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The impact of FDA regulatory activities on incident dispensing of LABA-containing medication: 2005–2011

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Abstract

Objective: Evidence of safety issues associated with long-acting beta₂-agonist (LABA) treatment has led to multiple regulatory activities by the U.S. Food and Drug Administration (FDA) on this class of medications. This study describes the impact of the regulatory activities on incident LABA-containing medication dispensing.

Methods: A monthly rolling cohort of asthma patients who were eligible to initiate a LABA-containing product was created in the Mini-Sentinel Distributed Database between January 2005 and June 2011. Cohorts of individuals who initiated LABA were examined for the changes in the

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Declaration of interest

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proportions of single-ingredient to fixed-dose inhaled corticosteroid (ICS)-LABA initiators, appropriate initiation of LABA-containing products, and use of controller medications. The impact of the 2005 and 2010 FDA regulatory activities associated with LABA-containing products was measured using interrupted time series with segmented regression.

Results: LABA-containing product initiation was declining prior to the 2005 regulatory activities and continued to decline over the study period, accompanied by increased initiation of fixed dose ICS-LABA among LABA initiators. While the 2010 regulatory activities had no immediate impact on the proportion of LABA initiation in patients with prior controller medication dispensing and/or poor asthma control, there was an increasing positive trend toward LABA initiation in the appropriate patient population after the regulatory activities.

Conclusion: The 2005 and 2010 FDA regulatory activities likely had an impact on communicating the safety concerns of LABA products. However, the impact cannot be viewed independent of scientific publications, guidelines for asthma treatment and other regulatory activities.

Keywords

Asthma; long-acting; beta₂-agonist; drug safety; sentinel; U.S. FDA

Introduction

Long-acting beta₂-agonists (LABAs), sympathomimetic agents that relax airway smooth muscle, were approved for use as controller medications for asthma management in the United States in the mid-1990s. However, safety concerns developed soon after they were marketed [1–4], leading to the Salmeterol National Surveillance Study in the United Kingdom and Salmeterol Multicenter Asthma Research Trial (SMART) in the United States [1,5]. A small, non-statistically significant increase in asthma-related deaths was noted when comparing patients randomized to single-ingredient LABA (SI-LABA) versus albuterol in the Salmeterol National Surveillance Study. The SMART study was stopped early due to interim results finding an increase in serious asthma exacerbations, including asthma-related deaths in the LABA treatment group.

The U.S. Food and Drug Administration (FDA) responded to these initial results of SMART by implementing labeling changes for salmeterol in 2003 and 2004 (Figure 1) [6]. After the final SMART results were available in 2005, risks were communicated again to the public, and health care professionals were advised to use LABA as add-on controller therapy [7]. The 2010 regulatory activities included the FDA Drug Safety Communications (DSC) for LABAs and product label changes [8]. The label changes were contraindication of LABA without controller medications such as inhaled corticosteroids (ICS); use of fixed-dose ICS-LABA among children instead of SI-LABA to reduce the potential for LABA monotherapy; use of LABA only in patients whose asthma is not adequately controlled on a long-term controller medication; and discontinuation of LABA when asthma control is achieved. The impact of these regulatory activities on incident LABA dispensing is incompletely understood.

The objective of this study was to measure the impact of the FDA LABA-related regulatory activities in 2005 and 2010 on the initiation of LABA-containing agents among patients with asthma, under the purview of the FDA-sponsored Mini-Sentinel program (now the Sentinel Initiative), a national resource that allows the FDA to monitor the safety of regulated medical products [9,10]. The analysis also assessed the proportion of new LABA treatment episodes started with fixed-dose ICS-LABA rather than single-agent LABA products.

Methods

Data source and study populations

Cohorts of patients with asthma from the nine Data Partners that contributed data to the Mini-Sentinel Distributed Database between January 2004 and June 2011 and met study specifications were included in this study [9–11]. Data was obtained from electronic administrative and claims data including demographic characteristics, health care utilization, diagnoses and medication dispensing records.

