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Prescription Patterns in Asthma Patients Initiating Salmeterol in UK General Practice

A Retrospective Cohort Study using the General Practice Research Database (GPRD)

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Abstract

Background: An association between salmeterol, a long-acting β_2-agonist (LABA), use and rare serious asthma events or asthma mortality was observed in two large clinical trials. This has resulted in heightened scrutiny of LABAs and comprehensive reviews by regulatory agencies.

Objective: The aim of this retrospective observational cohort study was to better characterize salmeterol medication use patterns in the UK. We describe asthma prescription patterns in a cohort of patients (n = 17 745) in the General Practice Research Database who initiated treatment with salmeterol-containing prescriptions between 2003 and 2006, including salmeterol and salmeterol/fluticasone propionate in a single device.

Methods: Prescriptions patterns by medication class, including concurrent prescription of salmeterol with inhaled corticosteroids (ICS), were described using 6-month intervals in the 1-year period before and after the salmeterol-containing index prescription.

Results: In the 0- to 6-month and 7- to 12-month periods prior to initiation of the salmeterol-containing prescription, the cohort experienced worsening of asthma, measured by an increase in the proportion of patients with prescriptions for short-acting β-agonists [SABA] (73–89%), ICS (70–81%) and systemic corticosteroids (14–28%). Nearly all patients prescribed salmeterol were concurrently prescribed ICS (≥95% within 90 days). In the 12 months following initiation of the salmeterol-containing prescription, a decrease in asthma prescriptions was observed.

Discussion: These results support the appropriate prescribing of salmeterol-containing medications, as per recommendations in asthma treatment guidelines in the UK.

Conclusion: Salmeterol was consistently prescribed as an add-on asthma-controller with an ICS for most patients, and was associated with improvements in asthma control, as indicated by decreases in SABA and systemic corticosteroid prescriptions following salmeterol introduction.

Background

Salmeterol, a long-acting β_2-agonist (LABA), has been used for many years for the treatment of asthma and chronic obstructive pulmonary disease (COPD), and is available as salmeterol or salmeterol/fluticasone propionate combination in a single device (SFC). According to IMS Health (www.imshealth.com), an international company with healthcare transaction data from across the globe from drug manufacturers, wholesalers, retail pharmacies, hospitals, long-term care facilities and healthcare professionals, salmeterol is available in more than 120 countries and has accumulated approximately 30 million patient-years of exposure during the 18 years that it has been marketed. SFC is available in more than 100 countries and has an estimated 44 million patient-years of exposure over its 10 years on the market.[1] In the management of asthma in the UK, LABAs, including salmeterol, are indicated only as an adjunct therapy with inhaled corticosteroids (ICS) in patients who require two controller therapies. In patients who do not achieve adequate asthma control while taking ICS, treatment guidelines recommend the addition of a LABA in preference to increasing the dose of ICS or adding a leukotriene, based on the available scientific evidence.[2-4]

Pharmacovigilance for all marketed medications requires ongoing effort, and studies of salmeterol conducted shortly after its launch as monotherapy in the UK and US in the early 1990s have meant that the drug has been under heightened scrutiny, including prescription event monitoring and safety review articles published in *Drug Safety*.[5-10] An association between salmeterol use and rare serious asthma episodes or asthma-related mortality, which occurred primarily in patients receiving salmeterol without concurrent ICS, was observed in two large clinical trials.[11,12] However, an association of excess risk for severe asthma outcomes was not seen for SFC or for salmeterol in a meta-analysis of clinical trials or in observational studies. A meta-analysis of 66 clinical trials in 20 699 patients found that salmeterol combined with ICS was found to decrease the risk for severe exacerbations relative to ICS, and did not alter the risk for asthma-related hospitalizations.[13] In order to further study rare serious outcomes, several large, population-based, observational studies were conducted in the UK and US.[14-21] These studies found that the use of LABA, including salmeterol, was not associated with a significant increase in the risk of asthma mortality, severe asthma morbidity, ischaemic heart disease or cardiac failure after controlling for confounding by asthma severity or preferential prescribing of salmeterol to patients with more severe asthma. Thus, these studies support asthma management guidelines that recommend LABA should be used concurrently with ICS.[2]

This descriptive study was performed to provide information for the Medicines and Healthcare products Regulatory Agency (MHRA) comprehensive reviews of LABA safety in 2008. It was designed to identify both expected and unexpected patterns of asthma medication use among asthma patients. For example, the MHRA was interested in any medication usage patterns that would be suggestive of asthma worsening as a result of using a salmeterol-containing medication; for example, an increase in short-acting β-agonist (SABA) use may indicate poor control following salmeterol introduction. The objectives of this study were to describe (i) asthma medications prescribed in a cohort of asthma patients in the year before and after their initiation of salmeterol-containing medications; and (ii) the proportion of patients prescribed salmeterol with concurrent ICS. As this study focused on those patients initiating salmeterol for asthma, other treatment guideline steps (e.g. doubling the dose of ICS, adding a different controller) were beyond the scope of this analysis. Index prescriptions from 2003 to 2006 were examined to focus on recent use and current practice.

