

Changes in Long-acting β -Agonist Utilization After the FDA's 2010 Drug Safety Communication

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ABSTRACT

Purpose: In February 2010, the US Food and Drug Administration (FDA) issued new recommendations for the safe use of long-acting β -agonists (LABAs) in patients with asthma. The objective of this study was to determine the impact of the FDA's 2010 safety advisory on LABA utilization.

Methods: Using administrative data from the Oregon Medicaid program, we performed an interrupted time series regression to evaluate changes in the trend in new LABA prescriptions before and after the FDA's 2010 advisory. Trends in incident fills were examined among those with and without an asthma diagnosis code and previous respiratory controller medication use; trends were also assessed according to patient age.

Findings: The average age of the 8646 study patients was 37 years, 53% had a diagnosis of asthma, 21% had no respiratory diagnosis, and 32% had not used a respiratory controller medication in the recent past. The trend in new LABA prescriptions declined by 0.09 new start per 10,000 patients per month (95% CI, -0.19 to -0.01) after the FDA's advisory. Among those with a diagnosis of asthma, there was an immediate drop of 0.48 (95% CI, -0.93 to -0.03) and a 0.10 (95% CI, -0.13 to -0.06) decline in the monthly rate of new starts per 10,000 patients. Immediately after the FDA's advisory, we observed a statistically significant 4.7% increase (95% CI, 0.8 to 8.7) in the proportion of new LABA starts with history of previous respiratory controller medication use. Utilization of LABAs did not change in those without a diagnosis of asthma.

Implications: The FDA's 2010 advisory was associated with modest reductions in LABA utilization overall and in ways highlighted in their recommendations. (*Clin Ther.* 2014;■:■■■-■■■) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key Words: adrenergic β_2 -agonists, Medicaid, US Food and Drug Administration, utilization.

INTRODUCTION

Controversy surrounding the use of long-acting β -agonists (LABAs) has persisted since salmeterol was originally approved by the US Food and Drug Administration (FDA) in 1994.^{1,2} Concerns about the association between salmeterol and the risk for serious asthma-related events were first noted in 1993 with publication of the Serevent National Surveillance study.³ The FDA-mandated SMART (Salmeterol Multicenter Asthma Research Trial) study corroborated these findings, suggesting a small but significant increase in asthma-related deaths and life-threatening events, particular among African-American subjects, in those randomized to receive salmeterol.⁴ After early termination of SMART, the FDA issued their initial black box warning for salmeterol in 2003. Over the past decade, this warning has been revised several times and expanded to the entire class of drugs.^{5,6}

Over this same period, meta-analytic reviews of SMART and other accumulated safety data have flourished, along with varying interpretations of their significance.⁶ Despite the ongoing safety debate, use and expenditures for LABAs have soared. Between

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2002 and 2009, the number of prescriptions dispensed for medications containing an LABA increased from 15.6 to 21.7 million.⁷ In 2012, nearly \$5 billion dollars were spent on fluticasone/salmeterol,^{*} making it the fourth largest drug market in the United States behind esomeprazole,[†] aripiprazole,[‡] and rosuvastatin.[§] There is growing evidence that certain aspects of LABA prescribing seem to be suboptimal. Although LABA monotherapy, which has been strongly discouraged by the FDA and in clinical practice guidelines, is uncommon,⁸ nearly 70% of asthma patients with a new prescription for a combination LABA/inhaled corticosteroid (ICS) have no history of controller use.^{9–13} In addition, LABA use in patients without a diagnosis of either asthma or chronic obstructive pulmonary disease (COPD) is considerable.^{14–16} Despite the revised warnings and extensive publicity, the existing literature shows that overall LABA utilization has been largely unaffected and, in fact, has grown substantially over the last decade.^{10–12}

On February 18, 2010, after extensive advisory committee deliberation, the FDA announced revised recommendations on the use of LABAs and further modified the LABA black box warnings. The revised recommendations included the following: (1) an emphasized contraindication to LABA monotherapy without another asthma controller medication; (2) using LABAs long term only in patients whose asthma cannot be adequately controlled on other asthma controller medications; (3) using LABAs for the shortest duration of time required to achieve asthma control and then discontinuing; and (4) using fixed-dose combination LABAs in pediatric and adolescent patients to ensure compliance to both medications.¹⁷ Manufacturers of LABA products were required to change package inserts, medication labels, and patient medication guides.

