**TABLE VII**

OBSERVED SUICIDE RATES BY AGE, RACE, AND SEX FOR EACH YEAR (1999 to 2006)
TABLE VIII

OBSERVED RATE OF PRESCRIPTIONS DISPENSED FOR LEUKOTRIENE-MODIFYING AGENTS BY YEAR

<table>
<thead>
<tr>
<th>Drug</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
<td>12.77</td>
<td>29.58</td>
<td>39.77</td>
<td>47.09</td>
<td>61.45</td>
<td>72.27</td>
<td>79.20</td>
<td>89.46</td>
<td>55.10</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>7.93</td>
<td>8.43</td>
<td>6.90</td>
<td>5.37</td>
<td>4.18</td>
<td>3.28</td>
<td>2.59</td>
<td>2.17</td>
<td>5.19</td>
</tr>
<tr>
<td>Zileuton</td>
<td>0.14</td>
<td>0.11</td>
<td>0.08</td>
<td>0.06</td>
<td>0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Class Overall</td>
<td>20.83</td>
<td>38.12</td>
<td>46.75</td>
<td>52.52</td>
<td>65.68</td>
<td>75.57</td>
<td>81.81</td>
<td>91.72</td>
<td>60.34</td>
</tr>
</tbody>
</table>

Prescriptions dispensed and the suicide rate. Specifically, we observed that within a given county a one unit increase in prescriptions dispensed for LTMA (i.e., 1 prescription per 1,000 population) was associated with a 0.03% decrease in the suicide rate (maximum marginal likelihood estimate [MMLE] = -0.0003, p = 0.0296). The between-county effect was not significant. To determine whether the observed association was specific to only certain drugs in the LTMA class we fit a model containing each of the individual drugs. Here we found a statistically significant negative (within-county but not between-county) association for montelukast (MMLE = -0.0003, p = 0.0217), but not zafirlukast (MMLE = -0.0016, p = 0.1687) or zileuton (MMLE = -0.0022, p = 0.8890), although the direction of the effect was consistent across all three drugs. The estimated rate multiplier for the montelukast within-county effect was 0.9997 (95% CI 0.9994–0.9999), which means that for every unit increase in montelukast prescriptions (i.e., 1 prescription per 1,000 population) there is a corresponding decrease in the rate of suicides by 0.03%.

Figure 7 shows graphically the relationship between county-level rate of montelukast prescriptions dispensed and the county-level suicide rate. The horizontal axis is montelukast prescriptions dispensed per 1,000 population in quartiles, while the corresponding mean suicide
Figure 7. Relationship between county-level montelukast prescribing rate per 1,000 population and county-level suicide rate per 100,000 population, 1999 to 2006.

rate per 100,000 is shown on the vertical axis. For example, the mean suicide rate for counties in the lowest quartile of montelukast prescriptions dispensed per 1,000 population was 12.97, while the rate was 10.02 in the highest quartile. The figure shows visually the negative association described above.

3.5 Discussion

Our analysis was performed by combining county-level data on suicide deaths with data on prescriptions dispensed for LTMAs, and as such was intended to be exploratory. Our main observation—that as the number of prescriptions dispensed for montelukast increases within a
given county the rate of suicides decreases—is contrary to that which one might anticipate
given the FDA warnings about LTMAs and the subsequent increase in spontaneous reports of
suicides linked to montelukast. Such a finding certainly does not necessarily negate the
importance of the FDA warning, which is intended to alert prescribers and the public about the
possibility that the development of suicidal thoughts or actions may occur in some patients. After
all, it is possible that in some patients LTMAs increase risk while in others risk is mitigated.
Nevertheless, because such warnings can result in drugs being withheld from patients who
might otherwise benefit from them, it is important to conduct research that might better inform
clinical decision making.

It is not clear how montelukast may reduce suicides, if indeed that is the case. However,
both asthma and allergic rhinitis (the two FDA-approved indications for montelukast) are
associated with increased risk for suicide and related behavior. Asthma has also been
associated with a 2-3 times higher risk for suicidal ideation,\textsuperscript{40-42} and more than 4 times higher
likelihood of suicide attempts.\textsuperscript{42, 43} Some data suggest that asthma symptoms including
“breathlessness”, pain, and functional limitations—may contribute to suicide, possibly via
depression.\textsuperscript{45} Similarly, higher rates of suicide have been observed in those with allergic rhinitis
and other allergic disorders, and season variation suicides rates has been linked to

Better control of asthma or allergic rhinitis results in reduced symptoms of disease.
Therefore, a reasonable explanation of our finding could be that LTMAs, because they are
effective in reducing symptoms, reduce the risk of suicide. Still, our results should be considered in the context of the limitations present in our data and in our study design. This was an ecologic study that, like all such studies, had certain limitations that could have confounded our results. These are described in the following paragraphs.