Materials and Methods

Database and Study Patients

This was a retrospective cohort of asthma patients in the UK General Practice Research Database (GPRD), an electronic health record

managed by the MHRA and maintained by general practitioners, covering approximately 7% of the population.[22] Participating practices agree to record healthcare information in the electronic primary care record, including healthcare encounters and prescriptions that are outside of the primary care setting (e.g. specialists). The GPRD has been used extensively for public health questions, including characterizing drug utilization patterns for respiratory conditions.[23,24] At the time of this analysis, patient data were available through the second quarter of 2007.

Patients were selected into the original study cohort if they had a first-time prescription written for a salmeterol-containing medication following their asthma diagnosis during the 2003–6 study period, and if they met the inclusion criteria. Patients were required to be at least 4 years of age at the index date, which was their first prescription for a salmeterol-containing medication. Salmeterol-containing medications included salmeterol and SFC. Patients were excluded from the study if they had a cystic fibrosis diagnosis, if they had previous use of a LABA (prescription prior to the study period) or if they did not have electronic health records in the GPRD in the 1-year periods before and after their index date. Because we were comparing medications dispensed in the year before and after their index salmeterol-containing prescription, a subject's asthma diagnosis was required at least 1 year prior to the index date to ensure a fair comparison between time periods.

Study Design

A retrospective cohort of asthma patients was examined for 2 consecutive years in this study (WEUSRTP2311), as illustrated in figure 1. The primary objectives of this retrospective initiation cohort study were to examine trends in asthma medication use by medication class in the 1-year periods before and after the initiation of a salmeterol-containing prescription using 6-month intervals, and to examine the concurrent prescribing of salmeterol with ICS. We identified a cohort of new salmeterol users to avoid potential biases of prevalent users who would be more likely to have a beneficial response. Similarly, we examined the period 1 year following the initiation of salmeterol but required only one prescription (index prescription) to avoid the bias of a sample of longer-term repeat users who would be more likely to have a favourable outcome. The primary medications of interest were SABA, ICS and systemic corticosteroids. Secondary medications of interest included leukotriene receptor agonists (LTRAs), anticholinergics, xanthines and cromolyn.

Exposure Definitions

We assumed that an asthma prescription recorded in the GPRD resulted in a patient's exposure to the corresponding asthma medication. In the years before and after the index date, asthma medication use by class (yes/no) was determined for each patient based on prescriptions recorded in the GPRD during the 6-month intervals. Medications prescribed on the same day

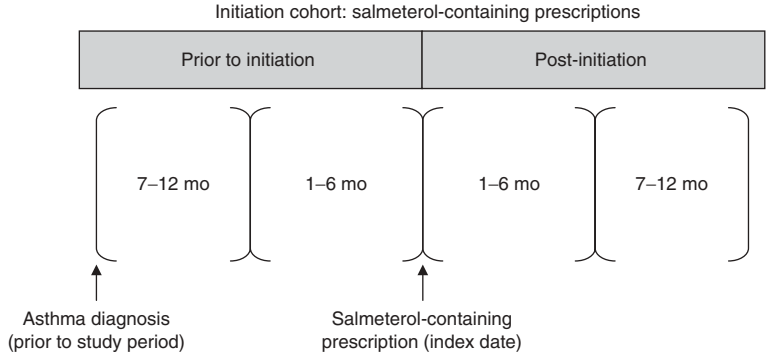

Fig. 1. Study design schematic. Medication usage patterns prior to and following the initiation of salmeterol-containing medication.

as the index salmeterol-containing prescription were considered as part of the 6-month interval before the index date rather than the 6-month period following the index date, to better reflect temporality of co-prescribing.

