

PHARMACOTHERAPY

Antidepressant medication dispensing among montelukast initiators

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Abstract

Objective: This study investigates the potential association between montelukast use and psychiatric adverse events by monitoring changes in antidepressant medication dispensing rates before and after initiating montelukast. **Methods:** The primary study group of montelukast initiators was identified using the Wolters Kluwer's SOURCE Lx[®] pharmacy claims database (WK). This group included 232 159 patients ≤45 years old who had at least two montelukast prescriptions from 2003 to 2007. Comparison groups comprised of 264 704 fluticasone initiators and 89 635 long-acting β-agonist corticosteroid (LABA/ICS) initiators were also identified. Antidepressant medication dispensing rates in these three groups were determined using WK, and changes in rates before and after the first asthma controller medication prescription date were evaluated using interrupted time-series analysis (ITS). ITS was performed separately for four age categories, with a focus on youth (12–17 years) and young adult (18–24 years). **Results:** For patients 18–24 years old, antidepressant medication dispensing rates increased significantly after initiating montelukast [1.93% (1.55–2.32%, $p < 0.001$)] but also after initiating fluticasone and LABA/ICS [1.72% (1.30–2.15%, $p < 0.001$) and 2.76% (2.35–3.17%, $p < 0.001$)]. Similar patterns were observed across the three medication groups for other age categories but these differences were not all significant. **Conclusions:** Small increases in antidepressant medication dispensing rates occurred after initiating montelukast. However, similar increases were observed in the fluticasone and LABA/ICS comparison groups. The results of this study cannot support a specific association between initiation of montelukast treatment and an increase in psychiatric adverse effects.

Keywords

Antidepressant, interrupted time-series analysis, montelukast

History

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Introduction

Montelukast is a leukotriene receptor antagonist (LTRA) first approved by the US Food and Drug Administration (FDA) in 1998. Indications of montelukast include prophylaxis and chronic treatment of asthma, prevention of exercise-induced bronchoconstriction, and relief of allergic rhinitis symptoms [1]. The post-marketing experience of montelukast was reported to include psychiatric adverse events (AEs), such as depression, suicidality and anxiousness [2]. The FDA responded with several regulatory actions. In March 2008, an Early Communication regarding these reports was released, followed by a request from the FDA that all available placebo-controlled clinical trial data on montelukast be analyzed for information about psychiatric AEs [2–4]. In August 2009,

FDA announced an update to the Precautions section of the drug label to include information about psychiatric events reported in patients using montelukast [5].

Several studies investigating the potential link between psychiatric AEs and montelukast use have been published. In 2009, Manalai et al. [6] reviewed available data on montelukast use and psychiatric events and concluded that there were insufficient data to prove an association. Later that year, Wallerstedt et al. [7] evaluated effects of montelukast treatment in children (<18 years old), using the Swedish adverse drug reactions database, and concluded that psychiatric AEs may occur during montelukast treatment in this age group. However, this database contained only 48 reports of psychiatric events in children undergoing treatment with montelukast [7]. Schumock et al. [8] conducted a nested case-control study of suicide attempts among youth (5–24 years old) and found no association between use of LTRA (including montelukast, zafirlukast or zileuton) and suicide attempts overall. This study did report an increased odds ratio [OR = 5.15, 95% confidence interval (CI): 1.16–22.86] in a young adult subgroup (19–24 years), but the sample size was small, with only 6 cases and 32 controls exposed to LTRA [8].

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The association of psychiatric AEs and montelukast use was further examined in two studies, which reviewed pooled data from available double-blind, placebo-controlled trials [9,10]. The frequency of AEs was found to be similar between the montelukast and placebo arms [9,10] except for patients aged 12–18 years, where the OR increased among patients using montelukast (12 AEs in 856 versus 5 AEs in 768 patients in the montelukast and placebo group, respectively, OR = 2.17, 95% CI: 0.71–7.89) [10]. However, even after pooling data from clinical trials, the numbers of montelukast users and AEs were relatively small. Thus, it is difficult to draw firm conclusions from these AE reports or randomized controlled trials (RCTs) [11,12].