We obtained data on suicides from the NCHS. These data are derived from death certificates. Biases associated miscoding in death certificates has been previously discussed.\textsuperscript{111} However, the sensitivity and specificity of coding of deaths due to suicide has been shown to be very high ( > 90%).\textsuperscript{112} Nevertheless, some uncontrolled variability may exist due to differences at the county-level in qualifications of coroners or medical examiners, frequency and extent of case investigations, and definitions of suicide, that may lead to differential suicide rates. The population estimates for subgroups (by age, sex, race) within counties were also obtained from NCHS CMF. These estimates are projected based on previous census figures and may not be accurate in counties where demographics are changing rapidly.

In our analysis we also used data on retail prescriptions for LTMAs dispensed in the United States. While the retail distribution channel from which these data come likely captured a majority of the use of these drugs, some utilization may occur in hospitals, mail order pharmacies, or other settings that is not included in these data. Further, while the data we used are projected to account for 100\% of the market, the accuracy of such projections at the county-level is unknown. It is also true that prescriptions dispensed are not necessarily the same as exposure because of the inability to measure patient adherence. However, there is substantial literature validating the use of prescriptions claims as a measure of drug exposure.\textsuperscript{106, 107} Last, while there was substantial use of montelukast across the United States in our data, the lower overall rate of prescriptions for zafirlukast and zileuton may have limited our power to detect an association with these drugs if one had existed.
Finally, while we controlled for a number of factors that could confound our results, the data sources we used did not contain many variables that could help us to adjust for confounding in the relationship between LTMA use and suicide. For example, we did not control for county-level prevalence of asthma or allergic rhinitis; or for other diseases (i.e., mental disorders), behaviors (i.e., drug abuse or alcoholism), or socioeconomic factors that have been shown to increase the risk of suicide. Nor did we control for homicide or fatal accident rates, availability of mental health services, or use of prescription drugs other than antidepressants that may be associated with suicide.

3.6 Conclusion

Because our study was ecologic in nature, we are not able to draw any causal inferences from these data. Nevertheless, these results raise questions about the potential LTMA-suicide relationship and provide preliminary evidence—at least for montelukast—that for some patients the association may actually be in the opposite direction (i.e., reduced risk) of that anticipated from the warnings. Clearly additional patient-level research is needed to more definitively establish the presence of an association between LTMAAs and suicide, and to better understand if there might be subgroups of patients that differ with respect to level of risk or even direction of effect.
4. RISK OF SUICIDE ATTEMPT IN ASTHMATIC CHILDREN AND YOUNG ADULTS
PRESCRIBED LEUKOTRIENE-MODIFYING AGENTS—A NESTED CASE-CONTROL STUDY

4.1 Preface

This chapter of the dissertation has been submitted for publication as article in the Journal of Asthma and Clinical Immunology and titled “Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents.” The manuscript is currently under review (as of February 24, 2012). This paper describes the third of the three studies that comprise the dissertation research.

4.2 Introduction

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

Treatment guidelines for asthma have been published by the National Heart Lung and Blood Institute that encourage stepwise therapy based on disease severity, with the goal of asthma control. Several classes of medications are available for long-term control of asthma. While inhaled corticosteroids (ICSs) are often used first, LTMA’s are an effective alternative. These drugs, which in the United States include montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo), are administered orally and therefore particularly useful in children. LTMA’s work by preventing the inflammatory effects of leukotrienes and therefore are also useful in
people with both asthma and allergic rhinitis. Among the LTMA, montelukast is the most popular, in fact the brand product, Singulair, has been among the top ten best selling drugs used in the United Stated for several years.

Beginning in 2008, when the United States FDA first issued a safety alert, there has been concern of a potential association between LTMA and increased risk of suicide. 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.” In June 2009 the FDA requested that manufacturers include a precaution in the drug prescribing information for all LTMA. While the number of suicide-related events related to LTMA reported to the FDA have increased since 2008, it is unclear if such reports are a result of the FDA warning or represent a true association. Ecologic studies have failed to find an association, and the only observational study that has been conducted was limited by a relatively small sample size and failure to include a comparison group. Nevertheless, prescribing of LTMA has declined since 2008.

More objective information is needed about the potential association between LTMA and suicide, particularly in children where because these drugs are easier to administer compared to alternatives. The purpose of this study was to assess the association between LTMA and suicide attempts in children, adolescents, and young adults with asthma.

4.3 Methods

We conducted a case-control study of the association between the LTMA and attempted suicides. Cases and controls 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's or other asthma medications, as shown in Figure 8.

Figure 8. Study design.