To evaluate the concurrent prescription of salmeterol with an ICS, concurrent prescription (yes/no) was defined for each patient as the prescription of an ICS 30 days before or after a salmeterol prescription. For sensitivity analysis, prescription of an ICS 90 days before or after a prescription for salmeterol was also examined. The 90-day interval for concurrent ICS/LABA therapy was included to allow for suboptimal adherence and different prescription intervals. An ICS and/or salmeterol inhaler, which is meant to be used for 30 days, may last intermittent users up to 90 days or more due to poor adherence. In addition, salmeterol may not be prescribed on the same day as an ICS inhaler, in particular when an ICS is not sufficient and the LABA is subsequently added before the ICS inhaler has been used completely. For patients with multiple salmeterol prescriptions in a 6-month period, each prescription was examined separately to identify if at least one prescription was concurrent with an ICS.

Confounding Variables

Because of potential differences in asthma management, we examined asthma medication patterns stratified by prognostic factors including age (4–11, 12–17, 18–44, 45–64, 65+ years), comorbid COPD status at any time in their medical record (yes/no) and formulation (salmeterol vs SFC). Smoking status was also examined to characterize the cohort. Because the distribution of the index dates was fairly uniform throughout quarters in the calendar year (January–March 29%, April–June 23%, July–September 22% and October–December 26%), overall results were not stratified by season.

Statistical Analysis

The proportion of patients who were prescribed an asthma medication by class was summarized over each 6-month interval. Co-prescribing on the index date was also tabulated separately. Following initiation of the salmeterol-containing prescription, the proportion of patients receiving concurrent ICS was calculated on the index date and during the subsequent 6-month intervals. Results were stratified by prognostic factors. In addition to tabular summaries for all patients, paediatric results are presented separately (4–11 years of age, 12–17 years of age) as evaluating the treatment patterns for children was of particular interest in the safety review.

Results

Applying the inclusion criteria, there were 17 745 patients in the initiation asthma cohort during the years 2003–6 (table I), with approximately half of the patients initiating SFC and half initiating salmeterol (SFC 49% vs salmeterol 51%). The majority of subjects were adults aged 18 years or older (81%) and female (57%). Smoking prevalence was similar to the overall UK population amongst adults aged 18 years and older during this period, with approximately one-quarter reporting current smoking (27%), one-quarter reporting former smoking (27%) and fewer than half classified as non-smoking (44%).[25] The prevalence of COPD among adults was 6.0%.

Table I. Demographic characteristics for the asthma cohort initiating a salmeterol-containing medication (index dates 2003–6)

Characteristic	All patients (n = 17 745) [n (%)]	Among adults aged ≥18 y (n = 14 492) [n (%)]
Age at index date (y)		
4–11	2 020 (11.4)	
12–17	1 233 (6.9)	
18–44	5 543 (31.2)	
45–64	4 795 (27.0)	
65+	4 154 (23.4)	
Female sex	10 166 (57.3)	
COPD diagnosis		872 (6.0)
Smoking status		
never		6 400 (44.2)
current		3 878 (26.8)
former		3 936 (27.2)
unknown		278 (1.9)

COPD = chronic obstructive pulmonary disease.

By-Interval Medication Summaries by Class

Prior to the initiation of a salmeterol-containing medication, the proportion of patients in the cohort who received prescriptions for SABA, ICS and systemic corticosteroids increased in the period 1–6 months prior to index date relative to the period 7–12 months prior to the index date, which suggests worsening of asthma control and/or presence of an asthma exacerbation. As summarized in figure 2, the percentage of patients receiving an SABA prescription increased from 73% in the period 7–12 months prior to the index date to 89% in the period 1–6 months prior to the index date, whereas the proportion of patients with an ICS prescription increased from 70% to 81%, respectively. During this same 1-year period, the proportion of patients with a systemic corticosteroid prescription doubled from 14% in the 7- to 12-month period prior to the index date to 28% in the 1- to 6-month period prior to the index date. Results were similar in the two paediatric age groups (figure 2), by COPD status, and by salmeterol versus SFC (data not shown). For the 7- to 12-month period after the index date, the use of SABA, ICS and systemic corticosteroids returned to levels observed in the 7- to 12-month period prior to the index date (within five percentage points) for all patients and subgroups (figure 2).