Although the FDA's LABA recommendations and black box revisions of 2010 are the most prescriptive to date, controversy remains about the relative benefits and safety of these agents.^{6,18,19} Utilization studies of previous FDA action have yielded mixed results; it

is therefore unclear if clinicians have modified their prescribing habits to better conform to the most recent FDA communication.^{10–12,20} The objective of the present study was to examine changes in LABA use and appropriateness in a state Medicaid program after the FDA's 2010 drug safety communication.

MATERIALS AND METHODS

Patient Population

This study used a retrospective interrupted time series design to evaluate longitudinal changes in incident (new) LABA prescriptions before and after the FDA's 2010 LABA advisory. Using state of Oregon administrative pharmacy and medical claims data, we identified monthly rolling cohorts of incident LABA users from January 2008 to December 2012. Patients were included if they had a new prescription claim for a single-source LABA or fixed-dose LABA/ICS combination product with no LABA claims in the 6 months prior; this was defined as their index claim. LABA products included salmeterol xinafoate,^{||} formoterol fumarate inhalation powder,[¶] arformoterol tartrate,[#] and indacaterol inhalation powder.^{**} Combination LABA/ICS products included fluticasone propionate and salmeterol inhalation powder,^{††} budesonide and formoterol fumarate dihydrate inhalation aerosol,^{‡‡} and mometasone furoate and formoterol fumarate dihydrate inhalation aerosol.^{§§}

To assess baseline patient characteristics, only patients with 6 months of enrollment before their index claim were included. Baseline patient characteristics were assessed by using pharmacy and medical claims data 6 months before each patient's index claim. Data from this period were used to summarize age in years as of the index date; sex; and race. Using codes from *International Classification of Diseases, Ninth Revision* (ICD-9), we quantified whether patients had diagnoses of asthma (ICD-9 493.x), COPD (ICD-9 4912x, 492.xx, 496xx, 5064x, 5181x, 5182x), both, or neither. We

*Trademark: Advair[®] (GlaxoSmithKline, Research Triangle Park, North Carolina).

†Trademark: Nexium[®] (AstraZeneca, London, United Kingdom).

‡Trademark: Abilify[®] (Otsuka America Pharmaceutical, Inc, Princeton, New Jersey).

§Trademark: Crestor[®] (AstraZeneca).

||Trademark: Serevent Diskus[®] (GlaxoSmithKline).

¶Trademark: Foradil[®] Aerolizer[®] (Merck Sharp & Dohme Corp, Whitehouse Station, New Jersey).

#Trademark: Brovana[®] (Sunovion Pharmaceuticals Inc, Marlborough, Massachusetts).

**Trademark: Arcapta[™] Neohaler[™] (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey).

††Trademark: Advair HFA[®], Advair Diskus[®] (GlaxoSmithKline).

‡‡Trademark: Symbicort[®] (AstraZeneca).

§§Trademark: Dulera[®] (Merck Sharp & Dohme Corp).

also determined if the patient had previous asthma or COPD controller medication use (see the [Supplemental Table](#) in the online version at <http://dx.doi.org/10.1016/j.clinthera.2014.10.025>) in the 3 months before their index claim. An expansive definition of controller medication was used that included most inhaled respiratory agents (with the exception of short-acting β -agonists).

Patients with fee-for-service Medicaid were excluded from our study because of a prior authorization restricting LABA use that took effect during the study period.²¹ Patients were also excluded if they had dual Medicare Medicaid enrollment because of the potential for missing Medicare data. Because the first 6 months of data were used to establish eligibility and define baseline characteristics, the actual study period ran from July 2008 to December 2012 (54 months).