4.3.1 **Data Source and Cohort**

The data for this study was obtained from the LifeLink™ Health Plan Claims Database from IMS Health Incorporated. The LifeLink™ Health Plan Database includes adjudicated medical and pharmaceutical claims along with demographic information (e.g. age, gender, and geographic region) and dates of enrollment for over 60 million unique anonymous patients from over 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 and whose age was between 5 and 24 on at least one 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. While the first FDA warnings about a potential association between LTMAs 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 influence prescribing thereafter.64

The cohort was limited to those patients with at least one prescription claim for an asthma controller medication, which included ICS, LTMAs, long-acting beta-agonists (LABAs), methylxanthines, immunomodulators, mast cell stabilizers, and inhaled anticholinergics (IACs); and the date of the first claim for an asthma controller medication was defined as the index date. Patients were excluded if the index date occurred more than 30 days prior to the diagnosis date, if they were less than 5 or greater than 24 years old on their index date, or if their last enrollment date was on or before their index date. The later was considered necessary for accurate assessment of exposure. Individuals were also excluded if they were not continuously enrolled for at least 6 months prior to the index prescription date, or if they had significant gaps in enrollment in either the pre-index or follow-up periods. Significant gaps were defined as greater than or equal to 2 months of continuous disenrollment and greater than or equal to 20% of total months.

Patients were followed until 1) a suicide attempt occurred, 2) disenrollment from the database, or 3) the end of follow-up period (December 31, 2006).
4.3.2 **Cases and Controls**

Cases were defined as those with a suicide attempt (SA) occurring after (at least 1 day) the index date. The ICD 9-CM codes used to identify SAs were E950-E959, where subcategories are E950-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 controls were individuals at risk for an event on the date of the event in a corresponding case. Up to 10 controls were randomly matched from the at risk population on 1) age (within groups 5 to 11, 12 to 18, and 19 to 24), 2) gender, 3) geographic region of country (East, Midwest, South, and West), and 4) cohort entry quarter and year using the incidence density sampling approach (without replacement), and assigned the “event” date of the case.¹¹⁶ Cases could serve as controls for other cases in the time period prior to event.

4.3.3 **Exposure**

LTMA exposure was determined in the 180 days prior to the event date (i.e., date of SA in cases and corresponding date in controls) based on prescription fill dates and the number of days supplied as recorded in prescription claims, and then classified as active, immediate past, past, or never users. “Active” exposure was assigned when the event date occurred during the dates included within an LTMA prescription. “Immediate past” exposure was assigned if the event date occurred within 30 days after the expiration of the supply of the past LTMA prescription, whereas “past” exposure was considered anything greater than 30 days and less than or equal to 180 days. Patients with no claims for LTMA in the 180 days prior to the event date were classified and “never” exposed.
In order to examine any dose-response relationship that might exist, we also created an exposure variables based on the cumulative dose of LTMA received. To do this we converted milligrams (mg) of LTMA received per day into “LTMA equivalents” in the same manner done previously by Heaton et al,\textsuperscript{118} where 1 LTMA equivalent is 10 mg of montelukast, 40 mg of zafirlukast, or 2,400 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 LTMAs, defined as the total days supply from dispensed prescription divided by number of days from first prescription.

4.3.4 Covariates

Patient characteristics and demographic data were assessed during the 6 months preceding the event date. In addition to the variables used to match cases and controls, we assessed co-morbidities (via ICD-9-CM codes) that could have been associated with higher risk for attempted suicide, including substance use disorders, bipolar disorder, depression, schizophrenia, or other mental disorders, human immunodeficiency virus/acquired immune disease (HIV/AIDS), malignant neoplasm/cancer, epilepsy, irritable bowel disease, migraine headaches, multiple sclerosis, renal disease, lupus, chronic pain, and allergic rhinitis.\textsuperscript{9-12, 15, 17, 33, 119-128} We also identified both previous SAs and previous psychological counseling (2 or more visits based on Current Procedural Terminology codes) as an indicator for patients likely to be at higher risk for future SAs. 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.

Asthma itself can be associated with suicide, and those with higher asthma severity may
be at even higher risk. Therefore, we assigned several covariates designed to assess asthma severity, and again all were based on the 180 days prior to the event. These included 1) ED visits with a diagnosis of asthma, 2) number of SABA canisters dispensed, 3) number of oral corticosteroid prescriptions, and 4) the number of asthma exacerbations. Asthma exacerbations were defined by a prescription for oral corticosteroids filled within 7 days of an outpatient encounter for asthma.

4.3.5 **Statistical Analysis**

Descriptive statistics were used to characterize the cases and controls. Conditional logistic regression was used to determine crude and adjusted OR and 95% CIs for the association between LTMA exposure and SAs. In the adjusted analyses a stepwise approach to model building was used where each covariate and possible interactions were examined and variables were retained only if considered clinically significant (based on previous literature) or that modified the risk estimate by greater than 10%. The best fitting multivariable model included bipolar disease, depression, other mental disorders, substance abuse, and ED visits with a diagnosis of asthma. For the final adjusted model we also included previous psychological counseling and previous SAs because both have been found to have strong associations with suicide attempts. Statistical analyses were performed in STATA version 11 (Statacorp, College Station, Texas). The study was considered non-human subjects research by the University of Illinois at Chicago Institutional Review Board.

