

PHARMACOTHERAPY

Characterization of Long-Acting Beta₂-Adrenergic Agonists Utilization in Asthma Patients

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Objective. Because of the serious safety risks, Food and Drug Administration (FDA) has recommended that long-acting beta₂-adrenergic agonists (LABAs) be reserved for patients whose asthma cannot be adequately managed with asthma control medication. The objective of the study is to assess prescribing patterns for LABAs prior to the FDA's drug safety communication issued on 2 June 2010. **Methods.** Data were extracted from IMS Health Plan Claims database for asthma patients who had a new LABA therapy during 2005–2009. The proportion of LABA incident episodes preceded by inhaled corticosteroid (ICS) or leukotriene receptor antagonists (LTRAs) was examined. The medication-concurrent ratio (MCR), defined as the ratio of overlapping therapy days of single-ingredient (SI) LABAs and non-LABA products to the total days of SI LABAs, was calculated. Four criteria were used to estimate poorly controlled asthma prior to LABA initiation. **Results.** Of the 228 047 asthma patients, fixed-dose combination (FDC) LABAs were used by the majority of patients (96%). Prior use of ICS or LTRAs was observed in 64% and 31% of SI and FDC LABA incident episodes, respectively. The median MCR for SI LABAs was 62%. Approximately half of the patients met at least one criterion for poorly controlled asthma prior to LABA use. **Conclusions.** Substantial proportion of patients was prescribed LABAs without prior use of ICS or LTRAs, or other indicators of poor asthma control. These findings suggest that asthma guidelines were not entirely followed in clinical practice during the study period.

Keywords asthma, drug concurrency, drug use, fixed-dose combination LABAs, long-acting beta₂-adrenergic agonists, single-ingredient LABAs

INTRODUCTION

Concerns over the risk–benefit profile of long-acting beta₂-adrenergic agonists (LABAs) have led to various Food and Drug Administration (FDA) actions, including FDA advisory committee meetings and LABA labeling changes (1, 2). In February 2010, FDA announced new labeling recommendations for LABAs, which were finalized in June 2010, to help ensure the safe use of these products for the management of asthma (3, 4). The new labeling recommendations for the use of LABAs in the treatment of asthma include the following: (1) LABA use for asthma are contraindicated without concomitant use of a long-term asthma control medication (ACM), such as an inhaled corticosteroid (ICS); (2) pediatric and adolescent patients, who require the addition of a LABA to an ICS, should use fixed-dose combination (FDC) LABA products to ensure adherence with both medications; (3) LABAs should not be used in patients whose asthma is controlled on low- or medium-dose ICS; and (4) once asthma control is achieved and maintained, a step-down therapy is warranted (e.g., discontinue LABA) if possible without loss of asthma control, and the patient should be maintained on a long-term ACM, such as an ICS (5–9).

We examined the prescribing and utilization patterns of LABA-containing products during 2005–2009 to obtain baseline data during the time period preceding FDA's new

labeling recommendations for LABAs. Specifically, we assessed use patterns of single-ingredient (SI) or FDC LABA products, factors related with their use over the study period, and the appropriate use of these products. This study will be used as the basis for future evaluation of changes in the prescribing patterns and utilization of LABAs following the FDA's drug safety communications and new labeling in 2010.

METHODS

Patient Population

A population-based retrospective study design of commercially insured patients from the IMS LifeLink™ database was used. This longitudinal health plan claims database represents over 98 managed care plans and covers approximately 61.8 million de-identified patients. Claims data are captured from physician's office visits, retail and mail order pharmacies, patient visits to specialists, hospitalizations, emergency department (ED) visits, home care, diagnostic tests, procedures, and injections. This study is covered under a blanket FDA Research Involving Human Subjects Committee (RIHSC) approval.