Analysis

We analyzed monthly trends and changes in incident LABA use before and after the FDA's LABA advisory was issued on February 18, 2010, by using segmented regression analyses.²² The general form of our segmented regression model was $Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{FDA advisory}_t + \beta_3 \times \text{time after advisory} + e_t$. The dependent variable (Y_t) was the number of new LABA starts per 10,000 Medicaid enrollees per month. *Time* was a continuous variable from 1 to 54 indicating time in months from the beginning of the study period. *FDA advisory* was a dummy variable set at 0 if the month was before the FDA's advisory (July 2008–January 2010; 19 months) and at 1 if the month was after the FDA's advisory (March 2010–December 2012; 34 months). The time point in February 2010 (month 20) was censored because the advisory was issued in the middle of the month. *Time after advisory* was a continuous variable indicating the number of months after the FDA's advisory; this variable was set at 0 if before the FDA's advisory. The β_0 estimates the number of new LABA starts per 10,000 patients at time 0 (intercept); β_1 estimates the change in new LABA starts over time (baseline trend) before the FDA advisory; β_2 estimates the immediate change in new LABA starts (level change) occurring between January 2010 (month 19) and March 2010 (month 21); and β_3 estimates the change in trend over time (trend change) of new LABA starts after the FDA advisory. Using the multivariate delta procedure described by Zhang et al.,²³ we derived absolute changes in new starts for

the final period of the time series (month 54, December 2012) by comparing the post-FDA advisory estimate with an estimate assuming a continuation of the baseline trend. Predications were generated only for those models with significant changes in trend over time. All regressions were performed by using PROC AUTOREG within SAS version 9.3 (SAS Institute, Inc, Cary, NC). Autocorrelation between error terms was assessed by using the Durbin-Watson test statistic. If significant autocorrelation was detected ($P < 0.05$), we adjusted the models with autocorrelation terms selected by using a stepwise approach that first fit a model with higher order autocorrelation terms. The least nonsignificant term was then dropped, and the reduced model was successively re-fit until all remaining autocorrelation terms were significant ($P < 0.05$).

Several models were fit to describe changes in LABA starts overall, if the patient had a baseline diagnosis of asthma alone (excluding those with no diagnosis and those with a co-occurring COPD diagnosis), and by age (<18 years). In addition, as a measure of potential appropriateness, we analyzed changes in the proportion of new starts with previous use of a respiratory controller medication. Finally, to minimize the possibility that observed LABA trends reflected larger asthma controller use, we analyzed an identically constructed cohort of new users of other asthma controller medications in those with a diagnosis of asthma.

This study was approved by the Oregon Health & Science University institutional review board, and data use agreements with the Oregon Health Authority were obtained.

RESULTS

Between July 2008 and December 2012, a total of 8646 patients started using an LABA-containing product and met our eligibility criteria. As summarized in [Table I](#), new LABA users during this period were predominately female and aged >18 years. Only 12% of the study sample were aged ≤ 12 years. The most commonly prescribed LABA during this period was combination fluticasone/salmeterol. Nearly two thirds of patients had a diagnosis of asthma, and 53% had a diagnosis of asthma without a concurrent diagnosis code for COPD. One in 5 patients had no respiratory diagnosis before initiating an LABA. Only 32% of patients initiating an LABA had a history of

Table I. Demographic and clinical characteristics of the new-user cohort (N = 8646).

Characteristic	Value
Female sex	5726 (66.2)
Age, mean (SD), y	37.2 (17.5)
≤ 12	1012 (11.7)
< 18 and > 12 y	739 (8.6)
≥ 18	6895 (79.8)
Race; non-white	1579 (18.3)
Entered rolling cohort more than once	1815 (21.0)
Index long-acting β -agonist	
Fluticasone/salmeterol	7345 (85.0)
Budesonide/formoterol	860 (10.0)
Mometasone/formoterol	120 (1.4)
Single long-acting β -agonist	321 (3.7)
Respiratory diagnoses	
Asthma only	4570 (52.9)
COPD only	1426 (16.5)
Asthma and COPD	828 (9.6)
No respiratory diagnosis	1822 (21.1)
Respiratory controller use	2723 (31.5)
Respiratory controller use, asthma only*	1470 (32.2)

Unless otherwise indicated, values are given as number (%). COPD = chronic obstructive pulmonary disease.