4.3.6 **Sensitivity Analysis**

In addition to examining the potential association in active, immediate past, and past users, and the effect of dose and MPR, we conducted several stratified analyses to examine the
association within specific populations. These included patients with and without previous mental disorders, and those with concomitant allergic rhinitis versus without. We also examined the association within categories by age and gender.

4.4 Results

Limiting the dataset based on exclusion criteria described above (as shown in Figure 9), resulted in an analytic cohort of 195,028 patients, from which cases and controls were drawn. There were 344 cases and all except one were able to be matched with 10 controls, one was matched with 8 controls, for a total of 3438 controls.

Demographic and clinical characteristics of the cases and controls are shown in Table IX. Cases were more likely than controls to have had previous SAs and to have previously received psychological counseling. Cases were also more likely to have been previously diagnosed with 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 visits with a diagnosis of asthma and were more likely to have had a prescription for an inhaled LABA in the past 6 months, but were otherwise similar to controls with respect to asthma severity and use of other asthma controller medications.

Among cases, 19 (5.52%) were using LTMAs at the time of the suicide attempt, compared to 224 (6.52%) controls (unadjusted OR 0.80 (95% CI 0.49–1.31)), as shown in Table X. All 19 cases and 219 controls were receiving montelukast, while 5 controls were receiving zafirlukast, and no cases or controls were receiving zileuton. When adjusted for other important covariates we found that current use of any LTMA was not associated with increased risk for suicide attempts. In fact, while not statistically significant, the adjusted OR of 0.70 (95% CI
0.36–1.39) suggests a reduction by 30% in the odds of suicide attempts in those using LTMA. Thirty-nine (11.34%) cases had ever used LTMA in the 180 days prior to the event, compared to 535 (15.56%) controls (unadjusted OR 0.69 (95% CI 0.49–0.97). Again, the adjusted OR of 0.74 (95% CI 0.46–1.20) suggests a lower risk but was not statistically significant.

We found no association between cumulative dose of LTMA and suicide attempts. The cumulative dose over the past 180 days was also very similar (mean 57.44 and 63.96 LTMA equivalent milligrams in cases and controls, respectively). Categories of cumulative dose were also assessed (<60 LTMA equivalent versus >60 LTMA equivalent) compared to never use and while the adjusted ORs suggested a protective effect (0.64 and 0.54, respectively), the confidence intervals for each included one, as shown in Table X. Adherence to LTMA, expressed as MPR, was also the same in cases and controls (mean 0.63% and 0.67%, respectively) as shown in Table X.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, n (%) or mean (SD)</th>
<th>Controls, n (%) or mean (SD)</th>
<th>P-Value</th>
</tr>
</thead>
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<tr>
<td><strong>Number</strong></td>
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<td>3,438</td>
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<td><strong>Demographic characteristics</strong></td>
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<td>Age, years&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5 to 11</td>
<td>15 (4.36%)</td>
<td>150 (4.36%)</td>
<td>NA</td>
</tr>
<tr>
<td>12 to 18</td>
<td>256 (74.42%)</td>
<td>2,558 (74.40%)</td>
<td>NA</td>
</tr>
<tr>
<td>19 to 24</td>
<td>73 (21.22%)</td>
<td>730 (21.23%)</td>
<td>NA</td>
</tr>
<tr>
<td>Gender, female&lt;sup&gt;a&lt;/sup&gt;</td>
<td>245 (71.22%)</td>
<td>2,448 (71.20%)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Risk factors for suicide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous suicide attempt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22 (6.40%)</td>
<td>11 (0.32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous psychological counseling</td>
<td>139 (40.41%)</td>
<td>197 (5.73%)</td>
<td>&lt;0.001</td>
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<td><strong>Mental health disorders</strong></td>
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<td>Substance abuse</td>
<td>105 (30.52%)</td>
<td>82 (2.39%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>48 (13.95%)</td>
<td>32 (0.93%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Depression</td>
<td>231 (67.15%)</td>
<td>192 (5.58%)</td>
<td>&lt;0.001</td>
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<td>Schizophrenia</td>
<td>11 (3.20%)</td>
<td>1 (0.03%)</td>
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<td>Other mental disorders</td>
<td>172 (50.00%)</td>
<td>215 (6.25%)</td>
<td>&lt;0.001</td>
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<td><strong>Other comorbidities</strong></td>
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<tr>
<td>Allergic rhinitis</td>
<td>68 (19.77%)</td>
<td>666 (19.37%)</td>
<td>0.853</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 (0.29%)</td>
<td>8 (0.23%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>7 (2.03%)</td>
<td>7 (0.20%)</td>
<td>&lt;0.001</td>
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<tr>
<td>HIV/AIDS</td>
<td>2 (0.58%)</td>
<td>2 (0.06%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>4 (1.16%)</td>
<td>17 (0.49%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Lupus</td>
<td>0 (0%)</td>
<td>3 (0.09%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Migraine</td>
<td>20 (5.81%)</td>
<td>68 (1.98%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0 (0%)</td>
<td>1 (0.03%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0 (0%)</td>
<td>2 (0.06%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Use of medications associated with suicide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>50 (14.53%)</td>
<td>55 (1.60%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>150 (43.60%)</td>
<td>293 (8.52%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>50 (14.53%)</td>
<td>47 (1.37%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>30 (8.72%)</td>
<td>87 (2.53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypnotics</td>
<td>17 (4.94%)</td>
<td>21 (0.61%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>1 (0.29%)</td>
<td>12 (0.35%)</td>
<td>0.861</td>
</tr>
<tr>
<td>Varenicline</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Asthma severity and treatment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of short-acting beta-agonist inhalers (# of inhalers dispensed in past 6 months)</td>
<td>2.12 (1.31)</td>
<td>1.79 (2.13)</td>
<td>0.297</td>
</tr>
<tr>
<td>0</td>
<td>213 (61.92%)</td>
<td>2,169 (63.09%)</td>
<td>0.643</td>
</tr>
<tr>
<td>1</td>
<td>54 (15.70%)</td>
<td>630 (18.32%)</td>
<td>0.213</td>
</tr>
<tr>
<td>2</td>
<td>25 (7.27%)</td>
<td>272 (7.91%)</td>
<td>0.669</td>
</tr>
<tr>
<td>3 or more</td>
<td>36 (10.47%)</td>
<td>255 (7.42%)</td>
<td>0.041</td>
</tr>
<tr>
<td>Missing</td>
<td>16 (4.65%)</td>
<td>112 (3.26%)</td>
<td>NA</td>
</tr>
</tbody>
</table>
### TABLE IX CONTINUED