Prescriptions of other asthma medications of interest, including LTRAs, anticholinergics, xanthines and cromolyn, were not frequent in this cohort; however, some general trends emerged. LTRAs were prescribed for 1.2% of the cohort in the 7–12 months prior to the index date. As seen in figure 2, LTRAs were more frequently prescribed to children, particularly younger children (aged 4–11 years), than the other age groups, and there was an increase in the proportion of patients with LTRA prescriptions observed over the study period both before and after the index date for all ages. In children 4–11 years of age (n = 2020), the proportion of patients with an LTRA medication tripled when comparing the 7- to 12-month period prior to the index date with the 7- to 12-month period after the index date (4.2% vs 12.9%, respectively). In adolescents 12–17 years of age (n = 1233), the proportion of patients with

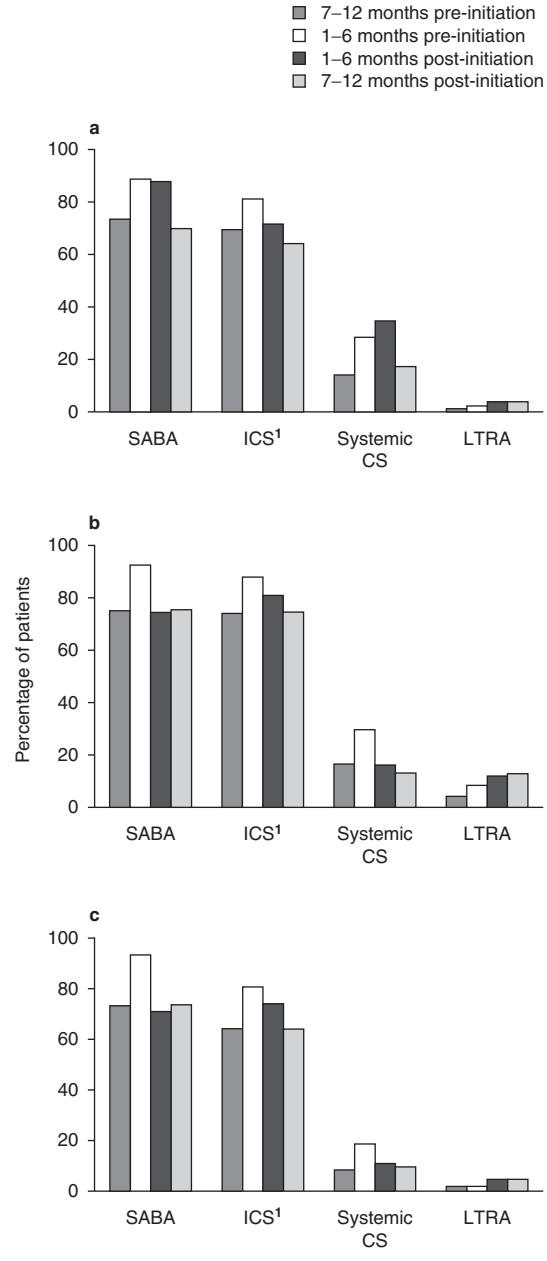

Fig. 2. Percentage of patients with asthma medication prescriptions in the two 6-month intervals pre-initiation and post-initiation of a salmeterol-containing index prescription. (**a**) All patients (n = 17 745); (**b**) children 4–11 years of age (n = 2020); (**c**) adolescents 12–17 years of age (n = 1233). **1** 6-month period post-index date excludes patients who initiated salmeterol/fluticasone propionate combination in a single device (SFC) since SFC includes ICS. **CS** = systemic corticosteroids; **ICS** = inhaled corticosteroids; **LTRA** = leukotriene receptor agonists; **SABA** = short-acting β-agonists.

an LTRA prescription increased in a similar manner from 1.8% to 4.9% over this same period. In the 7–12 months prior to the index date, anticholinergics, xanthines and cromolyn were prescribed infrequently (4.7%, 1.8% and 0.3% of the cohort, respectively), making trends difficult to assess (data not shown).

Co-Prescribing of Asthma Medications on the Index Date

Co-prescribing of asthma medications on the index date was frequent, with approximately one-third of patients receiving an SABA prescription (34%), approximately one-third receiving an ICS prescription (34% among those patients initiating salmeterol) and more than 5% receiving a systemic corticosteroid prescription (8.0%), as shown in table II. The frequency of asthma prescriptions on the index date among children and adolescents was generally similar to the overall cohort; however, prescribing of SABA (41% in children [4–11 years] and 46% in adolescents [12–17 years] vs 34% in the overall cohort) and ICS (40% and 43% vs 34%) on the index date was more frequent than in the overall cohort and prescribing of systemic corticosteroids was similar to (children 4–11 years) or less frequent (adolescents 12–17 years) than the overall cohort (8.5% and 4.5% vs 8%). Co-prescribing trends for other subgroups on the index date (other age groups, COPD status and salmeterol vs SFC) were similar to those seen for all patients (data not shown).