*Denominator, n = 4570.

previous respiratory controller use. This finding was similar in those with only a diagnosis of asthma.

Table II summarizes estimates from the segmented regression analyses of the trend in new starts of LABA from July 2008 through December 2012. As shown in **Figure 1**, after the FDA's advisory in 2010, incident LABA prescriptions declined significantly each month by 0.09 prescription per 10,000 patients (95% CI, -0.19 to -0.01; $P < 0.05$). Assuming a continuation of the baseline trend, this decline would be expected to result in a 3.16 (95% CI, -4.09 to -2.22) reduction in new starts per 10,000 patients by December 2012. There was no significant change immediately after the FDA's advisory. Examining LABA utilization according to baseline diagnoses (**Figure 2**), we found a similar decline in trend of 0.1 new start per 10,000 patients (95% CI, -0.13 to -0.06; $P < 0.001$) among

those with an asthma diagnosis, but no significant changes in those without an asthma diagnosis. In addition, among those with an asthma diagnosis, there was an immediate drop of 0.48 new starts per 10,000 patients (95% CI, -0.93 to -0.03; $P < 0.05$) after the FDA advisory. By the end of 2012, this decline would be predicted to result in a reduction of 3.76 (95% CI, -4.09 to -3.43) new starts per 10,000 patients. The trend in utilization was significantly reduced in both those <18 years of age and among those ≥18 years of age. During the same period, new starts of other asthma controller agents in those with an asthma diagnosis also declined in trend, but this change was not statistically significant.

As shown in **Figure 3**, there was a statistically significant 4.7% immediate increase (95% CI, 0.8 to 8.7; $P < 0.05$) in the proportion of incident users with a recent history of respiratory controller medication use. Significant changes in the overall trend were not observed. Consequently, the model does not predict an increase (or decrease) in the proportion of new LABA starts with a history of respiratory controller medication beyond the immediate 4.7% change. However, the trend in prior controller medication use was nonsignificantly reversed from negative in the pre-period to positive in the post-period.

DISCUSSION

In this study, we observed modest but significant changes in LABA utilization after the 2010 FDA drug safety communication. Specifically, there were significant declines in trend overall and among those with a diagnosis of asthma, a subgroup specifically addressed in the FDA's advisory. In addition, we observed a significant jump in the proportion of patients starting an LABA for the first time with a recent history of some other respiratory controller medication. Although the overall decline in trend seems modest, extrapolation to the last month of the time series results in a cumulative one-third reduction in new starts relative to predicted utilization. Although the FDA's advisory and the clinical data only pertain to treatment of asthma, it is conceivable that treatment of COPD or other conditions may also have been affected. Because of the anticipated limited number of patients with a diagnosis of COPD in Medicaid, we combined those with any COPD diagnosis with no respiratory diagnosis to evaluate spillover effect. We found no evidence suggesting that

Table II. Segmented regression model estimates and CIs for new-use cohorts.

Variable	Intercept [*]	Baseline Trend (95% CI) [†]	Level Change (95% CI) [‡]	Trend Change (95% CI) [§]	Predicted Absolute Change (95% CI)
LABA starts	9.59 (7.67 to 11.52)	-0.002 (-0.07 to 0.06)	-0.25 (-1.15 to 0.65)	-0.09 (-0.19 to -0.01) ^{††}	-3.16 (-4.09 to -2.22)
LABA starts by asthma diagnosis					
Yes	4.78 (3.83 to 5.73)	0.04 (0.003 to 0.07) ^{††}	-0.48 (-0.93 to -0.03) ^{††}	-0.10 (-0.13 to -0.06) [#]	-3.76 (-4.09 to -3.43)
No	4.64 (3.63 to 5.65)	-0.03 (-0.7 to 0.003)	0.19 (-0.29 to 0.68)	0.004 (-0.03 to 0.04)	NA
LABA starts by age ^{**}					
< 18 y	2.62 (1.37 to 3.87)	0.02 (-0.02 to 0.06)	-0.44 (-1.06 to 0.18)	-0.06 (-0.11 to -0.01) ^{††}	-2.55 (-3.05 to -2.05)
≥ 18 y	22.17 (16.05 to 28.30)	0.02 (-0.20 to 0.23)	0.24 (-2.74 to 3.22)	-0.30 (-0.53 to -0.08) ^{††}	-10.10 (-12.42 to -7.78)
Proportion of LABA starts with previous controller use [¶]	31.4% (23.4% to 39.4%)	-0.2% (-0.5% to 0.1%)	4.7% (0.8 to 8.7) [#]	0.3% (-0.01 to 0.6)	NA
Controller starts in those with asthma diagnosis [¶]	17.18 (12.50 to 21.86)	0.91 (-0.24 to 0.62)	2.02 (-3.71 to 7.75)	-0.42 (-2.63 to 0.07)	NA