In order to gather more data that are reliable on the potential association of montelukast use and psychiatric AEs, we sought a way to identify and evaluate large numbers of montelukast users. Since there is a large amount of data on medication use available from the Wolters Kluwer's SOURCE Lx[®] pharmacy claims database (WK), we decided to use this database to identify patients who initiated montelukast during a given time frame, then evaluate the rate of antidepressant medication dispensing in that population as an indication of psychiatric AEs. We hypothesized that, if montelukast use is specifically associated with an increase in psychiatric AEs, we would observe an increase in antidepressant medication dispensing after initiation of montelukast. We divided our subject population into four age categories but focused on youth (12–17 years old) and young adults (18–24 years old) since previous work suggested that montelukast use might be most highly associated with psychiatric AEs in those age groups.

Methods

This study is covered under a blanket FDA Research Involving Human Subjects Committee approval.

Data source

Medication dispensing data were taken from WK. The database is a longitudinal patient data source, which represents ~80% of all US retail prescriptions as well as 60% of all US mail order prescriptions.

Study population

Patients who met the following three criteria were included in the study as montelukast initiators: (i) had at least two montelukast prescriptions dispensed between 1/1/2003 and 12/31/2007, with the index date (InD) defined as the first montelukast prescription; (ii) aged 45 years old or younger on the InD and (iii) had at least one medical or pharmacy claim 12 months before and 12 months after the InD, to verify that their medications were captured in the database. Patients aged 46 years or older were excluded to decrease the likelihood of capturing patients with chronic obstructive pulmonary disease. We also excluded patients if they had other asthma controller medications (ACMs) during the 12 months before and up to 3 months after the InD. Due to limited use of other LTRAs in the US market, the current study focused only on montelukast.

Two comparison groups, fluticasone (inhaled or intranasal) initiators and LABA/ICS initiators, were established using the

same criteria above. We assumed that initiation of fluticasone or LABA/ICS is not associated with increased dispensing of antidepressant medication since no such reporting in the literature to the best of our knowledge.

Pre- and post-InD follow-up periods

We first constructed a post-InD follow-up period for each patient initiating use of one of the index drugs (montelukast, fluticasone, or LABA/ICS). Post-InD follow-up began 30 days after the InD (1-month lag period) and continued until (i) a gap in continuous index drug medication coverage exceeding 30 days; (ii) the date of the first dispensing of another long-term ACM, including inhaled ICS, LABA, cromones and oral systemic corticosteroids; (iii) a maximum of 180 days follow-up time; or (iv) the end of the study period, whichever came first. The 1-month lag period from the InD was used to allow for a potential delay in antidepressant medication dispensing.

Each patient was then assigned a pre-InD follow-up time equal to his post-InD follow-up time, thus resulting in symmetric pre- and post-InD follow-up periods. Follow-up days were recorded in 15-day intervals to increase accuracy of estimating outcome, antidepressant medication dispensing rate. Total number of patients in each 15-day interval served as the denominator of the dispensing rate. For each patient, a maximum of 12 time points (180 days) were used pre-InD (Segment I) and 12 time points (180 days) post-InD (Segment II) [13].

Outcome measure

The study outcome was antidepressant medication dispensing rate, used as a surrogate for psychiatric AEs. Antidepressant medications monitored in this study are listed in Table 1. Only medications used as monotherapy were included whereas drugs used as adjuvant therapy were not included. Antidepressant medications exposure duration were constructed [14]. Exposure duration was then determined for each 15-day follow-up interval within the follow-up period. We defined the antidepressant medication dispensing rate as the number of patients who had dispensed antidepressant medications in each 15-day interval, divided by the total number of patients in that same interval. This is the Y_t in the ITS model below.

Table 1. List of antidepressant medication drugs used to define outcome measure.

Drug type	Drug products
Antidepressant drugs	
SSRIs	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
TCA	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin (excluding topical formulations), imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
Other (including combinations)	Desvenlafaxine succinate, duloxetine, isocarboxazid, mirtazapine, nefazodone, phenelzine, selegiline, tranylcypromine, trazodone, venlafaxine, transdermal selegiline

SSRI = Selective Serotonin Reuptake Inhibitor.

TCA = tricyclic antidepressant.

Statistical analysis

First, we visually compared the antidepressant medication dispensing rate patterns pre- and post-InD. Second, we used ITS analysis to test whether these observed changes in level and trend are statistically significant. ITS was performed separately for four age categories, with a focus on the youth (12–17 years) and young adult (18–24 years) groups, as these are the age groups where psychiatric AEs have been seen previously. The following ITS model was used [13].

