

ORIGINAL ARTICLE

Long-acting beta₂-adrenergic agonist in pediatric and adolescent asthma patients, 2003–2011Esther H. Zhou, MD, PhD¹, Elizabeth M. Kang, MPH¹, Sally Seymour, MD², and Solomon Iyasu, MD, MPH¹¹Food and Drug Administration, Office of Surveillance and Epidemiology and ²Food and Drug Administration, Office of New Drugs, Silver Spring, MD, USA**Abstract**

Objectives: To evaluate changes in the dispensing patterns of long-acting beta₂-adrenergic agonist (LABA) in pediatric and adolescent asthma patients in relation to multiple Food and Drug Administration (FDA) regulatory activities from 2003 to 2011. **Methods:** We estimated LABA dispensing to pediatric asthma patients across three periods: 2003–2004 (after the first labeling change), 2005–2009 (after regulatory activities in 2005 and before 2010 LABA labeling change) and 2010–2011 (after 2010 LABA labeling change), using the IMS Health Plan Claims database. We estimated dispensing patterns over time for single-ingredient (SI) LABA and fixed-dose combination (FDC) of inhaled corticosteroid (ICS) and LABA (FDC-ICS/LABA). We also evaluated prior use of non-LABA asthma-control medication (ACM) before LABA initiation. **Results:** Of the 147 862 pediatric and adolescent asthma patients who initiated a LABA during the entire study period, the majority (96%) were FDC-ICS/LABA initiators. The proportion of SI-LABA among any LABA initiators was small and declined (9%, 4% and 2%, trend test $p < 0.001$) for the three periods. Among the patients who initiated, the proportions with prior use of an ACM (1–90 days prior) were 35%, 36% and 39% for the three periods. **Conclusions:** The significant decline in the proportion of SI-LABA initiation over these years is consistent with FDA's recommendations. However, the favorable trend cannot be solely attributed to FDA activities as changes to clinical practice guidelines, and media publicity may have played a role. Investigating the reasons for the low ACM use before LABA initiation may inform approaches to further improve appropriate use of LABA in young asthma patients.

Keywords

Asthma, FDA regulatory activity, LABA dispensing patterns

HistoryReceived 18 March 2014
Revised 6 May 2014
Accepted 15 June 2014
Published online 17 July 2014**Introduction**

Asthma is the most common chronic respiratory disease in children. In 2011, 7 million US children younger than 18 years had asthma (9.6%) [1]. Appropriate asthma management is critical and includes education, control of environmental factors and pharmacologic therapy. Asthma guidelines detail a step-wise management approach based upon assessment of impairment (symptoms and pulmonary function) and risk (exacerbations). Treatment guidelines recommend the use of long-term asthma-control medication (ACM), such as inhaled corticosteroids (ICSs) for persistent asthma. If symptoms warrant additional treatment, an increase in ICS dose or the addition of a long-acting beta₂-adrenergic agonist (LABA) is recommended [2]. LABA are bronchodilators, but in some studies, they have been associated with serious asthma exacerbation, intubation and asthma-related death [3].

Soon after the Food and Drug Administration (FDA) approved the first single-ingredient (SI) LABA, salmeterol, for patients with asthma in 1994, serious asthma