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES AND CONTROLS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases, n (%) or mean (SD)</th>
<th>Controls, n (%) or mean (SD)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergency Department visits for asthma (# in past 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>285 (82.85%)</td>
<td>3,245 (94.39%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>24 (6.98%)</td>
<td>87 (2.53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>18 (5.23%)</td>
<td>71 (2.07%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 or more</td>
<td>17 (4.94%)</td>
<td>35 (1.02%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Asthma exacerbations (# in past 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>306 (88.95%)</td>
<td>3,112 (90.52%)</td>
<td>0.340</td>
</tr>
<tr>
<td>1</td>
<td>11 (3.20%)</td>
<td>90 (2.62%)</td>
<td>0.522</td>
</tr>
<tr>
<td>2</td>
<td>5 (1.45%)</td>
<td>66 (1.92%)</td>
<td>0.546</td>
</tr>
<tr>
<td>3 or more</td>
<td>22 (6.40%)</td>
<td>170 (4.94%)</td>
<td>0.239</td>
</tr>
<tr>
<td><strong>Use of oral corticosteroids (# of prescription in past 6 months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>289 (84.01%)</td>
<td>2,954 (85.92%)</td>
<td>0.327</td>
</tr>
<tr>
<td>1</td>
<td>39 (11.34%)</td>
<td>369 (10.73%)</td>
<td>0.725</td>
</tr>
<tr>
<td>2</td>
<td>13 (3.78%)</td>
<td>84 (2.44%)</td>
<td>0.136</td>
</tr>
<tr>
<td>3 or more</td>
<td>3 (0.87%)</td>
<td>31 (0.90%)</td>
<td>0.957</td>
</tr>
<tr>
<td><strong>Use of other asthma controller medications in past 6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>109 (31.69%)</td>
<td>1,085 (31.56%)</td>
<td>0.957</td>
</tr>
<tr>
<td>Long-acting beta-agonists</td>
<td>80 (23.26%)</td>
<td>635 (18.47%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Inhaled anticholinergics</td>
<td>9 (2.62%)</td>
<td>48 (1.40%)</td>
<td>0.079</td>
</tr>
<tr>
<td>Mast cell stabilizers</td>
<td>5 (1.45%)</td>
<td>43 (1.25%)</td>
<td>0.742</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>1 (0.29%)</td>
<td>4 (0.12%)</td>
<td>0.412</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>0 (0.00%)</td>
<td>1 (0.03%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* matching variable