Patients who met the following criteria were included in the study as new LABA initiators; (1) a new prescription claim for an SI LABA (salmeterol, formoterol, or arformoterol) or FDC LABA (budesonide–formoterol or fluticasone–salmeterol) between 1 January 2005 and 31 October 2009, with the index date defined as the first LABA prescription filled date; (2) no prescription for LABA-

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containing products during the 6 months prior to the index date; (3) continuous enrollment in the health plan for a minimum of 365 days prior to the index date; (4) at least one asthma diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9CM code 493.xx) preceding the index date; (5) no COPD diagnosis (ICD-9CM codes 491.xx, 492.xx, or 496.xx). We excluded patients with no recorded age or gender. In addition, we excluded patients who had missing information on the days' supply or with >100 days' supply in one single prescription for LABA medications during the study period. The 100-day cut-off was used since many health insurance companies do not cover the cost of prescriptions that exceed 100 days' supply. A sensitivity analysis was conducted, in which patients with more than 100 days' supply in one single prescription were included (0.11% patients were excluded for FDC LABAs; 0.17% for SI LABAs). Patients aged 65 years or older at the index date were excluded as Medicare rather than commercial insurance may cover them. From this base cohort, two subsets of patient cohorts were established—one with SI LABAs and the other with FDC LABAs.

Measures

Demographic characteristics, including age, gender, and region, were examined. Comorbidities considered potentially relevant to the severity of respiratory symptoms—allergic bronchopulmonary aspergillosis, gastroesophageal reflux disease, obesity, obstructive sleep apnea, rhinitis, sinusitis, acute respiratory infection, and depression—were identified from the patient's medical claims for the 365 days prior to the index date (10). Prescriber specialty associated with initiation of a new LABA prescription was examined.

Treatment episode for LABA-containing products or non-LABA medications was constructed for each therapeutics drug class individually. A gap of >25% of the prior prescription days' supply between the dispensing date of a new prescription and the latest ending date of the prior prescription indicated a start of a new treatment episode. In all main analyses, except for concurrency analysis, we focused on ICS and leukotriene receptor antagonists (LTRAs) for long-term non-LABA asthma medications.

Duration of Therapy. We estimated the duration of the treatment episode for SI and FDC LABAs, and the episode was categorized as ≤ 30 days, 30–90 days, and >90 days. The median cumulative exposure days for LABAs was calculated.

Use of ICS or LTRAs Prior to LABA Initiation. The proportion of patients with ICS or LTRAs dispensed during 1–90 days prior to the index date of SI and FDC LABAs was estimated.

Concurrent Therapy with SI LABAs. Concurrent therapy was defined as having at least one overlapping therapy day of SI LABAs with either long-term non-LABA medications or quick-relief medications. Long-term non-LABA medications included ICS, LTRAs, cromones, oral systemic

corticosteroids, immunomodulators, and methylxanthines, and the quick-relief medications included anticholinergics, short-acting beta-agonist bronchodilators, and quick-relief combination.

The mean medication-concurrent ratio (MCR) was defined as the ratio of number of days a patient on concurrent medications to the total number of day on SI LABAs. The MCR was calculated for each SI LABA treatment episode, as well as for each patient.

Use of SI LABAs over the Study Period. The proportion of SI LABAs out of all prescriptions for LABA-containing products were examined every 6 months between 1 January 2005 and 31 December 2009, and further stratified by age groups.

Poorly Controlled Asthma Prior to LABA Initiation. We attempted to assess the consistency of LABA use with asthma management guidelines in initiators of LABAs (10). One or more of the following criteria were used to estimate poorly controlled asthma in the pre-index period after which LABA therapy might be deemed appropriate: (a) ≥ 1 prescription of an ICS or a LTRAs dispensed during 1–90 days prior to the index date; (b) ≥ 1 asthma-related ED visit or hospitalization 1–90 days prior to the index date; (c) ≥ 2 oral corticosteroid (OCS) prescriptions ≤ 21 days' supply each (indicates asthma exacerbation) 1–90 days prior to the index date; or (d) ≥ 3 canisters of a short-acting beta-agonist (SABA) during the 1–180 days prior to the index date. These measures correlate with patient-centered measures of disease severity and control and they have been used in a variety of studies as markers for poor asthma control (11–18). While they were not validated or confirmed as measures for poorly controlled asthma, these measures could be used for sensitivity analysis to approximate the extent of potential inappropriate LABA use.