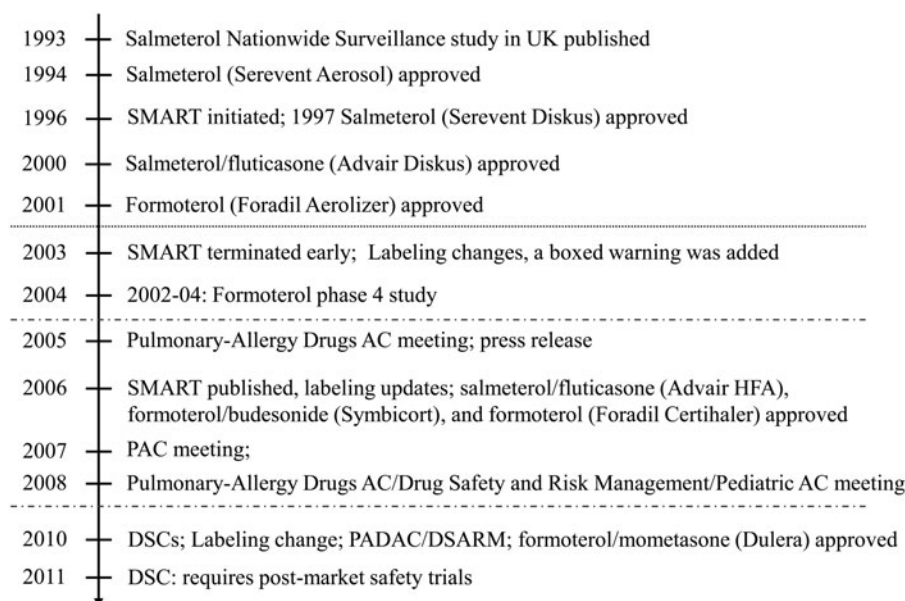
exacerbations and deaths were reported. This led to the start of a large safety randomized controlled trial (RCT) in 1996, the Salmeterol Multicenter Asthma Research Trial (SMART). In 2000, the fixed-dose combination of ICS and LABA (FDC-ICS/LABA), salmeterol/fluticasone (Advair Diskus) was approved for asthma patients. SMART was terminated early in 2003 after a planned interim analysis suggested an increased risk of severe asthma exacerbations, including asthma-related death, and because difficulty in enrollment precluded completion of SMART in a timely manner [4–6]. A boxed warning was added to salmeterol and salmeterol/fluticasone product labels for these risks in August 2003.

Formoterol, another SI-LABA, was approved for asthma patients in 2001. A phase 4 RCT showed an increase in serious asthma exacerbations with high-dose formoterol [7,8]. Based on the final results of SMART and the formoterol phase 4 RCT, FDA held a public Advisory Committee (AC) meeting in July 2005 on the safety of LABA. The AC recommended that formoterol labeling include the same warning as salmeterol products. FDA issued communications regarding the safety of LABA in November 2005 [9].

From 2005 to 2009, continued concerns regarding the safety of LABA triggered several regulatory activities, including additional AC meetings. One of the main issues

Correspondence: Solomon Iyasu, Director, Food and Drug Administration, Office of Pharmacovigilance and Epidemiology, 10903 New Hampshire Ave, Bldg 22, Rm 2472, Silver Spring, MD 20993, USA. Tel: 301-796-1683. E-mail: Solomon.Iyasu@fda.hhs.gov

Figure 1. The LABA regulatory history.



discussed by the AC was the potential increased risk of serious asthma exacerbations in children. In February 2010, FDA issued a Drug Safety Communication (DSC) and recommended additional labeling changes after conducting a comprehensive review of the benefits and risks of using LABA [10,11]. Specifically, for pediatric and adolescent patients, FDA recommended the use of FDC-ICS/LABA to ensure adherence with both medications. The DSC also recommended “use of LABA only in patients whose asthma is not adequately controlled on a long-term ACM”. Figure 1 illustrates the time of initial US approval and the regulatory history of LABA-containing products.

Pediatric and adolescent asthma patients may be at greater risk attributable to LABA use [12], therefore, it is important to understand how LABA are used in these patients. This study examined trends and patterns in incident SI-LABA and FDC-ICS/LABA dispensing in asthma patients aged 17 years or younger over a 9-year period (2003–2011) coinciding with multiple FDA regulatory activities, publication of asthma treatment guidelines, as well as media and publication impacts on LABA usage.

Methods

Design and data source

This study used a longitudinal new user cohort design to assess the SI-LABA and FDC-ICS/LABA dispensing patterns in pediatric and adolescent asthma patients in order to monitor the temporal changes in LABA usage in association with FDA safety-related regulatory activities and media publicity. Since these regulatory activities occurred over a long period at multiple time points, we broadly divided the 2003–2011 study time into three periods based on the timing of the key FDA regulatory activities. As shown in Figure 1: 2003–2004 (after the first labeling change and before regulatory activities in 2005), 2005–2009 (after regulatory activities in 2005 and before the 2010 DSC and labeling change) and 2010–2011 (after the 2010 DSC and labeling change).

The data used were from the IMS LifeLink™ Health Plan Claims Database that captures adjudicated claims from approximately 101 managed care plans comprised of 65.8 million de-identified patients (~9% of the commercially insured US population) across the United States. This study was approved by FDA’s Research Involving Human Subjects Committee.