*b measured in the pre-index period
### TABLE X

**EXPOSURE TO LEUKOTRIENE-MODIFYING AGENTS AND RISK OF SUICIDE ATTEMPT**

<table>
<thead>
<tr>
<th>Exposure associations</th>
<th>Cases, n (%) or mean (SD)</th>
<th>Controls, n (%) or mean (SD)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never use of LTMA</strong></td>
<td>305 (88.66%) 2903 (84.44%)</td>
<td>Reference Reference</td>
<td>Reference Reference</td>
<td>(0.49-1.31) (0.36-1.39)</td>
</tr>
<tr>
<td><strong>Current use of LTMA</strong></td>
<td>19 (5.52%) 224 (6.52%)</td>
<td>0.80 (0.49-1.31)</td>
<td>0.70 (0.36-1.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Immediate past use of LTMA</strong></td>
<td>8 (2.33%) 100 (2.91%)</td>
<td>0.75 (0.36-1.57)</td>
<td>0.95 (0.36-2.50)</td>
<td></td>
</tr>
<tr>
<td><strong>Past use of LTMA</strong></td>
<td>12 (3.49%) 211 (6.14%)</td>
<td>0.54 (0.30-0.98)</td>
<td>0.69 (0.32-1.50)</td>
<td></td>
</tr>
<tr>
<td><strong>Ever use of LTMA</strong></td>
<td>39 (11.34%) 535 (15.56%)</td>
<td>0.69 (0.49-0.98)</td>
<td>0.74 (0.46-1.20)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose-response associations</th>
<th>Mean cumulative LTMA equivalent dose among ever users&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean MPR (%) among LTMA current users</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Never users</strong></td>
<td>57.44 (46.46) 63.96 (83.02)</td>
<td>0.55 (0.32-0.92)</td>
<td>0.64 (0.32-1.28)</td>
<td>1.00 (0.99-1.01) (0.96-1.01)</td>
</tr>
<tr>
<td>&lt;=60 LTMA equivalents</td>
<td>16 (4.65%) 277 (8.06%)</td>
<td>(0.37-1.23)</td>
<td>0.54 (0.37-1.23) (0.23-1.30)</td>
<td></td>
</tr>
<tr>
<td>&gt; 60 LTMA equivalents</td>
<td>12 (3.49%) 166 (4.83%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>11 (3.02%) 92 (2.68%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Mean MPR (%) among LTMA current users</td>
<td>0.63 (0.28) 0.67 (0.37)</td>
<td>0.51&lt;sup&gt;b&lt;/sup&gt; (0.08-3.43)</td>
<td>1.03&lt;sup&gt;b&lt;/sup&gt; (0.02-50.98)</td>
<td></td>
</tr>
</tbody>
</table>

**Footnotes**

<sup>a</sup> One LTMA equivalent dose equals 10mg of montelukast, 40mg of zafirlukast, or 2,400 mg of zileuton

<sup>b</sup> Reference is never use of LTMA
We conducted several stratified analyses to determine if the relationship between LTMA use and suicide attempts varied within subgroups, as shown in Table XI. All analyses compared current use of LTMA to never use (reference, not shown). We examined the effect in males and females and found results similar to that of the full dataset. We also stratified the data by presence of two key concomitant diagnoses, 1) allergic rhinitis, and 2) any mental disorder. Among those with allergic rhinitis the adjusted OR was 0.26 (95% CI 0.02–3.27) while in those without allergic rhinitis the adjusted OR was 1.02 (95% CI 0.44–2.35). Among those with any mental disorder the adjusted OR was 1.12 (95% CI 0.53–2.72) while in those with no mental disorder it was 0.82 (95% CI 0.22–3.03).

Last, we examined the potential association between LTMA use and suicide attempts within different ages (5 to 11, 12 to 18, and 19 to 24 years). The adjusted OR in the 5 to 11 and 12 to 18 age groups was not much different from the full dataset. However, in the 19 to 24 age group we found a statistically significant 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 to the full sample, patients in the 19 to 24 age group had overall higher prevalence of risk factors for suicide, including previous SA, 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 impact of these differences on our analysis, we then re-assessed the covariates included in our adjusted model and revised the model accordingly. We add previous exposure to 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).
### TABLE XI