RESULTS

The total number of patients with an ICD-9 code for asthma (493.xx) was 3,601,563 between 2005 and 2009. A total of 228,047 asthma patients who had a new claim for LABA-containing products and met the inclusion criteria were identified between 2005 and 2009. The majority of the patients (96%) initiated FDC LABAs ($N = 219,012$), only 6% initiated SI LABAs ($N = 13,920$), and 2% initiated both. Overall, 72% of all patients initiating any LABA were adults (≥ 18 years old), 60% were women, and the mean age was 33 years (standard deviation (SD) = 17.6). The mean age in the SI LABAs cohort was 38 years (SD = 17.3), and in the FDC LABAs cohort was 33 years (SD = 17.6). Demographic and clinical characteristics of FDC LABAs and SI LABAs cohorts are shown in Table 1. Of all age groups, adults (≥ 18 years old) accounted for approximately 80% of the SI LABAs and 72% of the FDC LABAs. Comorbidities pertinent to the severity of respiratory symptoms, including rhinitis and sinusitis, were present in approximately 38% and 25% of all SI LABA, and 36% and 24% of all FDC LABA cohorts, respectively. The prevalence of

TABLE 1.—Demographic and clinical characteristics of asthma patients initiating single-ingredient (SI) LABAs or fixed-dose combination (FDC) LABAs, IMS LifeLink™ Health Plan Claims database, 2005–2009.

Characteristics	SI LABA (N = 13,920)		FDC LABA (N = 219,012)	
	N	%	N	%
Age group (years)				
0–3	107	0.8	521	0.2
4–11	1,142	8.2	29,548	13.5
12–17	1,504	10.8	31,970	14.6
18–45	5,037	36.2	87,504	40.0
46–64	6,130	44.0	69,469	31.7
Gender				
Female	8,788	63.1	131,119	59.9
Male	5,132	36.9	87,893	40.1
Region				
East	3,222	23.2	64,605	29.5
Mid-West	4,956	35.6	82,300	37.6
South	2,023	14.5	37,610	17.2
West	3,719	26.7	34,497	15.8
Comorbidities ^a				
Rhinitis	5,223	37.5	78,634	35.9
Sinusitis	3,446	24.8	53,052	24.2
Gastroesophageal reflux disease (GERD)	1,720	12.4	21,994	10.0
Allergic bronchopulmonary aspergillosis	6	0.0	41	0.0
Obstructive sleep apnea	156	1.1	2,712	1.2
Obesity	616	4.4	11,138	5.1
Depression	1,348	9.7	20,144	9.2
Physician specialty at treatment initiation				
General practice	3,052	21.9	50,565	23.1
Internal medicine	1,752	12.6	27,816	12.7
Allergy-immunology	2,155	15.5	26,011	11.9
Pulmonology	1,454	10.4	14,211	6.5
Pediatrics	608	4.4	24,122	11.0
Hospital	297	2.1	5,513	2.5
Unknown	3,452	24.8	52,600	24.0
Other specialties	1,150	8.3	18,174	8.3

^aA patient may have none, one, two, or more comorbidities; denominators are SI or FDC LABA initiators; cumulative percentage is not 100%.

comorbidities of interest was similar across the groups. Patients initiating therapy had the majority of the FDC LABA prescriptions (23%) prescribed by general practice, 13% by internal medicine, and 12% by allergy-immunology specialties. Similar patterns were observed in the two cohorts, except for the pediatric specialty that initiated only 4% of the SI LABA prescriptions compared to 11% of the FDC LABA prescriptions; and pulmonology specialists initiated 10% of the SI LABA and 7% of the FDC LABA prescriptions.