Study population

Among pediatric and adolescent asthma patients aged 0–17 years, SI-LABA and FDC-ICS/LABA new user cohorts were defined as those who had a new LABA prescription (index date) during 2003–2011. LABA are currently approved for asthma patients as young as 4 years of age. We expect limited LABA initiators younger than 4 years old; therefore, we did not separate 0–3 years from 0–11-year-old group for major analyses. Patients were included in the study if they were continuously enrolled for 12 months prior to the index date with at least one asthma diagnosis (ICD-9 CM code 493.xx, including asthma-related ED visit or hospitalization) during the preceding year. We required that there was no LABA prescription during the 6 months prior to the index date. We also excluded patients with diagnoses of chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, pulmonary hypertension or embolism, bronchopulmonary dysplasia or congestive heart failure during the 12 months prior to or on the index date.

We considered LABA initiators with at least one asthma diagnosis sufficient to define the pediatric and adolescent asthma patient cohort. However, we performed a sensitivity analysis, where we included patients with at least two asthma diagnoses on different dates during the preceding year. This would minimize the inclusion of patients with only a “rule-out” diagnosis of asthma.

Outcomes

First, we evaluated the proportion of SI-LABA initiators among all LABA initiators between 2003 and 2011.

We included the SI-LABA and FDC-ICS/LABA products marketed for the maintenance treatment of asthma. Second, we estimated the percentage of young asthma patients who were dispensed any non-LABA ACM during 1–90 days prior to the initiation of SI-LABA, FDC-ICS/LABA or any LABA during each of the three study periods [13]. We also estimated non-LABA ACM dispensing during 1–180 and 1–365 days prior to the initiation of LABA to better capture and better understand the patterns of prior ACM use. Non-LABA ACM included ICS, leukotriene modifiers (LMs), cromones, oral systemic corticosteroids, immunomodulators (omalizumab) and methylxanthines. Finally, we investigated the proportion of incident dispensing (new prescription, only count once per patient for each drug category) of asthma medications among the pediatric and adolescent asthma patients during 2003–2011.

Statistical analyses

We evaluated the patient characteristics and dispensing patterns in SI-LABA and FDC-ICS/LABA initiators for the three periods: 2003–2004, 2005–2009 and 2010–2011. First, a time series plot was used to portray and examine the proportion of patients who initiated SI-LABA among all LABA initiators over the study period. Then we tested the trends over the three study periods using the two-sided Cochran–Armitage trend test [14]. The proportion of SI-LABA initiators was stratified into two age groups: 0–11 and 12–17 years olds. We also tested for trends in the proportion of patients who were dispensed ACM before initiating a LABA. Descriptive statistics were used for the proportion of

incident asthma medications dispensing among pediatric and adolescent asthma patients. All analyses were performed using SAS, v. 9.2 (SAS Institute, Inc., Cary, NC).

Results

Among 2 046 833 asthma patients aged 0–17 years, a total of 147 862 patients met the inclusion criteria had a new dispensing of a LABA-containing product between 2003 and 2011 in the IMS LifeLink database. The majority of the patients were FDC-ICS/LABA initiators, and the proportions increased over the three periods, 91%, 96% and 98%, respectively. The proportion of the 12–17 years old patients among all the SI-LABA initiators (0–17 years old) decreased from 53% (2003–2004) to 47% (2005–2009) to 39% (2010–2011). A small proportion of 0–3-year-old patients dispensed a LABA (4–15% of SI-LABA and 0–1% FDC-ICS/LABA initiators). The most common prescriber specialty was pediatrics for new SI-LABA (19–26%) and FDC-ICS/LABA (25–37%). Allergy-immunology or pulmonology specialties wrote the fewest prescriptions for LABA at the first encounter for asthma diagnosis (Table 1).

Among all LABA initiators, 9% initiated SI-LABA in the period of 2003–2004 and significantly decreased to 4% and then 2% in the period of 2005–2009 and 2010–2011, respectively (trend test $p < 0.001$ by two-sided Cochran–Armitage test). Similar decreasing patterns were observed for pediatric (0–11 years old) and adolescent (12–17 years old) patient cohorts (Figure 2).

There were only 10%, 10% and 15% of patients dispensed an ICS during 1–90 days prior to the initiation of FDC-ICS/

Table 1. Characteristics of pediatric and adolescent asthma patients (0–17 years old) who initiated LABA-containing products ($N = 147\,862$) over the three periods: 2003–2004, 2005–2009 and 2010–2011.