LABA = long-acting β -agonist; NA = not applicable.

^{*}Utilization level on July 2008.

[†]Monthly change in new LABA starts per 10,000 patients per month.

[‡]Estimate of change immediately after the February 2010 US Food and Drug Administration advisory.

[§]Change in the trend of new LABA starts per 10,000 patients per month.

^{||}Projected difference in the dependent variable on month 54 (December 2012) assuming continuation of baseline trend.

[¶]Controllers include inhaled corticosteroids, leukotriene modifiers, and theophylline.

[#] $P < 0.05$.

^{**}Denominator reflects age criteria on first of month.

^{††} $P < 0.001$.

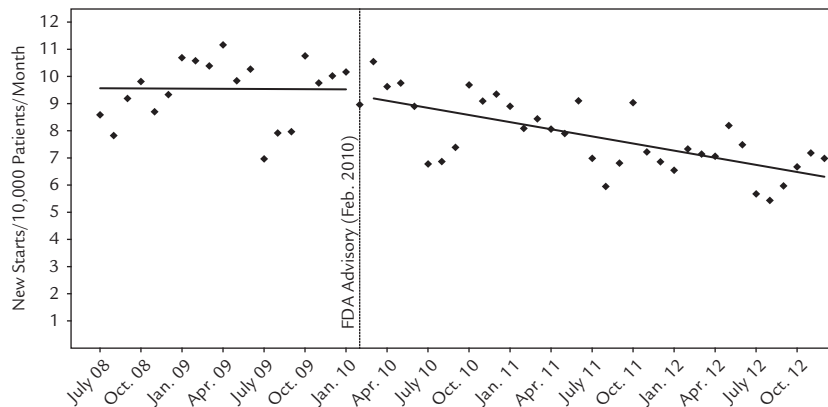


Figure 1. New long-acting β -agonist starts per 10,000 enrollees per month. FDA = US Food and Drug Administration.

prescribing behavior changed for patients without a diagnosis of asthma, for whom the FDA's advisory does not apply.

Our data suggest a trend toward further conformity to both the revised FDA label and practice guidelines. Specifically, we observed an increase in the proportion of new users who have used a respiratory controller medication immediately before starting an LABA.

Despite this change, the proportion of new users with a history of controller medication use remains <50%. Although speculative, the decline in use

among those with an asthma diagnosis may indicate increasing reluctance of prescribers to begin LABA therapy, given the ongoing safety concerns.²⁴ There were significant declines in trend for both those <18 and ≥ 18 years of age.

Previous investigations of the FDA's LABA labeling changes have generated equivocal or ambiguous findings. Using a commercial health insurance dataset, Stockl et al¹² found that the FDA's 2005 advisory had no impact on the likelihood of being prescribed an asthma controller medication before starting an LABA,