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{index event} + \beta_3 \times \text{time after InD}_t + e_t$$

where, time_t = continuous variable counting time (1–24) beginning from the start of time series; index event = dummy variable representing the initiation of montelukast or comparison drugs, before InD (=0) or after InD (=1); time after InD_t = continuous variable counting time points after InD at time t ; Y_t = antidepressant medication dispensing rates; β_0 = baseline antidepressant medication dispensing rates; β_1 = trend of antidepressant medication dispensing rates before InD; β_2 = immediate level change in antidepressant medication dispensing rates after InD; β_3 = trend change in antidepressant medication dispensing rate after the InD; e_t = random error and correlated error.

The post-InD immediate level (β_2) and slope/trend coefficients (β_3) were estimated controlling for baseline level (β_0) and trend estimates (β_1). To account for autocorrelation of the data, autoregressive moving average models (ARMA) were applied to find the best fit for each time series and forecasts. Best-fitted ARMA model with the smallest Akaike Information Criterion and Schwarz’s Bayesian Information Criterion values was selected for each ITS analysis [13]. Statistical analyses were performed using Statistical Analysis Software, version 9.3 (SAS Institute Inc., Cary, NC).

Results

We identified 232 159 montelukast initiators aged 45 years or younger with at least two montelukast prescriptions during the study period. For comparison groups, we identified 264 704 fluticasone initiators and 89 635 LABA/ICS initiators. Table 2 shows patient characteristics

and prescription information for the three study groups. About 15% of the population in the montelukast and fluticasone groups consisted of youth (12–17 years) compared to 21% in the LABA/ICS group. There were 6, 9 and 12% young adults (18–24 years) in the three study groups, respectively. The gender distribution was similar in the three groups, with the percentage of females were ranging from 52 to 58%.

The median number of days per prescription was 30 for all three drugs. The median number of prescriptions dispensed per patient was four for montelukast and three for the two comparison drugs. The median follow-up duration was 95 days for the montelukast group and 60 days for the two comparison groups (Table 2).

Figure 1 illustrates overall trends of antidepressant medication dispensing rates for patients 12–17 (Figure 1A) and 18–24 years old (Figure 1B). For patients 12–17 years old, the baseline rates were ~5% in both montelukast and fluticasone groups, and 3% in the LABA/ICS group. For patients 18–24 years old, the baseline rates were 7% in montelukast and fluticasone groups, and 4% in the LABA/ICS group. Rates increased slightly immediately after InD in montelukast initiators in both age categories, but also increased in both comparison groups. The increases were small, ~1% for 12–17 year olds in all three study groups, and ~2–3% for 18–24 year olds in all three study groups.

ITS analysis was then carried out to determine whether the observed increases were statistically significant (Table 3). Baseline antidepressant medication dispensing rates (β_0) were very low for 1–11 year olds (<1%) but did increase some with age (3–6% for 12–17 and 4–8% for 18–24 year olds compared to 8–11% for 25–45 year olds).