Period	SI-LABA ($n = 5817$), %			FDC-ICS/LABA ($n = 142\,045$), %		
	2003–2004 ($n = 1795$)	2005–2009 ($n = 3493$)	2010–2011 ($n = 529$)	2003–2004 ($n = 18\,736$)	2005–2009 ($n = 92\,649$)	2010–2011 ($n = 30\,660$)
Female	47	43	37	43	42	42
Age						
0–3	4	10	15	0	1	1
4–11	43	43	46	46	45	44
12–17	53	47	39	54	54	55
Region						
East	23	18	13	26	28	30
Mid-West	36	22	15	41	30	23
South	16	43	44	19	29	35
West	25	16	27	15	13	13
Specialty						
General practice	18	12	13	14	12	11
Allergy-immunology	20	22	17	19	17	18
Pulmonology	7	23	12	5	6	6
Pediatrics	25	19	26	37	28	25
Other/unknown	30	25	31	26	38	39
Subset of patients who were prescribed a LABA at their first encounter for asthma diagnosis						
	($n = 250$)	($n = 356$)	($n = 44$)	($n = 2600$)	($n = 13\,458$)	($n = 3809$)
Specialty						
General practice	40	37	45	26	24	23
Allergy-immunology	4	8	14	7	6	9
Pulmonology	2	7	7	2	2	2
Pediatrics	35	32	18	49	50	49
Other/unknown	19	17	16	17	18	18

LABA, long-acting beta₂-adrenergic agonist(s); SI-LABA, single-ingredient LABA; and FDC-ICS/LABA, fixed-dose combination fixed-dose combination of inhaled corticosteroid (ICS) and LABA

Figure 2. Proportion of single-ingredient (SI) SI-LABA initiators among all LABA initiators, stratified by age groups: 0–11 and 12–17 years old, 2003–2011 (by half-year). Numbers represent mean (SD) proportion of SI-LABA initiators among all LABA initiators (%) for the three periods: 2003–2004, 2005–2009 and 2010–2011. For both age groups, $p < 0.001$ by two-sided Cochran–Armitage test.

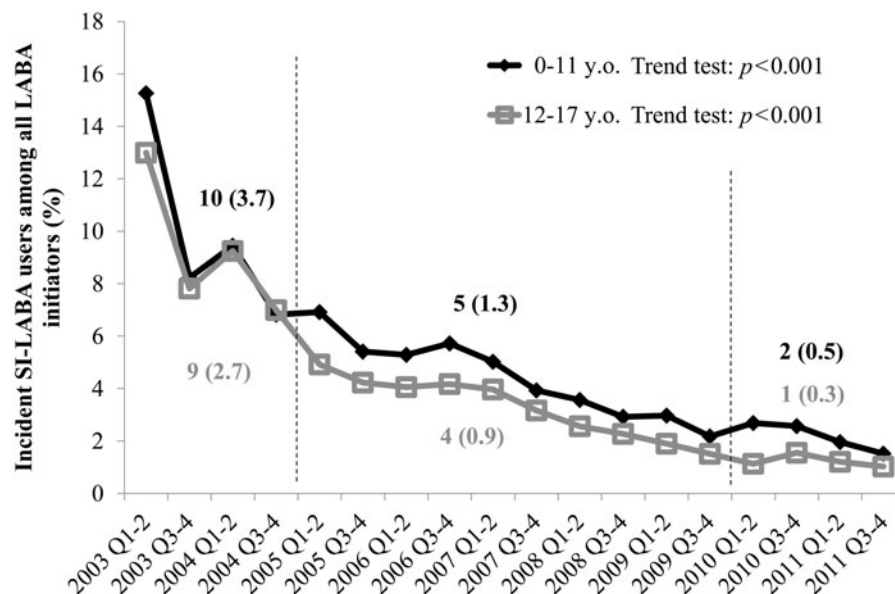


Table 2. Proportion of pediatric and adolescent asthma patients (0–17 years old) who were dispensed non-LABA ACM three months (1–90 days prior) or 6 months (1–180 days prior) before initiating SI-LABA or FDC-ICS/LABA over the three periods: 2003–2004, 2005–2009 and 2010–2011.