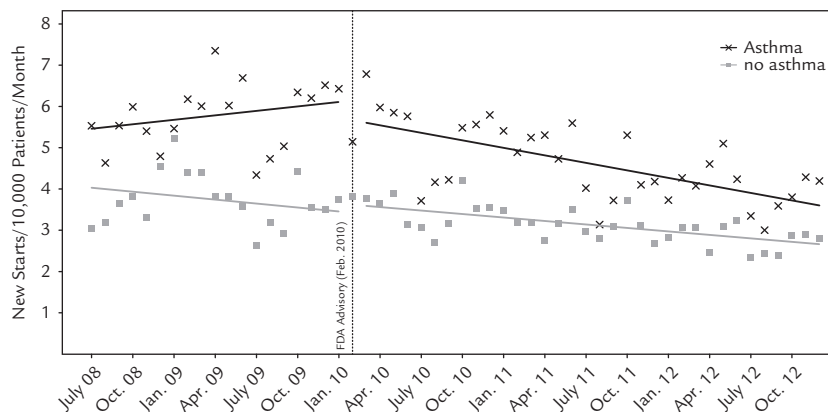


Figure 2. New long-acting β -agonist starts per 10,000 enrollees per month in those with and without a diagnosis of asthma. Crosses represent new LABA starts in those with an asthma-only diagnosis, and gray boxes represent new LABA starts in those without an asthma-only diagnosis. FDA = US Food and Drug Administration.

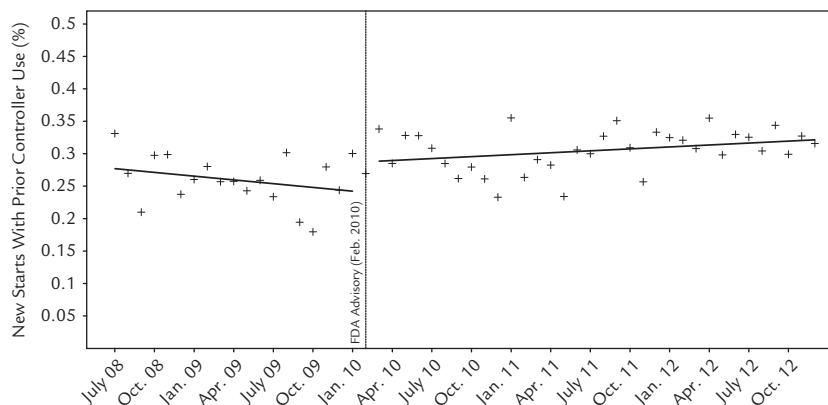


Figure 3. Proportion of new long-acting β -agonist starts with a recent history of respiratory controller medication use. FDA = US Food and Drug Administration.

a recommendation added in the black box warning. Similar conclusions were reached by 2 other studies examining quarterly trends in use of a fluticasone/salmeterol combination inhaler as initial therapy for both adults and children before and after the FDA's 2005 communication.^{10,11} In these and other studies, the proportion of patients prescribed an asthma controller agent before initiating LABA therapy ranged from 30% to 40%,^{8,9,25} similar to what we observed. A study by Zhou et al²⁰ found that the rate of single-ingredient LABA declined significantly between 2003 and 2011, with growing use of other asthma controller medications concurrent with single-agent LABAs.

Our findings may contrast with previous studies because of how the FDA advisory was formulated. In a recent systematic review assessing how FDA drug risk communication affects utilization and outcomes, Dusetzina et al²⁶ found considerable heterogeneity in measured responses. Synthesized results suggest that FDA advisories offering specific guidance may be more effective than general risk communications. This finding may explain why the 2010 advisory seems to have produced changes in prescribing behavior while previous studies of the 2005 label changes were largely unheeded, with the exception of single-agent LABA use. In situations in which FDA advisories are issued targeting a specific subpopulation, such as with the use of LABAs, studies have found some evidence of spillover onto nontargeted populations.^{27,28} The FDA's LABA risk communication is directed toward those with asthma and not COPD. Our data show that the

impact on prescribing was largely confined to those with a diagnosis of asthma, although COPD is relatively uncommon in a younger Medicaid population.

We acknowledge several limitations of the present study. First, our data were derived from 1 state Medicaid program of modest size. Although Medicaid is the largest provider of health care for low-income children and adolescents who are disproportionately affected by asthma, trends in Oregon may not reflect utilization in other states.^{29,30} Replication of findings in larger, more diverse populations would be helpful. Second, interrupted time series with a control group is the strongest quasi-experimental research design.³¹ Our analysis lacks a control group, precluding true counterfactual comparisons. It is unlikely that prescribing data acquired from a non-US source would be an adequate control because the influence of FDA communication has been shown to affect utilization in other countries.³² However, causality is strengthened because the decline in new starts was confined to LABAs, as opposed to other asthma controllers. Third, inferences from time series data may be confounded by secular changes in behavior unrelated to the intervention under study. In 2012, GlaxoSmithKline agreed to a civil settlement for off-label use of fluticasone/salmeterol, the most commonly prescribed LABA.³³ The US Department of Justice alleges that through 2010, GlaxoSmithKline promoted this agent for milder forms of asthma and other indications not approved by the FDA.³⁴ It is unclear if cessation of promotional activities also