Cohort of asthma patients eligible for LABA initiation

Eligibility for the rolling cohort was assessed on the 1st day of each month. Patients were included if they had continuous enrollment with pharmacy benefits, were between the ages of 1 and 65 years and had a diagnosis of asthma in the 365 days prior to the 1st of each month. Children were defined as patients <18 years of age, and adults were defined as ≥18 years of age. Patients were excluded if they had used LABA-containing products in the 183 days prior to the 1st of the month. A diagnosis of asthma was defined by International Classification of Diseases, 9th Revision, Clinical Modification code (493.xx) for at least two office visits, one emergency department visit, or one hospitalization (primary diagnosis). We excluded patients with a diagnosis of chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, pulmonary hypertension or embolism, bronchopulmonary dysplasia, or congestive heart failure [11].

The case definition is derived from commonly used case definitions based on administrative data. We required two outpatient visits to reduce the chance of a rule out diagnosis. Inpatient definitions use discharge diagnosis codes, often established after diagnoses have been confirmed; therefore, we only required one diagnosis from a hospitalization. Many definitions looking at persistent asthma have included asthma medications, but our focus was not limited to persistent asthma [11,12].

Cohort of LABA initiators

Within the eligible asthma population, we established a rolling cohort of patients who initiated LABA products. Patients could have multiple episodes of new use as long as each episode had a 183-day LABA-free window between them.

Outcomes

In the asthma cohort, we measured the proportion of asthma patients initiating LABA-containing products on a monthly basis.

In the LABA initiator cohort, we measured four outcomes: (1) the proportion of new LABA users who started fixed-dose ICS-LABA therapy; (2) appropriate LABA initiation – measured by the proportion of new LABA users with a history of controller medication dispensed in the 90 days prior to the LABA index date, or a history of poor asthma control in the 365 days prior to the LABA index date [13,14]. Poor-control was established if a patient had any of the following events in the 12-month pre-index period: an asthma-related hospitalization or emergency department visit, fills for ≥ 2 oral corticosteroids with less than a 21-day supply of medication, or ≥ 6 dispensings of short-acting beta₂-agonists. We defined LABA treatment episodes by total day supply of LABA dispensing with gap <30 days.

Statistical analysis

We used interrupted time-series (ITS) analyses to model changes in the levels and trends of LABA initiation associated with the LABA-related FDA regulatory activities [15,16]. The ITS models included three periods: January 2005–November 2005, December 2005–January 2010, and February 2010–June 2011 to account for the regulatory activities in 2005 and 2010, with up to six parameter estimates in the segmented regression models (intercept, baseline trend, level change in 2005, change in trend after 2005, level change in 2010 and change in trend after 2010). Only two periods, before and after January 2010 were included in the analysis of appropriate use of LABA as the 2010 DSCs address this issue. We used p -values <0.2 as the model selection criterion for the final segmented models [17,18]. Seasonality and autocorrelation were controlled using autoregressive integrated moving average models and back-step elimination, respectively [15,19].

Meta-analyses techniques based on random effects models were used to combine all of the regression models' parameters across Data Partners. All analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

Results

Cohort of asthma patients eligible for initiation of LABA

There were over 1.4 million children and adults with asthma who met the eligibility criteria for new initiators of LABA products over the study period. A small proportion of the asthma cohort initiated single-agent LABA; more patients initiated fixed-dose ICS-LABA compared to single-agent LABA. In January 2005, approximately 0.1% children and 0.3% adults initiated SI-LABA, while 0.8% and 1.4% initiated fixed-dose ICS-LABA, respectively. Overall, initiation of LABA-containing products was declining (Figure 2).