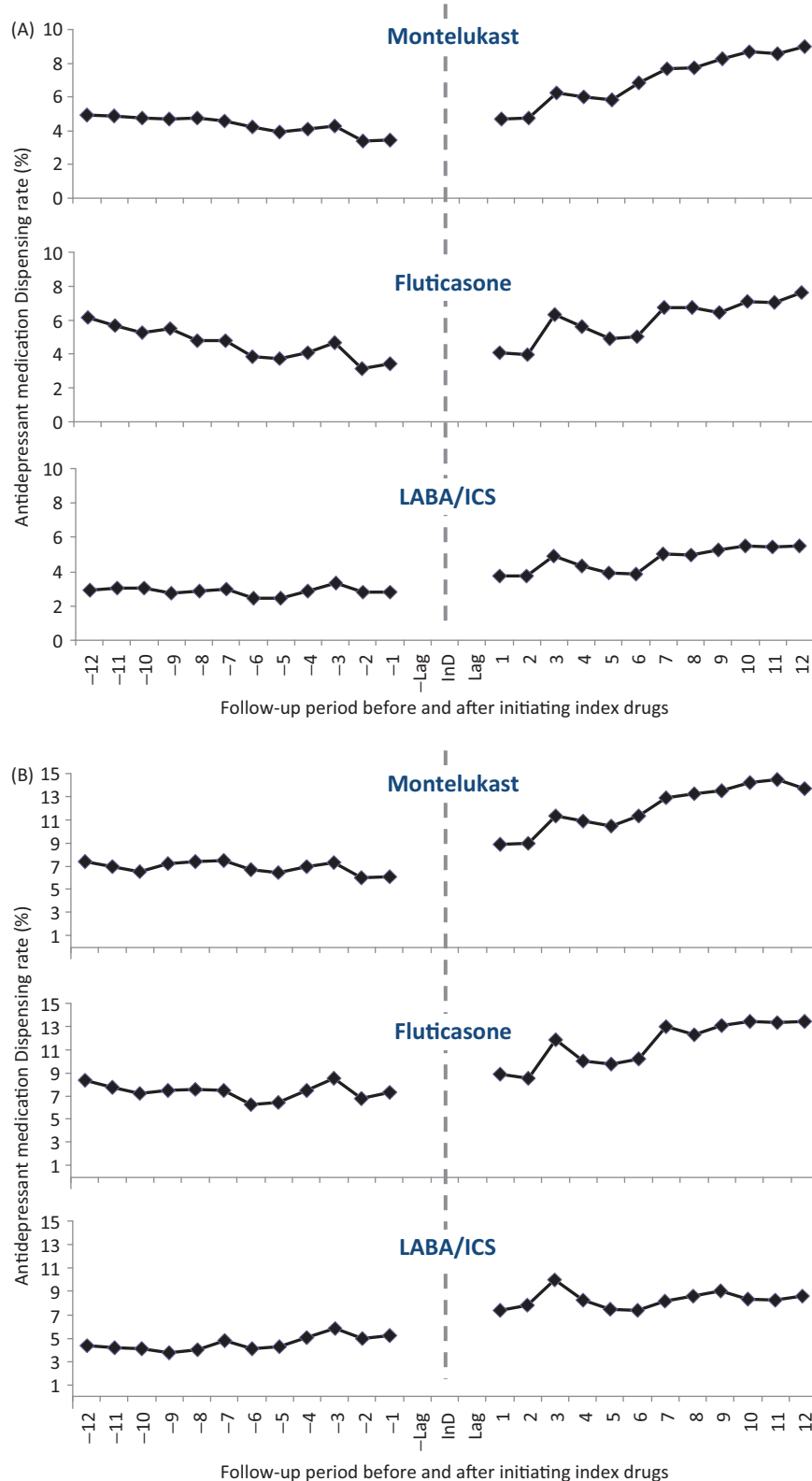
In the 18–24 year age category, a significant increase in immediate level change after the InD (β_2) was observed in montelukast initiators [1.93% (1.55–2.32%, $p < 0.001$)]. However, a similarly significant increase in β_2 was also observed in fluticasone initiators and LABA/ICS initiators in this age category [1.72% (1.30–2.15%, $p < 0.001$) and 2.76% (2.35–3.17%, $p < 0.001$), respectively]. Trend change after the InD (β_3) also increased significantly in montelukast initiators in the 18–24 year age category, a similarly significant increase was observed in the fluticasone initiators but not in the LABA/ICS initiators in this age category (Table 3).

Table 2. Characteristics of patients by the study groups, montelukast, fluticasone (inhalation or intranasal) and LABA/ICS, WK, 1 January 2003 to 31 December 2007; data extracted 7 October 2009.

Characteristics	Montelukast		Fluticasone		LABA/ICS	
	(<i>n</i> = 232 159)	(%)	(<i>n</i> = 264 704)	(%)	(<i>n</i> = 89 635)	(%)
Age (years)						
1–11	125 135	53.9	61 540	23.3	15 333	17.1
12–17	35 690	15.4	40 277	15.2	18 468	20.6
18–24	14 263	6.1	23 582	8.9	10 614	11.8
25–45	57 071	24.6	139 305	52.6	45 220	50.5
Gender						
Female	121 186	52.2	151 758	57.3	52 383	58.4
Male	110 973	47.8	112 946	42.7	37 252	41.6
	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)	Mean ± SD	Median (Q1, Q3)
No. of Rx	7.0 ± 7.2	4 (2, 8)	4.3 ± 4.1	3 (2, 5)	5.6 ± 5.8	3 (2, 6)
No. of episode	2.6 ± 1.6	2 (1, 3)	2.9 ± 1.9	2 (2, 3)	3.1 ± 2.1	2 (2, 4)
Follow-up duration (days)	132.3 ± 97.5	95 (60, 159)	80.0 ± 51.6	60 (59, 88)	100.3 ± 74.8	60 (60, 111)

SD = standard deviation.