**STRATIFIED ANALYSES**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Cases, n (%) or mean (SD)</th>
<th>Controls, n (%) or mean (SD)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Association in age groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 11</td>
<td>15 (4.36%)</td>
<td>150 (4.36%)</td>
<td>0.75 (0.09-6.19)</td>
<td>0.78 (0.03-18.09)</td>
</tr>
<tr>
<td>12 to 18</td>
<td>256 (74.42%)</td>
<td>2,558 (74.40%)</td>
<td>0.65 (0.36-1.19)</td>
<td>0.47 (0.20-1.09)</td>
</tr>
<tr>
<td>19 to 24</td>
<td>73 (21.22%)</td>
<td>730 (21.23%)</td>
<td>2.01 (0.79-5.09)</td>
<td>5.15 (1.16-22.86)</td>
</tr>
<tr>
<td><strong>Association in gender groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>245 (71.22%)</td>
<td>2,448 (71.20%)</td>
<td>0.63 (0.34-1.19)</td>
<td>0.65 (0.27-1.59)</td>
</tr>
<tr>
<td>Male</td>
<td>99 (28.78%)</td>
<td>990 (28.80%)</td>
<td>1.47 (0.68-3.18)</td>
<td>0.71 (0.23-2.16)</td>
</tr>
<tr>
<td><strong>Association in disease subgroups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant mental disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>52 (15.12%)</td>
<td>3,074 (89.41%)</td>
<td>0.79 (0.23-2.66)</td>
<td>0.82 (0.22-3.03)</td>
</tr>
<tr>
<td>Present</td>
<td>292 (84.88%)</td>
<td>364 (10.59%)</td>
<td>0.73 (0.35-1.50)</td>
<td>1.12 (0.53-2.72)</td>
</tr>
<tr>
<td>Concomitant allergic rhinitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>276 (82.23%)</td>
<td>2772 (80.63%)</td>
<td>0.98 (0.56-1.70)</td>
<td>1.02 (0.44-2.35)</td>
</tr>
<tr>
<td>Present</td>
<td>68 (19.77%)</td>
<td>666 (19.37%)</td>
<td>0.66 (0.20-2.19)</td>
<td>0.26 (0.02-3.27)</td>
</tr>
</tbody>
</table>

*a All associations are among current users of LTMA, compared to never users*

4.5 **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. This finding is consistent with previous research on the association between LTMAs and suicide, including a retrospective review of LTMA clinical trials conducted by the FDA.29
Following the FDA warning, Jick and others conducted a population based cohort study to examine the potential association. The investigators identified 23,500 patients exposed to one or more prescription for montelukast from 1998 to 2007, representing 21,050 person-years at risk. Only one case of suicide was identified, but that was ruled-out because montelukast had been prescribed as a single 28-day course two years prior to 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 conducted two ecologic studies that yielded mixed results. In the first we examined the association between the number of prescriptions for LTMAs dispensed in the United States from 1999 to 2009 (obtained from IMS Health Inc.) and the number of completed suicides reported the FDA AERS over the same time period. We calculated the rate of completed suicides per million prescriptions and, using a mixed-effects Poisson regression analysis, determined the empirical Bayes rate multipliers and 95% confidence intervals for each LTMA drug. Selective SSRIs and SABAs were analyzed for comparison purposes. There were 105 completed suicides reported where a LTMA was implicated, most of which involved montelukast, and all but 9 occurred in 2008 to 2009, following an FDA warning. Aggregated suicide rates over the 1999 to 2009 period were 0.51, 0.24, and 4.09 per million prescriptions for montelukast, zafirlukast, and zileuton. The suicide rate as a class was 0.06 per million prescriptions in the pre-warning period and 1.82 per million prescriptions in the post-warning period. Montelukast was associated with a significantly lower rate of suicide when compared to SSRIs and a significantly higher rate when compared to SABAs.

We also examined the association between LTMAs and completed suicides on a county level using data from the CDC. In this mixed-effects Poisson regression analysis, counts of
suicide deaths in each United States county (stratified by race, age group, gender, and year) were compared to counts of LTMA prescriptions dispensed in each United States 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. While not statistically significant, this suggests an overall reduction in risk by LTMA. It is not clear why risk might be reduced except that LTMA may result in better control of asthma. Asthma itself has been associated with a more than 4-fold (OR 4.34, p < 0.001) increase in the likelihood of a SA.\textsuperscript{42, 43} Further, a study by Harwood and others 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.\textsuperscript{45} By controlling asthma symptoms and improving asthma control LTMA could reduce 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 results suggest that the effect of LTMA on risk of SA may 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 age group. While not statistically significant there does appear to be an elevated risk in this group. Patients in this age group are generally at higher baseline risk for suicide than those age 18 or younger,\textsuperscript{4} and it was also clear in our study that cases differed from controls with respect to suicide risk factors, but these were controlled for in the analysis. However, it is possible that other unmeasured confounders are present that have impacted our findings. For this reason we believe the effect of age on risk of SA in those exposed to LTMA requires further investigation.
Our stratified analyses also suggested reduced risk in those with a concomitant diagnosis of allergic rhinitis. Again, it is unclear why this might be the case. Allergic rhinitis and other allergic disorders have also been associated with suicide, though the evidence is not as strong as it is for asthma.\textsuperscript{58, 59} Treating allergic rhinitis with LTMAs may ameliorate risk of SA in a similar manner to that suggested above for asthma, but again we know of no evidence for LTMAs or other allergy medications to support this.

There are several limitations to our study 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 may suffer from various potential problems described below. Nevertheless these databases are commonly used for retrospective research and have advantages of large sample sizes and long follow-up time.

