Asthma Treatments and Mental Health Visits After a Food and Drug Administration Label Change for Leukotriene Inhibitors

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ABSTRACT

Purpose: In 2009, the US Food and Drug Administration (FDA) mandated a label change for leukotriene inhibitors (LTIs) to include neuropsychiatric adverse events (eg, depression and suicidality) as a precaution. This study investigated how this label change affected the use of LTIs and other asthma controller medications, mental health visits, and suicide attempts.

Methods: We analyzed data (2005-2010) from 5 large health plans in the US Population-Based Effectiveness in Asthma and Lung Diseases (PEAL) Network. The study cohort included children and adolescents (n = 30,000), young adults (n = 20,000), and adults (n = 90,000) with asthma. We used interrupted time series to examine changes in rates of LTI dispensings, non-LTI dispensings, mental health visits, and suicide attempts (using a validated algorithm based on a combination of diagnoses of injury or poisoning and psychiatric conditions).

Findings: The label change was associated with abrupt reductions in LTI use among all age groups (relative reductions of 8.3%, 15.1%, and 6.0% among adolescents, young adults, and adults, respectively, compared with expected rates at 1 year after the warnings). Although we detected immediate offset increases in non-LTI asthma medication use, these increases were not sustained among adolescents and young adults. There were small increases in mental health visits among LTI users.

Implications: The FDA label change for LTIs communicated possible risk of neuropsychiatric events. Communication and enhanced awareness may have increased reporting of mental health symptoms among young adults and adults. It is important to assess intended and unintended consequences of FDA warnings and label changes. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: asthma, drug tolerability, FDA, leukotriene inhibitors, montelukast, risk communication.

INTRODUCTION

During the last decade, there has been increasing recognition of the potential for certain prescription medications to increase the risk of psychiatric symptoms and suicidality.[1] Primarily on the basis of spontaneous adverse drug event reports (eg, via the MedWatch system), the US Food and Drug Administration (FDA) has issued communications and

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warnings about psychiatric symptoms and suicidality for whole classes of medications. These warnings initially included selective serotonin receptor inhibitors and were later expanded to all antidepressants, antiepileptic drugs, the smoking-cessation drug varenicline,[2] and leukotriene inhibitors (LTIs).

LTIs include montelukast, zafirlukast, and zileuton in the United States and are the second most commonly used controller medications for asthma after inhaled corticosteroids. LTIs are also used for seasonal allergies. The FDA first issued alerts in March 2008[3] and reviewed postmarketing reports of patients taking LTIs and clinical trial data submitted by manufacturers. Most reported neuropsychiatric adverse events were associated with montelukast. Although these data do not suggest that LTIs are associated with suicidality, these clinical trials were not designed specifically to examine neuropsychiatric events.

In June 2009, the FDA required manufacturers of LTIs to include neuropsychiatric adverse events as a precaution on the drug label.[4] In the risk communications, the FDA recommended that "patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents."[3] Neuropsychiatric events include agitation, aggression, anxiety, sleep disorder, depression, and suicidal thinking and behavior (including suicide and suicide attempts).[4] The widespread use of LTIs heightened 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. The aims of this study were to examine the effects of the FDA label change for LTIs on patterns of treatment for asthma, mental health visits, and suicide attempts.

METHODS

Data Sources

This study included individuals with asthma in the Population-Based Effectiveness in Asthma and Lung Diseases (PEAL) Network.[5–7] Five health plans from this network participated in this study: Harvard Pilgrim Health Care, HealthPartners, Kaiser Permanente Northern California, Kaiser Permanente Georgia, and Kaiser Permanente Northwest. Electronic data from subjects from each of the 5 sites were pooled to form the PEAL Data Warehouse, which includes information on demographic characteristics, health plan enrollment, dispensings of medications, and use of inpatient and outpatient health care services. The institutional review board at each site approved this study.

Study Design and Cohorts

Randomized controlled trials are not able to evaluate nationwide policy changes such as FDA warnings. We used an interrupted times series design,[8–12] which can provide strong evidence of causal effects because it controls for prepolicy secular trends in study outcomes. The approach measures whether a policy causes abrupt changes in the level and/or the preexisting trend (slope) of study outcomes.[8–12] To calculate population-level time series, we created a rolling cohort from January 2005 through December 2010. For every month, we identified and included health plan members who had (1) continuous enrollment for the past 12 months, (2) continuous enrollment for the current month, (3) at least one outpatient or inpatient visit in the past 12 months with a diagnosis of asthma (*International Classification of Diseases, Ninth Revision* (ICD-9) code for asthma [493.x]), and (4) no history of chronic obstructive pulmonary diseases (ICD-9 codes 491, 492, and 496); cystic fibrosis (ICD-9 code 277.0x); bronchiectasis (ICD-9 code 494); pulmonary hypertension or embolism (ICD-9 codes 416.0 and 415.1); bronchopulmonary dysplasia (ICD-9 code 770.7); or congestive heart failure (ICD-9 code 428) in the past 12 months. We excluded subjects with these comorbid illnesses, as we have done in previous studies,[13,14] because asthma medications can be used for these chronic illnesses, which are distinct from asthma. These criteria were consistent with recent studies of FDA warnings among the asthma population using similar data.[15] We included children and adolescents (ages 5–17 years), young adults (ages 18–29 years), and adults (ages 30–64 years) because the prevalence of suicidality is higher among young adults aged 18 through 29 years than among adults 30 years and older based on the US Centers for Disease Control and Prevention data.[16] In addition, we identified users of LTIs; for each month, we identified and included individuals who had a dispensing for a LTI agent in the previous 6 months and met the above study criteria.

Outcome Measures

Among the rolling cohorts of asthmatic patients, we calculated the monthly percentage of individuals dispensed an LTI, dispensed a non-LTI medication, or