In children, there was a -0.008 percentage point absolute decrease at December 2005 (10.7% compared to the January 2005 intercept) in the initiation of SI-LABA ($p = 0.0105$); and a similar decline was noted in fixed-dose ICS-LABA initiation (-0.122 percentage points, $p < 0.001$; 16.2% relative decline) (Table 1). There was a -0.053 percentage point level change observed in fixed-dose ICS-LABA initiation following January 2010 DSCs ($p = 0.018$). This absolute decline was smaller than that in 2005. SI-LABA initiation declined from the beginning of the study with a monthly slope of -0.002 , $p < 0.001$. The decline in initiation slowed after the 2005 regulatory activity (0.001 percentage points per month, $p =$

0.043) resulting in a negative slope of -0.001 (the sum of the baseline trend, -0.002 , and the change in trend after 2005, 0.001). After 2010, the slope flattened. Similarly, fixed-dose ICS-LABA initiation declined from baseline at a monthly slope of -0.013 ($p < 0.001$), and the slope flattened toward the end of the study period (Table 1 and Figure 2).

In adults, the regulatory activities did not have an immediate impact on SI-LABA nor fixed-dose ICS-LABA dispensing initiation (Table 1). Baseline initiation of SI-LABA was declining at a slope of -0.009 percentage points per month ($p < 0.001$). After the regulatory activities in 2005, the monthly rate of decline slowed down (slope changed from -0.009 to -0.004 , $p < 0.001$), and the slope flattened after the 2010 regulatory activities. The baseline slope of fixed-dose ICS-LABA was declining at a monthly slope of -0.033 ($p < 0.001$); however, between the regulatory activities, the relative change in slope resulted in a minor positive monthly slope of 0.002 (the sum of the baseline trend, -0.033 , and the change in trend after 2005, 0.035), and the slope flattened after the 2010 regulatory activities (Table 1 and Figure 2).

Cohort of LABA Initiators

Over 159,064 episodes of new LABA initiation occurred during the study period among 135,601 patients. In January 2005, children initiated fixed-dose ICS-LABA products (90.5%) more often than adults (81.3%) (Table 2 and Figure 3). The baseline slope for initiating fixed-dose ICS-LABA increased significantly in children, while the adult baseline slope did not. Following the 2005 regulatory activities, there was a decline in initiation of fixed-dose ICS-LABA in both children and adults; however, it was relatively small (relative decrease $< 2\%$). There were neither significant slope changes between the 2005 and 2010 regulatory activities nor level changes after the 2010 activities in either age group. After the 2010 DSCs, fixed-dose ICS-LABA initiation slope flattened. By June 2011, 98.9% of children and 95.0% of adults were initiating fixed-dose ICS-LABA instead of SI-LABA.

Almost three quarters of the patients (73.5%) had either a history of prior controller medication dispensed within 90 days (47.1%) or a history of poor asthma control within 365 days of the LABA index date (50.6%) (Table 3). Prior to the 2010 DSCs, the slope for the overall measure of appropriate use was declining (-0.03 percentage points per month), and a positive slope was noted after the 2010 DSCs (0.1 percentage points increase per month).

Discussion

Our study had several key findings. A few adults and children with asthma initiated LABA-containing products each month during the study period. The proportion of patients who did initiate a LABA product declined over time with the largest declines occurring prior to the 2005 FDA regulatory activities in both children and adult cohorts. We observed positive trends of appropriate initiation of LABA after 2010 DSCs. This study used the Mini-Sentinel Distributed Database, which was created to help the FDA develop a national system for monitoring the safety of medical products [9]. Even though the proportions of patients who initiated LABA were small (Figure 2), with 1.4 million eligible asthma patients in our cohort, there were more than 150,000 episodes of LABA initiation. The study findings suggested that messaging conveyed in DSCs may have reached prescribers.