affected utilization of LABAs during the study period. There were no other policies or trends in utilization that may have acted to confound this analysis. Finally, our study used paid pharmacy claims as an indicator of changes in prescribing. Along with the many limitations associated with using administrative data, it is also important to recognize that during this period, fluticasone/salmeterol was heavily promoted and sampled. As such, patients we have characterized as new users of an LABA may in fact be former users of sampled medication who are merely filling their first prescription through a pharmacy. The extent and impact of this phenomenon are unclear.

CONCLUSIONS

We observed a modest decline in the trend of new LABA starts after the FDA's 2010 recommendations. New LABA starts were significantly reduced over time among those with a diagnosis of asthma but largely unchanged in those without such a diagnosis. Finally, we observed a significant increase in the proportion of new users with a history of respiratory controller use, an indicator of possible inappropriate use. In addition to the limitations noted earlier, other questions remain. Several of the FDA's 2010 recommendations have caused concern among clinicians because they are somewhat inconsistent with existing treatment guidelines and evidence.^{18,35} For example, although the FDA now recommends LABAs be discontinued after asthma control is achieved, the most recent National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR-3) guidelines recommend step-down consideration only after at least 3 months of therapy.^{13,17} Updated labeling also states that LABAs should not be added to therapy for patients who can be adequately controlled on low or medium doses of an ICS, a recommendation that some believe is at odds with the clinical evidence.³⁶ In patients who remain symptomatic on low-dose ICS, EPR-3 guidelines acknowledge the additional benefits of LABA step-up therapy on lung function and symptom control, but in deference to LABA safety concerns, the guidelines consider medium-dose ICS escalation or LABA additions as equally acceptable options.¹³

It is unclear how these complex clinical decisions are being made in light of potentially conflicting recommendations. The FDA has mandated the conduct of 5 additional randomized controlled trials by

LABA manufacturers to further clarify the benefits and harms of adding LABAs compared with continued ICS treatment.³⁷ Results from these trials, expected in 2017, will likely prompt further modifications to product labeling for LABAs.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

SUPPLEMENTAL MATERIAL

A supplemental table accompanying this article can be found in the online version at <http://dx.doi.org/10.1016/j.clinthera.2014.10.025>.

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Supplemental Table. Respiratory controller drugs
(generic names).

Inhaled corticosteroids

Beclomethasone dipropionate
Budesonide
Flunisolide
Flunisolide/menthol
Fluticasone propionate
Mometasone furoate
Triamcinolone acetonide

Inhaled anticholinergics

Ipratropium bromide
Ipratropium/albuterol sulfate
Tiotropium bromide

Miscellaneous asthma or COPD agents

Montelukast sodium
Omalizumab
Zafirlukast
Zileuton
Roflumilast
Theophylline

Mast cell stabilizers

Cromolyn sodium
Nedocromil sodium

COPD = chronic obstructive pulmonary disease.

Supplemental Table.

Respiratory controller drugs (generic names).

Inhaled	corticosteroids		
	Beclomethasone	dipropionate	
	Budesonide		
	Flunisolide		
	Flunisolide/menthol		
	Fluticasone	propionate	
	Mometasone	furoate	
	Triamcinolone	acetanide	
Inhaled	anticholinergics		
	Ipratropium	bromide	
	Ipratropium/albuterol sulfate		
	Tiotropium	bromide	
Miscellaneous	asthma	or	COPD agents
	Montelukast	sodium	
	Omalizumab		
	Zafirlukast		
	Zileuton		
	Roflumilast		
	Theophylline		
Mast	cell	stabilizers	
	Cromolyn	sodium	
	Nedocromil	sodium	