Period	SI-LABA ($n = 5817$), %				FDC-ICS/LABA ($n = 142\,045$), %			
	2003–2004 ($n = 1795$)	2005–2009 ($n = 3493$)	2010–2011 ($n = 529$)	p -value ^a	2003–2004 ($n = 18\,736$)	2005–2009 ($n = 92\,649$)	2010–2011 ($n = 30\,660$)	p -value ^a
1–90 days prior								
ICS	20	28	37	<0.001	10	10	15	<0.001
LM	22	25	20	0.531	19	20	19	0.062
ICS/LM	34	41	46	<0.001	25	26	28	<0.001
Any ACM	39	49	53	<0.001	35	35	39	<0.001
1–180 days prior								
ICS	27	36	47	<0.001	15	15	21	<0.001
LM	26	31	25	0.216	24	25	24	0.341
ICS/LM	42	50	55	<0.001	32	33	36	<0.001
Any ACM	48	59	63	<0.001	44	45	49	<0.001

^a p -values were determined by two-sided Cochran–Armitage test.

LABA, long-acting beta₂-adrenergic agonist(s); ICS, inhaled corticosteroid(s); SI-LABA, single-ingredient LABA; FDC-ICS/LABA, fixed-dose combination of ICS and LABA; LM, leukotriene modifier(s); and ACM, asthma controller medication(s).

LABA, for the three time periods, respectively. These proportions only increased to 15%, 15% and 21% during 1–180 days prior (Table 2); and only 23%, 21% and 28% during 1–365 days prior, for the three time periods, respectively.

Among the patients who initiated any LABA, the proportions with prior use of an ICS were 11%, 11% and 16% (1–90 days prior); and 16%, 16% and 21% (1–180 days prior); while prior use of an ACM were 35%, 36% and 39% (1–90 days prior); and only 45%, 46% and 50% (1–180 days prior), for the three periods, respectively (trend test $p < 0.001$) (Figure 3). Even during one year before LABA initiation, only 25%, 22% and 29% of patients dispensed an ICS; and only 68%, 71% and 75% dispensed an ACM for the three periods.

During the study period, there were 6% incident LABA dispensing; 16% and 11% ICS and LM dispensing among the pediatric and adolescent asthma population, respectively (Figure 4).

For the sensitivity analysis, there were 90 464 LABA initiators (96% initiated a FDC-ICS/LABA) aged 0–17 years

who had at least two asthma diagnoses (61% of patients from the primary analysis). We observed the same patterns as in the primary analysis – 8%, 4% and 2% of patients initiated a SI-LABA over the three periods, respectively (trend tests: $p < 0.001$). Overall, 17% of patients had ICS dispensed before they initiated a LABA. Sensitivity analysis yielded similar patterns for the incident asthma medication dispensing.

Discussion

To promote the safe and effective use of LABA in asthma patients, FDA has communicated to healthcare professionals and the public through a series of regulatory activities (Figure 1) since 2003. The main recommendations are that LABA should not be used alone for the treatment of asthma; LABA should be used as additional therapy in patients who are not adequately controlled on an ACM, such as ICS. In addition, the labeling changes and DSC in 2010 had specific recommendations for pediatric patients – pediatric and adolescent patients who require the addition of a LABA to an ICS should use a FDC-ICS/LABA to ensure adherence

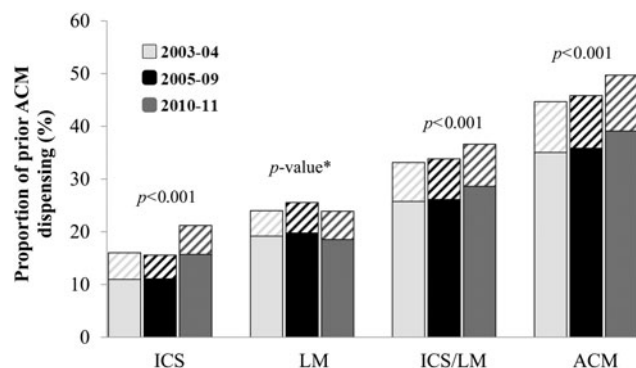


Figure 3. Proportion of pediatric and adolescent asthma patients (0–17 years old) who were dispensed non-LABA asthma controller medication (ACM) three months (1–90 days prior – in solid color) or 6 months (1–180 days prior – in solid color plus upward diagonal pattern) before initiating any LABA during the three periods: 2003–2004 (light grey), 2005–2009 (black) and 2010–2011 (dark grey). The p -value for the increasing trend of the three periods 1–3 were determined by two-sided Cochran-Armitage test. ACM included ICS, LM, cromones, OSC, immunomodulators and methylxanthines.

*trend for LM dispensing: $p = 0.012$ for the 90 days prior; and $p = 0.159$ for the 180 days prior, by two-sided Cochran-Armitage test. OSC, oral systemic corticosteroid(s); ICS, inhaled corticosteroid(s); LM, leukotriene modifier(s); FDC-ICS/LABA, fixed-dose combination of ICS and LABA; ACM, asthma controller medication(s); SI-LABA, single-ingredient LABA.