Duration of Therapy

The median number of SI and FDC LABA episodes per person was two and ranged from 1 to 40 episodes (interquartiles, one to four episodes). The median duration of SI LABA episode was 30 days (interquartiles, 30–60 days), and FDC LABA episode was 30 days (interquartiles, 30–32 days). The mean number of days of LABA therapy was 63 days (SD = 101.9) and 53 days (SD = 73.8) for SI and FDC LABAs, respectively. About 12% and 9% of the episodes had a length greater than 90 days for the two

TABLE 2.—Use of non-LABA asthma control medications prior to single-ingredient (SI) LABA or fixed-dose combination (FDC) LABA initiation, IMS LifeLink™ Health Plan Claims database, 2005–2009.

Prior use of controller drug	SI LABA episodes (N = 13,920)		FDC LABA episodes (N = 219,012)	
	N	%	N	%
ICS	6,852	49.2	17,590	8.0
LTRAs	4,484	32.2	56,553	25.8
ICS or LTRAs	8,928	64.1	66,943	30.6

study cohorts, respectively. The duration of LABA therapy was longer among patients who were 46 years and older (data not shown). The median cumulative therapy was 90 days for both SI and FDC LABAs (interquartiles, 30–240 days and 30–225 days, respectively).

ICS or LTRAs Prior to LABA Initiation

Any use of ICS or LTRAs within 1–90 days prior to LABA initiation occurred in 64% and 31% of all incident episodes for SI and FDC LABAs, respectively (Table 2).

Concurrent Therapy with SI LABAs

Of 46,231 SI LABA episodes, the MCR was 52% (SD = 45.9) on concurrent with long-term non-LABA medications, and median MCR was 62% (interquartiles, 0–100%). The proportion of SI LABA episodes that were concurrent with long-term medications was 61%. The median duration of concurrency was 30 days (interquartiles, 27–57 days).

For 13,920 SI LABA patients, the median MCR was 8% (interquartiles, 0–20%); 9808 patients (70%) had at least more than 1 day on concurrent with other long-term non-LABA medications during their entire SI LABA therapy. For those patients who had concurrent therapy, 40% of them had 1–30 days cumulative duration of concurrent days (Table 3).

SI versus FDC LABA Use over the Study Period

Over the study period, the proportion of SI LABA prescriptions of all LABA-containing products has been decreasing gradually from 9% in the first half of 2005 to 3% in the second half of 2009. These changes occurred across all age groups but were most prominent in the youngest age group (0–3 years) (Figure 1).

Poorly Controlled Asthma Prior to LABA Initiation

Of all patients using any LABA-containing products, 45% met at least one of the four criteria for poorly controlled asthma 1–90 days prior to LABAs use and 11% met the criteria for having either ≥ 1 asthma-related ED visit/hospitalization or ≥ 2 short-term OCS use (Table 4). Examining the individual criteria for poorly controlled asthma, we found that (a) 32% had prior prescription for ICS or LTRAs during the 90 days prior to LABA initiation; (b) 7% had ≥ 1 asthma-related ED visit or hospitalization during the 90 days prior to LABA initiation; (c) 5% had ≥ 2 prescriptions for short-term use of OCS during the

TABLE 3.—Concurrent asthma medication use with single-ingredient LABAs, IMS LifeLink™ Health Plan Claims database, 2005–2009.

	Concurrent with long-term non-LABA medications		Concurrent with quick-relief medications	
	Episodes (N = 46,231)	Patients (N = 13,920)	Episodes (N = 46,231)	Patients (N = 13,920)
Medication–concurrent ratio				
Mean, % (SD)	52 (45.9)	16 (23.6)	23 (35.1)	8 (15.8)
Median, % (Q1, Q3)	62 (0, 100)	8 (0, 20)	0 (0, 49)	2 (0, 9)
Medication–concurrent ratio categories				
Very low (<25%)	42.4	78.1	68.3	90.6
Low (25–49.9%)	4.4	11.6	6.9	5.7
Moderate (50–74.9%)	6.6	5.2	10.0	2.0
High (≥75%)	46.5	5.1	14.9	1.8
Concurrent use, N (%)	28,331 (61)	9,808 (70)	17,688 (38)	8,133 (58)
Duration of concurrent days				
Mean, days (SD)	58 (97.1)	167 (259.5)	36.3 (54.9)	79.0 (130.5)
Median, days (Q1, Q3)	30 (27, 57)	60 (30, 180)	25 (16, 30)	30 (19, 85)
Duration of concurrent days categories				
1–30 days (%)	70.3	39.5	78.0	51.3
31–90 days (%)	18.5	22.7	16.6	27.1
>90 days (%)	11.2	37.9	5.4	21.6