The negative slopes of SI-LABA initiation after both the 2005 and 2010 regulatory activities for children and adults are consistent with National Asthma Education and Prevention Program (NAEPP) Expert Panel Report guidelines and the FDA recommendations [7,8,20]. The patterns of initiation of fixed-dose ICS-LABA differed from SI-LABA. The relative slope changes after the 2005 regulatory activities resulted in a flat slope in children, while the slope in adults became positive. The 2005 regulatory activities may have clarified when and in whom it was appropriate to initiate fixed-dose ICS-LABA. Additionally, the asthma clinical guidelines released between the policy periods could have played a role in the change in trajectory [20]. After the 2010 DSCs, the initiation slope in children remained steady; however, the slope in adults began to decrease once again. Hartung et al. used ITS analyses to study the impact of the 2010 DSCs on any LABA initiated from 2008 to 2012 in an Oregon Medicaid population [21]. Both adults and children were pooled for their analysis. There was an increase in new LABA initiation prior to the 2010 regulatory activities and a decline thereafter. This pattern was similar to the pattern observed in the adult population of this study, possibly because almost 80% of their cohort consisted of adults.

The proportion of patients initiating LABA appropriately was higher than other studies [21–23], possibly due to our more stringent cohort definition requiring two asthma diagnoses prior to the LABA initiation. The population of patients with poor asthma control prior to LABA initiation drove the changes seen in the overall appropriate initiation measure. Prior to the 2010 DSCs, the NAEPP Expert Panel Report guidelines in 2007 recommended adding LABA to ICS therapy if a patient with persistent asthma was not adequately controlled [20]. The positive slope associated with controller medication dispensing prior to 2010 may have reflected adoption of the guideline recommendations.

This study has several strengths. The rolling cohort design allowed us to include patients once the continuous enrollment criteria were met. We did not restrict our study population based on age of approved medication use. Without the restriction, we are able to assess how LABA-containing products are actually being initiated in practice. We were able to assess the impact of two regulatory activities during the study period, allowing us to have a better perspective on the true impact of the 2010 regulatory activities. Our study population was geographically and demographically diverse in the insured population.

Limitations of the study included no concurrent comparator to measure the effects these national regulatory activities. As a result, it is possible that contemporaneous factors other than the FDA regulatory activities influenced the observed changes. Symptoms and disease severity often drive asthma medication use, and we did not assess how potential trends in disease severity might have affected the results. Some clinicians do not document a diagnosis of asthma until a child reaches 2–4 years of age, and our study required a diagnosis for cohort entry. Therefore, LABA initiation in children may be under-estimated [23,24]. Furthermore, our study focused on an insured population and we are unable to generalize our results to an uninsured population. Last, we were not able to assess whether the impact of the regulatory activities differed by prescriber specialty as prescriber specialty was not available in the data.

Despite these limitations, the study findings have important implications for future DSC messages related to prescription drugs from which the FDA and others disseminating drug safety information could gain insight. For example, this study and a couple other studies illustrate that DSCs and other regulatory activities may have some impact on prescribing patterns [25,26]. In the case of LABA-products, however, the overall effect was small, suggesting that DSCs should be supplemented with additional efforts to promote evidence-based prescribing practices [27].

In summary, our findings of decreasing initiation of LABA-containing products in an asthma population, increasing initiation of fixed-dose ICS-LABA agents compared to SI-LABA agents among new LABA users and increasing appropriate use of LABA medications may indicate that the 2005 and 2010 regulatory activities had some impact on communicating the safety concerns of LABA agents. However, the impact cannot be viewed independent of low initiation of LABA-containing products at the start, the publication of the SMART results, formulary restrictions, and the updated 2007 clinical guidelines for asthma.

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Abbreviations

CI	confidence interval
DSC	Drug Safety Communication
FDA	U.S. Food and Drug Administration
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICS	inhaled corticosteroid
ITS	interrupted time-series
LABA	long-acting beta ₂ -agonist
NAEPP	National Asthma Education and Prevention Program
SI-LABA	single-ingredient LABA
SMART	Salmeterol Multicenter Asthma Research Trial

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Figure 1.
LABA-related FDA regulatory activities.

Figure 2.

Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.

Figure 3.

Percentage of fixed-dose ICS-LABA initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults who initiated any LABA-containing product.

Table 1.

Parameter estimates, 95% confidence intervals and *p* values from the most parsimonious segmented regression models predicting monthly rates of LABA-containing agents initiation in children and adults with asthma and no history of LABA dispensing in 180 days.