One potential limitation is the inability to measure true exposure. We defined exposure of LTMAs 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. However, there is substantial literature validating the use of prescriptions claims as a measure of drug exposure.\textsuperscript{105, 106}

Another limitation is in identification of SAs. In this study we used ICD-9-CM codes in medical claims to identify SAs. This method may under-report 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.\textsuperscript{134}

Similar to 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 may be a potential confounder in the association between LTMAs and SA. We did,
however, adjust for proxy measures such ED visits with a diagnosis code of asthma, SABA canisters dispensed, and number of acute exacerbations in the 180 days before the event date. Last, while we did our best to identify covariates in our database that could be potential confounders in the relationship between LTMA and SA, 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, or family relationships, all of which have previously been associated with suicide in children and young adults. 

4.6 Conclusion

In conclusion, in this analysis we found that use of LTMA were not associated with an increased risk of SAs in children, adolescents, and young adults with asthma. In fact, we found an overall protective effect of LTMA across all the age groups we studied, though this was not statistically significant. However, we did find evidence that the association between LTMA and SAs may vary by age group, and in the 19 to 24 age group we found an increased risk, though again it was not statistically significant. Further research needs to be conducted to more fully understand the association between LTMA and suicide—particularly in subgroups.
5. OVERALL CONCLUSIONS

The primary goal of this dissertation was to examine the association between the LTMAs—montelukast, zafirlukast, and zileuton—and suicide behavior (suicide attempts and completed suicides). Before now there were no well-conducted observational studies of this association. Nevertheless, based primarily on case reports, the United States FDA issued safety alerts and required manufacturers of these agents to include suicide and neuropsychiatric events as a precaution in the drug label.28, 29, 64

The LTMAs are effective and commonly used drugs for the treatment of asthma and allergic rhinitis. In 2008 Singulair was ranked number seven among the top selling prescription drugs in the United States, with $2.9 Billion in sales.99 World-wide sales of Singulair were $3.6 Billion (2006).31 We found that prescribing of these drugs decreased after the FDA warnings.1 If the warnings are unfounded than it is possible that LTMAs are needlessly being withheld from patients who need them. Clearly, more objective evidence to confirm or refute the association between LTMAs and suicide is needed so that clinicians and patients can make informed decisions about the balance of risks and benefits from their use. The purpose of this dissertation was to provide that evidence.

The primary aim for this dissertation was to examine the association between LTMAs and suicide behavior. The null hypothesis was that there is no association between LTMAs and risk of suicide. Three approaches were used to test this hypothesis. The first was an analysis of spontaneously reported completed suicides in the FDA AERS using the Poisson method developed by Gibbons and others, included a proxy denominator of LTMAs prescriptions dispensed in the United States.104 The second was an ecologic analysis of completed suicides and the prescribing rates of LTMAs at the county-level using data on suicide deaths from the
CDC. The third was a patient-level case-control study using data from a national prescription
and medical insurance-based claims database with SAs as the outcome of interest.

In the first study it was found that montelukast was associated with a significantly lower
rate of reported complete suicide when compared to SSRIs, and a significantly higher rate when
compared to SABAs. However, this effect was primarily driven by increased rates of reporting of
LTMA-associated suicide events in the post-warning period.

To avoid this limitation, the second study used data on suicide deaths at the county-level
reported to the CDC. Here a negative within-county association between the rate of total LTMA
prescriptions dispensed and the suicide rate by county ($p = 0.0296$) was identified. This
association was primarily driven by montelukast. These results provided preliminary evidence
that the association between LTMA and suicide could be different (i.e., reduced risk) than that
which might be anticipated based on FDA warnings.

Finally, a case-control study to determine the association between LTMA and
attempted suicide using patient-level data was conducted. Current use of any LTMA was
associated with reduced risk (though not statistically significant) of SA [adjusted OR 0.70, 95%
CI 0.36–1.39]. However, an elevated risk (OR 5.64 CI 0.87–36.66) was observed in those 19 to
24 years of age, and a reduced risk in those with concomitant allergic rhinitis (OR 0.26 CI 0.02–
3.27), though also not statistically significant. It is possible that the later (subgroup) association
could have been due to unmeasured confounding in our data.

The overall conclusion from this body of work is that LTMA are not associated with
suicide. This finding was generally consistent across the three studies conducted. While it is the
responsibility of the FDA to alert providers and the public in the event of suspected risk of
pharmaceuticals, once evidence to the contrary becomes available then such warnings should
be removed. In the case of LTMA, this dissertation provides evidence that these drugs are safe
and not associated with suicide.

Nevertheless, additional research on this subject can only be beneficially. Independent confirmation of these results would provide additional assurance about the safety of LTMA s. Further, more examination of subgroups of patients may be warranted—particularly for the 19 to 24 year age group.


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