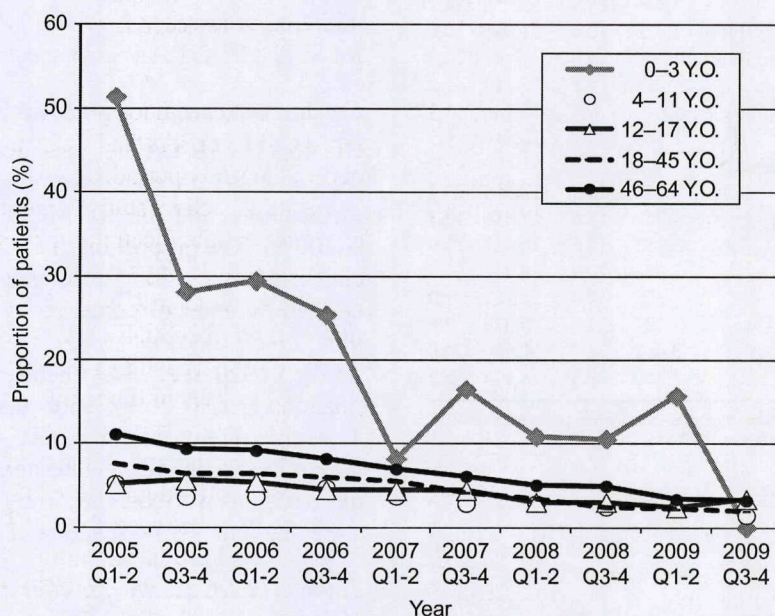


FIGURE 1.—Proportion of single-ingredient LABAs of all LABA-containing products in asthma patients by age groups, IMS LifeLink™ Health Plan Claims database, 2005–2009 (by half-year time segments (first and second quarters, third and fourth quarters)).

TABLE 4.—Indicators of poorly controlled asthma prior to initiation of (SI) LABAs or fixed-dose combination (FDC) LABAs, or any LABA-containing products, IMS LifeLink™ Health Plan Claims database, 2005–2009.

Poorly controlled asthma criteria	SI LABA (N = 13,920)		FDC LABA (N = 219,012)		Any LABA (N = 228,047)	
	N	%	N	%	N	%
(a)	8,928	64.1	66,943	30.6	72,842	31.9
(b)	798	5.7	15,901	7.3	16,348	7.2
(c)	793	5.7	11,527	5.3	11,914	5.2
(d)	2,391	17.2	33,561	15.3	34,823	15.3
(a, b, or c)	1,398	10.0	24,261	11.1	25,007	11.0
(a, b, c, or d)	9,783	70.3	96,965	44.3	103,278	45.3

Poorly controlled asthma criteria:

(a) ≥1 prescription of an ICS or a LTRA dispensed during 1–90 days prior to the index date.

(b) ≥1 asthma-related ED visit or hospitalization 1–90 days prior to the index date.

(c) ≥2 OCS consisting of ≤21 days' supply each (indicates asthma exacerbation) 1–90 days prior to the index date; or

(d) ≥3 canister of a SABA 1–180 days prior to the index date.