Concurrent Salmeterol with Inhaled Corticosteroids (ICS) on the Index Date

On the index date, the majority of patients were prescribed salmeterol with concurrent ICS either in two separate devices or as SFC, in accordance with the salmeterol product labelling. In patients receiving a salmeterol prescription (excluding SFC) on the index date, 73% were prescribed salmeterol concurrently with ICS within 30 days, increasing to 90% when examining concurrent prescriptions within 90 days, as shown in table II. The proportion of patients receiving a concurrent prescription of salmeterol with ICS was similar in adults and children; however, slightly higher proportions of 4- to 11-year-olds received concurrent salmeterol with ICS relative to the overall cohort, with 79% and 95% of 4- to 11-year-olds receiving a concurrent ICS prescription within 30 and 90 days of a salmeterol prescription, respectively. All patients using SFC received salmeterol delivered concurrently with ICS as both

Table II. Frequency of asthma medications co-prescribed on the index date (initiation of a salmeterol-containing medication)

Medication class	All patients [n = 17 745] (%)[a]	Children aged 4–11 y [n = 2020] (%)[a]	Adolescents aged 12–17 y [n = 1233] (%)[a]
SFC	50.7	44.2	53.9
Salmeterol	49.3	55.8	46.1
number of salmeterol users	8753	1128	568
with ICS on the index date[b]	33.8	40.1	42.5
with ICS (±30 days)[b]	73.4	79.3	71.8
with ICS (±90 days)[b]	90.2	94.8	88.7
SABA	34.4	40.6	46.3
Systemic corticosteroids	8.0	8.5	4.8
LTRA	0.7	2.6	0.9
Anticholinergics	1.6	0.2	0.2
Xanthines	0.5	0.4	0.0
Chromolyn or nedocromil	0.0	0.0	0.0

a Unless specified otherwise.

b Among patients initiating salmeterol (excluding SFC).

ICS = inhaled corticosteroids; **LTRA** = leukotriene receptor agonist; **SABA** = short-acting β-agonists; **SFC** = salmeterol/fluticasone propionate combination in a single device.

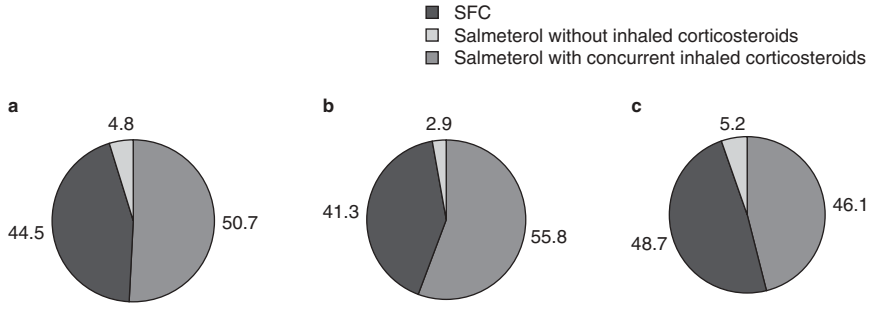

Fig. 3. Percentage of asthma patients with concurrent prescription of salmeterol with inhaled corticosteroids (±90 days) at their index salmeterol-containing prescription. (**a**) All subjects (n = 17 745); (**b**) children 4–11 years of age (n = 2020); and (**c**) adolescents 12–17 years of age (n = 1233). **SFC** = salmeterol/fluticasone propionate combination in a single device.

medications were in a single device. Therefore, when accounting for a concurrent prescription of salmeterol with ICS in all salmeterol-containing prescriptions (salmeterol and SFC), 95% of all patients and 97% of children 4–11 years of age were prescribed salmeterol concurrently with ICS within 90 days of the index date, as presented in figure 3.

Concurrent Salmeterol with ICS after the Index Date

Rates of concurrent prescribing of salmeterol with ICS were similar for the index prescription and subsequent 6-month periods following initiation of a salmeterol-containing prescription. During the two 6-month periods following the initiation prescription, approximately 45% and 25% of patients in each group reported using SFC and salmeterol, respectively, as shown in table III. In patients prescribed salmeterol (not including SFC), approximately 85% and ≥91% of patients were prescribed an ICS within 30 and 90 days of their salmeterol prescriptions, respectively. Trends in children prescribed salmeterol were similar to the overall concurrent use; however, 4- to 11-year-olds experienced higher concurrent use, with ≥90% and ≥95% of salmeterol recipients in this age group using ICS within 30 and 90 days, respectively.