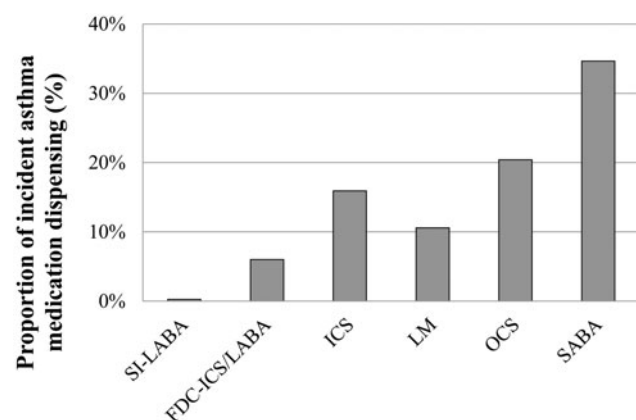


Figure 4. Proportion of incident asthma medications dispensing among pediatric and adolescent asthma patients (0–17 years old), 2003–2011. SI-LABA, single-ingredient LABA; FDC-ICS/LABA, fixed-dose combination of ICS and LABA; ICS, inhaled corticosteroid(s); LM, leukotriene modifier(s); OSC, oral systemic corticosteroid(s); and SABA, short acting beta-agonist bronchodilator(s). Patients may have more than one new (incident) asthma medication categories; but each drug category was only counted once. We did not include those less commonly used asthma medications, such as omalizumab, cromone or methylxanthine; which the incident use were <0.5% among these asthma patients.

with both medications [9,10]. The DSC is one of FDA's communication tools for postmarket safety issues [15]. LABA DSCs included data that suggested that the risk of severe exacerbations was increased in pediatric patients using SI-LABA [10].

This study shows among 147 862 insured young asthma patients newly initiating a LABA, the proportion of SI-LABA initiators was small and declined significantly (9%, 4% and 2% for the three periods). The sharp decline starting from

2003 coincided with FDA's action that added of the first boxed warning to the LABA labels. However, this decline was also preceded by the publication updated practice guidelines for the long-term management of asthma in children in 2002 [16]. The continued decline after 2005 was consistent with continued regulatory activities (FDA public AC discussions in 2005, 2007 and 2008) that resulted in further FDA-labeling changes and increasing awareness and adoption of the treatment practice guidelines. After 2010, the proportion of SI-LABA initiators further declined to less than 2%. This continued decline coincided with the period following FDA 2010 DSCs that discouraged the use of LABA as monotherapy [2,10].

We observed a small number of SI-LABA initiators after 2010, which may be due to several reasons. First, because new SI-LABA user was defined as no LABA prescription during the 6 months prior to the index date, it is possible that some of these patients had previously received and tolerated SI-LABA treatment. Second, SI-LABA is also indicated for exercise-induced bronchospasm; and it is difficult to tease out in our study as these patients may be coded as asthma or exercise induced asthma. Third, off label use may also occur, as observed in this study, that some 0–3 year old patients were dispensed LABA.

In our study, the majority of children (96%) who were dispensed a LABA were dispensed a FDC-ICS/LABA. These results are consistent with the report from National Health and Nutrition Examination Survey, about 96% of children and adolescents with current asthma (1–19 years old, $N = 832$) who used LABA also used ICS from 2005 to 2008 [17].

Despite the observed overall favorable decreasing trends in SI-LABA usage, the proportion of ACM use, such as ICS, before LABA initiation is low. Before 2010, only 11% of young asthma patients were dispensed at least one ICS during three months before LABA initiation, and this only increased to 16% after 2010. Less than half of the patients had any ACM during three or even six months before LABA initiation. It is unclear why many pediatric patients are not receiving a trial of an ICS prior to receiving a LABA. This stepwise approach to asthma care is recommended by asthma treatment guidelines, FDA communications and LABA product labels. The low use of ICS or any ACM before LABA initiation observed in our study was consistent with findings from other studies [18–20]. Friedman et al. reported that within US insured children aged 1–11 years who initiated a LABA from 2004 to 2006 ($N = 13\,306$), 22.6% had an ICS one year before LABA initiation [19]. Stockl et al. reported only 7.4% asthma patients (children and adults) filled a prescription for ICS, and 40% filled an ACM during the 6-month period before LABA initiation, from 2003 to 2006 [20]. Ye et al. reported only 10% of asthma patients older than 12 years filled a prescription for ICS one year before starting a FDC-ICS/LABA in 2007 [21]. No study showed high ACM use before LABA initiation in the United States to the best of our knowledge; however, this pattern is different compared to the UK. A study reported 81% patients over 4 years old received an ICS prescription 6 months prior to the LABA initiation [21].