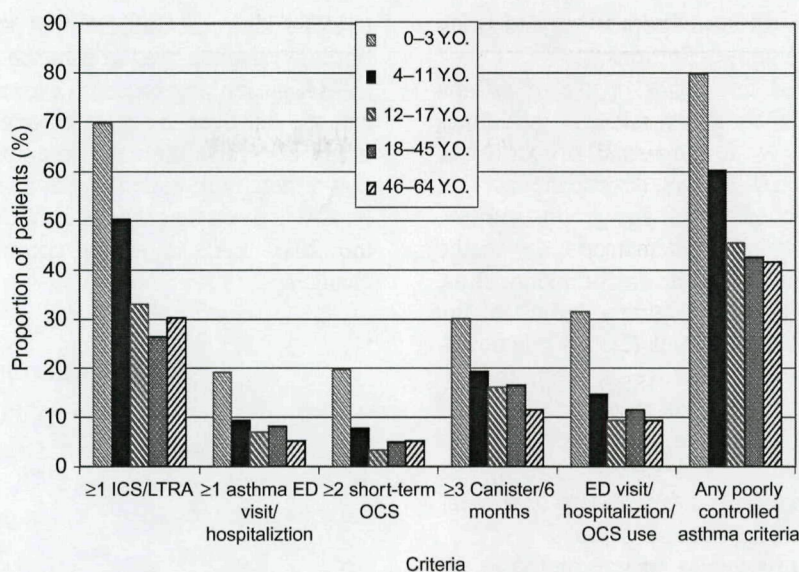


FIGURE 2.—Proportion of patients with poorly controlled asthma criteria* prior to initiation of any LABA-containing products by age groups, IMS LifeLink™ Health Plan Claims database, 2005–2009. *Poorly controlled asthma criteria: (a) ≥ 1 prescription of an ICS or a LTRA dispensed during 1–90 days prior to the index date; (b) ≥ 1 asthma-related ED visit or hospitalization 1–90 days prior to the index date; (c) ≥ 2 OCS consisting of ≤ 21 days' supply each (indicates asthma exacerbation) 1–90 days prior to the index date; or (d) ≥ 3 canister of a SABA 1–180 days prior to the index date.

90 days prior to LABA initiation; and (d) 15% had ≥ 3 canisters of SABAs, during the 6 months prior to LABA initiation. Children aged 0–11 years were generally more likely to have indicators for poorly controlled asthma, prior to any LABA use (Figure 2).

DISCUSSION

During the study period from 2005 to 2009, SI LABA use declined for all age groups, especially for pediatric population. However, a substantial proportion of LABA initiators, the majority of whom were dispensed an FDC LABA, did not appear to have indicators that would suggest that LABA treatment is warranted, including prior use of ICS or LTRAs before initiating a LABA-containing medication. We found that more than half of all FDC LABAs incident episodes were not preceded by ICS or LTRAs, and the proportion of patients on ICS or LTRAs prior to LABA initiation has not changed over the study period. Moreover, prior use of ICS occurred in only 8% of the patients using FDC products, and this finding was somewhat comparable to a recent retrospective study (19). Therefore, the new FDA's LABA labeling recommendations may increase patients' and prescribers' awareness regarding the safe use of LABAs and may reduce the risk of serious adverse events associated with LABAs.

One area of interest in this study that has not been previously investigated is the concurrent use of SI LABAs with non-LABA medications. Based on the national asthma education and prevention program (NAEPP) guidelines and LABA labeling, LABAs are not to be used as monotherapy for long-term asthma control (5–10). We found that only 47% of all SI LABA episodes had an MCR $\geq 75\%$, on concurrent use with long-term non-LABA medications. Moreover, 39% of the SI LABA episodes were not on

concurrent use with long-term asthma medications, suggesting that SI LABAs had been prescribed as monotherapy during the study period.

A retrospective study conducted from 2000 to 2002 reported that the mean number of treatment days for FDC products was 85 days (95% CI, 79.8–89.7) and for fluticasone and salmeterol in separate inhalers about 27 days (95% CI, 17.11–36.40) (12). These minor differences in duration of therapy days compared to our study may stem from differences in the study design, including age of the study population and measurement methods of therapy duration. For therapy duration, we used a relatively stringent definition—a gap of $>25\%$ of the prior prescription days' supply, between the dispensing date of a new prescription and the latest ending date of the prior prescription. In addition, we excluded patients with more than 100 days' supply. We did a sensitivity analysis, where patients with more than 100 days' supply were included. The study results have not changed substantially, mainly because the proportion of these patients was very low: 0.11% for FDC LABAs and 0.17% for SI LABAs.