	Parameter	Estimate	95% confidence interval	p value	
Children	Intercept	0.075	0.069	0.081	<0.0001
	Baseline trend	-0.002	-0.003	-0.001	0.0004
	2005 level change	-0.008	-0.014	-0.002	0.0101
	2005 trend change	0.001	0.000	0.002	0.0433
	2010 trend change	0.001	0.000	0.001	0.0006
Fixed-dose ICS-LABA	Intercept	0.754	0.700	0.800	<0.0001
	Baseline trend	-0.013	-0.021	-0.006	0.0005
	2005 level change	-0.122	-0.170	-0.074	<0.0001
	2005 trend change	0.012	0.005	0.020	0.0012
	2010 level change	-0.053	-0.097	-0.009	0.0184
Adults	Intercept	-0.003	-0.007	0.001	0.1528
	Baseline trend	0.323	0.297	0.348	<0.0001
	2005 level change	-0.009	-0.011	-0.006	<0.0001
	2005 trend change	0.005	0.002	0.008	0.0005
	2010 trend change	0.002	0.001	0.004	0.0035
Fixed-dose ICS-LABA	Intercept	1.417	1.312	1.523	<0.0001
	Baseline trend	-0.033	-0.047	-0.018	<0.0001
	2005 level change	-0.092	-0.187	0.003	0.0587
	2005 trend change	0.035	0.020	0.050	<0.0001
	2010 level change	-0.069	-0.162	0.023	0.1393
	2010 trend change	-0.009	-0.018	-0.001	0.0331

Note. LABA: long-acting beta2 agonists; ICS: inhaled corticosteroids.

Table 2.

Parameter estimates, 95% confidence intervals and p values from the most parsimonious segmented regression models predicting monthly rates of fixed-dose ICS-LABA initiation in children and adults who initiated any LABA-containing product.

		95% confidence			
	Parameter	Estimate	interval		<i>p</i> value
Children	Intercept	90.5	89.9	91.1	<0.0001
	Baseline trend	0.15	0.13	0.16	<0.0001
	2005 level change	−1.52	−2.41	−0.63	0.0011
	2010 trend change	−0.13	−0.20	−0.06	0.0004
Adults	Intercept	81.3	80.1	82.6	<0.0001
	Baseline trend	0.13	−0.05	0.30	0.1640
	2005 level change	−1.29	−2.47	−0.10	0.0338
	2005 trend change	0.13	−0.05	0.31	0.1409
	2010 trend change	−0.23	−0.30	−0.16	<0.0001

Table 3.

Interrupted time series analysis of appropriate LABA initiation among new LABA episodes in percentage points.

	95% confidence			
Parameter	Estimate	interval	p value	
Controller medication [*] use 90 days prior to initiation				
Intercept	47.1	45.7	48.6	<0.01
Trend Prior to the 2010 Policy [†]	0.02	−0.01	0.05	<0.2
Poor control prior to initiation				
Intercept	50.6	50.0	51.2	<0.01
Trend prior to the 2010 policy	−0.04	−0.05	−0.02	<0.01
Trend after the 2010 policy	0.21	0.12	0.30	<0.01
Any appropriate use [‡]				
Intercept	73.5	72.9	74.2	<0.01
Trend prior to the 2010 policy	−0.03	−0.04	−0.01	<0.01
Trend after the 2010 policy	0.10	0.02	0.19	<0.05

^{*} Controller medications include ICS, leukotriene modifiers, cromones, immunomodulators and methylxanthines.

[†] Poor control was established if a patient had any of the following events in the 12-month pre-index period: an asthma-related hospitalization or emergency department visit, fills for two or more oral corticosteroids with less than a 21-day supply of medication or 6 dispensings of *short-acting* beta₂ agonists.

[‡] Any appropriate LABA initiation: if a new LABA user had a history of controller medication dispensing in the 90 days prior to the LABA index date, or with a history of poor asthma control in the 365 days prior to the LABA index date.