Reasons for low ACM use prior to the initiation of LABA are not fully understood; but one potential reason may be

due to the aggressive marketing of ICS/LABA [22]. Detailing by pharmaceutical representatives could potentially contribute to the findings, as there are studies that show that physicians are more likely to prescribe medications for which they have samples in their offices [23,24]. In addition, the NAEPP EPR 3 guidelines that more carefully positioned ICS and LABA across a broader age range of children were published late in 2007, but may not have been fully adopted by prescribers [25]. Our findings underscore the continued need for investigating the reasons for the low ACM use before LABA initiation in the United States in order to further improve adherence with the latest recommendations. The use of electronic health record alerts that second line therapy is being prescribed without evidence of a trial of first line therapy might be a potential tool to improve adherence to the asthma treatment guidelines. Of note, even though <50% of patients were receiving any ACM 6 months prior to ICS/LABA (Table 2), this is a smaller proportion among all asthma patients; since only about 6% of all asthma patients initiate a LABA during the study period (Figure 4).

We acknowledge several limitations of our analyses. First, the specific indication for drug dispensing is not always apparent in the insurance claims data; therefore, the use of LABA and other asthma medications may not be limited to asthma treatment. Since these FDA regulatory activities are focusing on asthma patients only, we excluded patients with other respiratory diseases that may use these medications. In addition, we performed a sensitivity analysis including patients with at least two asthma diagnoses, and we did not see difference in overall trends and patterns. Second, claims data do not capture prescriptions that are not filled, such as medication samples obtained during an office visit, which may lead to an incomplete picture of patients' ICS dispensing before LABA initiation. However, there is no evidence that either LABA initiation or ICS dispensing would have any systematic change in claims processing or payment patterns over the years. Third, the data we used are a health plan claims database. The prescription dispensing patterns of children among the insured may be very different than among those without insurance. Children who have insurance are more likely to have an asthma diagnosis; while uninsured patients more commonly reported delaying or failure to fill a prescription and have issues with access to health care [17,26,27]. Therefore, these results lack generalizability for uninsured children. In addition, we do not have information on socio-economic and region of the country (urban, suburban or rural). Even though we observed an increased LABA dispensing in the south region during the time, we do not have a good explanation. The LABA dispensing patterns may also be very different among different groups. Finally, our trend analysis was based on average results for each of the three periods, not measuring an effect of any specific intervention time point where more commonly used interrupted time series analysis may be applicable. Because multiple important regulatory events took place since 2003, we expect continuous changes of LABA dispensing patterns over these years. Therefore, the Cochran–Armitage test for trend was used to test the hypothesis of multiple regulatory activities on LABA dispensing patterns.

Conclusion

The significant decline in the proportion of SI-LABA initiation over the 2003–2011 period is encouraging. Investigating the reasons for the low ACM use before LABA initiation may inform approaches to further improve adherence with the latest LABA use recommendations for pediatric and adolescent asthma patients.

Acknowledgements

We thank Margie Goulding, PhD, Lead Epidemiologist, Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology/Division of Epidemiology II, for the thoughtful comments and suggestions.

Declaration of interest

All authors are employees of the US FDA and have no financial relationships relevant to this article to disclose.

All authors have no conflicts of interest to disclose. The views expressed in this manuscript represent the opinions of the authors and do not necessarily represent the views of the US FDA.

Contributors' Statements

E. H. Z. designed the study, carried out the analyses, drafted and revised the manuscript and approved the final manuscript as submitted.

E. M. K. carried out the analyses, drafted the manuscript, reviewed and revised the manuscript and approved the final manuscript as submitted.

S. S. assisted in the study design and data interpretation, critically reviewed and edited the manuscript and approved the final manuscript as submitted.

S. I. conceptualized and designed the study, supervised the study process and interpreted the results, critically reviewed and edited the manuscript and approved the final manuscript as submitted.