In the absence of clinical measures to assess asthma severity and whether LABA therapy might be deemed appropriate, we constructed proxy definitions for asthma exacerbations or poorly controlled asthma in the period preceding LABAs. Our results showed similar proportion of poorly controlled asthma patients (45%) compared to results from studies that used similar criteria (11, 13, 14). A retrospective cohort study found 38% of the patients met ≥ 1 criteria, in asthma patients aged ≥ 12 years; 58.4% of *budesonide/formoterol fumarate dihydrate* patients versus 36.7% of *fluticasone propionate/salmeterol* patients met ≥ 1 criteria, respectively (14). Only 4% had asthma-related hospitalization or ED visit, but 10% had more than two courses of OCS therapy (14). These minor differences may

derive from differences in the study population and study design, including measurement definitions.

In this study, we noted deviations in use of asthma medications from FDA labeling and national guidelines related to children (5–10). We found a small proportion of LABA use in children aged 0–3 years, despite the fact that these agents are not approved in that age group. Another claims data study has also reported that contrary to the current asthma treatment guideline recommendations, FDC LABAs were used as initial therapy in half of the children with mild to moderate asthma (20). While deviation in LABA prescribing from approved labeling in children raises concern, the proportion of prescriptions for SI LABAs was decreasing over the study period. This decreasing trend in the SI LABAs seems more in line with the 2010 labeling change and drug safety communication regarding LABA use in that age group.

Findings from this study should be interpreted in the context of the known limitations of the study. LABAs are indicated for asthma as well as for non-asthma indications (e.g., chronic obstructive pulmonary disease (COPD)). Non-LABA medications used to treat asthma may also have indications other than asthma. Even though this study population consisted of all patients that had asthma but not COPD diagnosis, this study presents data on LABAs and non-LABA medications use based on their prescribing. The specific indication for prescribing these products is unknown, and thus, the use of these products may not be limited to asthma treatment. The duration of therapy calculated in this analysis was determined from the number of days' supply. However, pharmacy claims data may be miscoded and data may be missing. It is possible that this measure is not accurate for asthma medications, especially for dosage forms of inhalers or solutions for inhalation. In addition, the definition of concurrency was inclusive; so patients were defined as concurrent even though they may have only 1 day of concurrency. If a more rigorous definition was used, the proportion of the non-concurrent patients might be even be larger. To provide a more intuitive measure of concurrent therapy with SI LABAs, the MCR was also used.

It should be noted that claims databases do not collect information on asthma severity, clinical symptoms, and pulmonary function. As such, the measurement for poorly controlled asthma used in this study was based on factors that have been suggested and used in previous research (10, 13, 14). Therefore, it is possible that patients have been misclassified.

CONCLUSIONS

This report assesses drug utilization patterns for LABA-containing products from 2005 to 2009, prior to the drug safety communication released on 18 February and 2 June 2010. Throughout the study period, SI LABA use continuously declined for all age groups, especially for the pediatric population. Our findings suggest that many patients were prescribed LABAs without prior use of ICS

or LTRAs, or other indicators of poor asthma control. These findings raise the need to enhance awareness of appropriate LABA prescribing based on asthma guidelines among specialists, but even more so among general practitioners. It might also raise the need to emphasize step-up and step-down therapy in patients with asthma. Future LABA analyses will evaluate changes in LABA prescribing following the 2010 LABAs safety communication and labeling changes.

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DECLARATION OF INTEREST

The authors do not have any conflict of interest. The authors alone are responsible for the content and writing of the article.

The views expressed are those of the authors and do not necessarily represent that of the U.S. Food and Drug Administration.

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