Figure 1. Overall trend for antidepressant medication dispensing rate (Y_t) for patients (A) 12–17 and (B) 18–24 years old in the montelukast, fluticasone (inhaled or intranasal) and LABA/ICS groups. Dash line is the drug InD. Follow-up period is divided into 12 15-day intervals pre- and post-InD. Lag = 30 days. WK, 1 January 2003 to 31 December 2007. Data extracted 7 October 2009.



In the 12–17 year age category, a small but significant increase in β_2 was observed in montelukast initiators [0.80% (95% CI: 0.31–1.29%, $p=0.001$)]. Similar increases in β_2 were seen in the two comparison groups, although they were not as significant [0.83% (–0.08–1.73%, $p=0.07$) and 0.76% (0.22–1.30%, $p=0.01$)]. β_3 increased significantly in all three groups. Similar pattern changes were also seen in the younger and older age categories among the three study groups. These results suggest that montelukast initiation may not be

specifically associated with an increase in antidepressant medication dispensing rate (Table 3).

Discussion

Previous reports have suggested a potential association between montelukast use and psychiatric AEs, particularly in patients 12–24 years old [8,10]. However, the study groups have generally been small, making it difficult to draw firm

Table 3. Interrupted time-series model results measuring antidepressant medication dispensing rate (unit is percentage) for montelukast, fluticasone and LABA/ICS groups by age categories, WK, 1 January 2003 to 31 October 2007; data extracted 7 October 2009.

	Montelukast		Fluticasone		LABA/ICS	
	Rate	(95% CI)	Rate	(95% CI)	Rate	(95% CI)
1–11 years old						
β_0	0.62	(0.57–0.68) ^a	0.71	(0.57–0.84) ^a	0.47	(0.31–0.62) ^a
β_1	–0.01	(–0.02 to –0.00) ^c	0.01	(–0.01–0.02)	0.03	(0.01–0.05) ^a
β_2	0.14	(0.06–0.22) ^a	0.17	(–0.01–0.35)	0.16	(–0.06–0.37)
β_3	0.05	(0.04–0.06) ^a	0.02	(–0.01–0.04)	0.00	(–0.03–0.03)
12–17 years old						
β_0	5.20	(4.83–5.57) ^a	6.15	(5.47–6.82) ^a	2.92	(2.51–3.32) ^a
β_1	–0.13	(–0.18 to –0.08) ^a	–0.24	(–0.33 to –0.15) ^a	–0.01	(–0.06–0.05)
β_2	0.80	(0.31–1.29) ^a	0.83	(–0.08–1.73)	0.76	(0.22–1.30) ^c
β_3	0.54	(0.47–0.61) ^a	0.53	(0.40–0.66) ^a	0.18	(0.10–0.26) ^a
18–24 years old						
β_0	7.40	(7.24–7.56) ^a	7.70	(7.44–7.96) ^a	3.65	(3.36–3.95) ^a
β_1	–0.08	(–0.10 to –0.05) ^b	–0.06	(–0.10 to –0.02)	0.13	(0.09–0.17) ^c
β_2	1.93	(1.55–2.32) ^a	1.72	(1.30–2.15) ^a	2.76	(2.35–3.17) ^a
β_3	0.63	(0.60–0.67) ^a	0.51	(0.46–0.55) ^a	–0.10	(–0.15 to 0.04)
25–45 years old						
β_0	10.75	(10.40–11.10) ^a	9.89	(9.26–10.51) ^a	8.04	(7.52–8.56) ^a
β_1	0.01	(–0.03–0.06)	0.15	(0.07–0.24)	0.19	(0.12–0.26) ^b
β_2	3.62	(3.15–4.09) ^a	2.38	(1.54–3.21) ^b	4.03	(3.34–4.73) ^a
β_3	0.53	(0.47–0.60) ^a	0.19	(0.07–0.31)	–0.02	(–0.12–0.08)