References

1. Center for Disease Control and Prevention. National Center for Health Statistics. Health Data Interactive. Summary Health Statistics for U.S. Children: National Health Interview Survey, 2011, Table 1. Available from: <http://www.cdc.gov/nchs/fastats/asthma.htm> [last accessed 17 July 2013].
2. National Asthma Education and Prevention Program. 2007. Expert panel report 3: guidelines for the diagnosis and management of asthma. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm> [last accessed 8 July 2013].
3. Sears MR. Safe use of long-acting β -agonists: what have we learnt? Expert Opin Drug Saf 2011;10:767–778.
4. Perera BJ. Salmeterol multicentre asthma research trial (SMART): interim analysis shows increased risk of asthma related deaths. Ceylon Med J 2003;48:99.
5. Wooltorton E. Salmeterol (Serevent) asthma trial halted early. CMAJ 2003;168:738.
6. Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists – the influence of values. N Engl J Med 2009;360:1592–5.
7. Martinez FD. Safety of long-acting beta-agonists – an urgent need to clear the air. N Engl J Med 2005;353:2637–2639.

8. Sears MR, Ottosson A, Radner F, Suissa S. Long-acting beta-agonists: a review of formoterol safety data from asthma clinical trials. *Eur Respir J* 2009;33:21–32.
9. Long-Acting Beta Agonist (LABA) Information. Available from: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm199565.htm> [last accessed 8 July 2013].
10. FDA Drug Safety Communication: new safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs) 2/18/2010. Available from: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm> [last accessed 8 July 2013].
11. Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *New Engl J Med* 2010;362:1169–71. doi: 10.1056/NEJMp1002074. Epub 2010 Feb 24.
12. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics* 2011;128:e1147–e1154.
13. Kaplan S, Zhou EH, Iyasu S. Characterization of long-acting beta(2)-adrenergic agonists utilization in asthma patients. *J Asthma* 2012;49:1079–1085.
14. Agresti A. An introduction to categorical data analysis. 2nd ed. New York: John Wiley & Sons; 2007.
15. Dal Pan, GJ. Communicating the risks of medicines: time to move forward. *Med Care* 2012;50:463–465.
16. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics – 2002. *J Allergy Clin Immunol* 2002; 110:S141–S219.
17. Kit BK, Simon AE, Ogden CL, Akinbami LJ. Trends in preventive asthma medication use among children and adolescents, 1988–2008. *Pediatrics* 2012;129:62–69.
18. Friedman HS, Eid NS, Crespi S, Wilcox TK, Reardon G. Retrospective claims study of fluticasone propionate/salmeterol fixed-dose combination use as initial asthma controller therapy in children despite guideline recommendations. *Clin Ther* 2009;31: 1056–1063.
19. Stockl KM, Le L, Harada AS, Zhang S. Use of controller medications in patients initiated on a longacting beta2-adrenergic agonist before and after safety alerts. *Am J Health Syst Pharm* 2008;65:1533–1538.
20. Ye X, Gutierrez B, Zarotsky V, Nelson M, Blanchette CM. Appropriate use of inhaled corticosteroid and long-acting beta(2)-adrenergic agonist combination therapy among asthma patients in a US commercially insured population. *Curr Med Res Opin* 2009;25: 2251–2258.
21. DiSantostefano RL, Davis KJ. Prescription patterns in asthma patients initiating salmeterol in UK general practice: a retrospective cohort study using the General Practice Research Database (GPRD). *Drug Saf* 2011;34:511–520.
22. The US Department of Justice, Office of Public Affairs. GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data. IMMEDIATE RELEASE: July 2, 2012. Available from: <http://www.justice.gov/opa/pr/2012/July/12-civ-842.html> [last accessed 2 May 2014].
23. Hurley MP, Stafford RS, Lane AT. Characterizing the relationship between free drug samples and prescription patterns for acne vulgaris and rosacea. *JAMA Dermatol* 2014;150:487–493.
24. Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. *Am J Med* 2005;118: 881–884.
25. Rouleau R, Beauchesne MF, Laurier C. Impact of a continuing education program on community pharmacists' interventions and asthma medication use: a pilot study. *Ann Pharmacother* 2007;41: 574–580.
26. Centers for Disease Control and Prevention (CDC). Vital signs: asthma prevalence, disease characteristics, and self-management education: United States, 2001–2009. *MMWR Morb Mortal Wkly Rep* 2011;60:547–552.
27. Stevens D, Sharma K, Kesten S. Insurance status and patient behavior with asthma medications. *J Asthma* 2003;40:789–793.