β_0 = baseline antidepressant medication dispensing rates, β_1 = trend of antidepressant medication dispensing rates before InD, β_2 = immediate level change in antidepressant medication dispensing rates after InD, β_3 = trend change in antidepressant medication dispensing rate after InD. ^a $p < 0.001$; ^b $p < 0.01$; ^c $p < 0.05$.

conclusions from the results. In this study, we took the novel approach of using data from a large pharmacy claims database to identify montelukast initiators, and to examine the rate at which they were prescribed antidepressants as an indicator of psychiatric AEs. We also evaluated the rate of antidepressant dispensing in fluticasone and LABA/ICS initiators for comparison. While we did observe a statistically significant increase in the rate of antidepressant dispensing after initiation of montelukast, we observed a similarly significant increase in the comparison groups. Therefore, the current results cannot support the hypotheses that montelukast use is specifically associated with increased psychiatric events.

An alternative explanation for the observed increase in antidepressant medication dispensing rates after the initiation of the study drugs could be that patients with asthma or rhinitis have a generally higher prevalence of sleep disorders, depression, and other serious psychiatric events [15–18]. Additionally, this increase may be due to surveillance bias. It is conceivable that when patients are newly diagnosed with asthma, their increased contact with their physicians may trigger the diagnosis and treatment of previously undiagnosed psychiatric conditions [19,20]. Similarly, other drug-related AEs may result in a more frequent interaction with health care providers. This situation was observed during the Women's Health Initiative Study [21].

A strength of this current study is the large number of subjects, identified by using a large nationwide pharmacy claims database containing longitudinal patient demographic and adjudicated drug prescriptions. Pharmacy claims databases have been shown to accurately capture prescription drug dispensing [22] and thus are a reliable source for this information. Since we cannot know from the information in the database whether the patients actually took the prescribed

drugs, we chose to include only those patients who had at least two prescriptions of the index drug during the study period.

We also used information from this database to evaluate psychiatric AEs, tracking antidepressant medication dispensing as an indication of psychiatric events. This approach does have some drawbacks, including the facts that antidepressants are sometimes prescribed for conditions other than depression, and that temporal changes during the 5-year study period could affect the antidepressant medication dispensing rate levels. Examples of temporal effects include reports in the news media, regulatory actions for antidepressant drugs, and market introduction of generic selective serotonin reuptake inhibitors (SSRI). However, the total follow-up period was a maximum of a year for each patient, which mitigates the impact of these factors. We also intentionally ended the study period on 31 December 2007 to avoid any potential impact of the FDA's March 2008 Early Communication regarding montelukast and psychiatric AEs. Nonetheless, due to these limitations, the results should be interpreted with caution.

In this study, we included only patients who had a medical or pharmacy claim at least 12 months before and 12 months after the InD. This criterion excludes individuals who died in the year after drug initiation, possibly including severely depressed patients who committed suicide. However, we expect the number of suicides to be extremely small relative to the total number of patients and not likely to affect our results [23]. Furthermore, exclusion of these cases would only result in an underestimation of the observed trend of antidepressant use.

An additional strength of this study is the use of ITS analysis. ITS is a quasi-experimental design, in which patients serve as their own controls by design. Such study design may

reduce known and unknown confounding effects due to fixed factors. Only time dependent variables, such as age and health status, might potentially confound the results; however, the use of a maximum of 180 days follow-up time pre- and post-InD minimized this risk [13]. It should be noted that our ITS analyses were done using the minimum number of observations required for this method (12 time points pre- and post-InD). Also, since the ITS models for each of the three medication groups were built separately, we cannot directly compare across medication groups to see if the changes in dispensing rates are different.

Conclusions

Small increases in antidepressant medication dispensing rates occurred after initiating montelukast. However, similar patterns were observed in the fluticasone and LABA/ICS comparison groups. Therefore, the current results do not support the hypothesis that montelukast is specifically associated with increased psychiatric events. The observed increases may be partially due to surveillance bias or to psychiatric comorbidities previously reported to be associated with indications of these drugs. Further research is needed to tease out the impact of the development of asthma from the effect of the initiation of asthma therapy on the risk of psychiatric events.

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Declaration of interest

The authors report no conflicts of interest. The views expressed are those of the authors and do not necessarily represent that of the US Food and Drug Administration. The authors alone are responsible for the content and writing of this article.

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