Discussion

The asthma treatment guidelines recommend that for patients whose asthma is not adequately controlled on ICS, the treatment options include doubling the dose of ICS or adding another asthma-controller medication such as salmeterol. This study provides information on frequency of classes of asthma prescriptions (SABA, ICS and systemic corticosteroids) written before and after the initiation of a salmeterol-containing prescription in adults and children treated in the UK. The results indicate that, during the 2003–6 period, salmeterol-containing medications were prescribed with concurrent ICS, as per labelling, and when markers consistent with disease severity (i.e. increased prescription of SABA, ICS and systemic corticosteroids) warranted a second asthma-controller medication. There were no unexpected findings with the results regarding patterns of medication prescribed, which is consistent with salmeterol safety; for example, patient worsening of asthma measured via increased SABA following salmeterol introduction. Results were similar for adults and children, patients initiating SFC versus those initiating salmeterol, and patients with co-morbid COPD versus no record of COPD.

The primary limitation of this observational study is the lack of clinical detail in the GPRD with respect to how prescribed medications were actually used by patients; this is a limitation of all studies conducted using electronic medical record databases. Prescribed medications are recorded in the database by general practitioners; however, there are no data captured to indicate what percentage of these medications went unfilled or were not filled in a timely manner relative to the prescribed date. In addition, there is no measurement of the variation in actual patient behaviours

Table III. Frequency of concurrent prescription of salmeterol with inhaled corticosteroids (ICS) in the 6-month period following the index date (i.e. date of initiation of a salmeterol-containing medication)

Salmeterol-containing prescription	All patients [n = 17 745] (%)[a]	Children aged 4–11 y [n = 2020] (%)[a]	Adolescents aged 12–17 y [n = 1233] (%)[a]
1–6 months following index date			
SFC	47.1	43.8	47.9
Salmeterol	30.5	34.7	24.8
number of salmeterol users	5416	700	306
with ICS (±30 days)[b]	84.3	92.3	84.3
with ICS (±90 days)[b]	92.7	97.3	91.5
7–12 months following index date			
SFC	46.4	43.6	47.1
Salmeterol	24.3	27.7	19.4
number of salmeterol users	4309	559	239
with ICS (±30 days)[b]	85.3	90.0	87.9
with ICS (±90 days)[b]	91.1	95.3	93.3

a Unless specified otherwise.

b Among patients initiating salmeterol as opposed to SFC.

SFC = salmeterol/fluticasone propionate combination in a single device.

with respect to patterns of asthma medications on a daily basis or divergence in usual patterns immediately prior to an exacerbation (emergency department visit or hospital admission). We did not examine differences in medication prescription by race, because race/ethnicity is not recorded in the GPRD. Similarly, we were unable to determine the effect of 'on medication' utilization patterns; however, one might expect variations as described with utilization of ICS and SABA in a previous study.[26] An additional limitation of this study is inherent in the design requiring a 1-year period prior to the index prescription; patients with incident asthma or newly diagnosed asthma who were prescribed a salmeterol-containing medication were excluded from the cohort.

This study is descriptive in nature and contains no formal statistical comparisons of changes in medication prescription patterns within or between salmeterol-containing treatment groups. This study design did not adjust for factors that might be related to changes in medication use, including asthma severity. Analysis of within-group changes should have minimized potential confounding by severity/indication bias since a comparison group that was never prescribed a salmeterol-containing medication was not examined. Asthma severity is typically measured in part by medication prescriptions or dispensings in an observational study utilizing automated electronic healthcare databases, making it difficult to separate disease severity from descriptive outcomes related to asthma control or disease worsening.

Despite these limitations, this study suggests appropriate prescribing of salmeterol-containing medications from 2003 to 2006 in adults and children in the UK, in accordance with asthma treatment guidelines. Salmeterol was prescribed consistently with an ICS, as an add-on asthma-controller, for the overwhelming majority of patients in the initiation cohort (≥95% within 90 days) on the index date and in the year after the index date. The initiation of salmeterol-containing prescriptions was preceded by a pattern consistent with worsening asthma, as measured by an increase in SABA, ICS and systemic corticosteroid prescriptions. After initiation of a salmeterol-containing medication, there was no subsequent increase in SABA or systemic corticosteroid prescriptions in the following year. Rather, a pattern of decreasing prescriptions for SABA and systemic corticosteroids to levels consistent with those reported in the period prior to asthma worsening was observed. Overall, in this population-based UK cohort

study, we observed that salmeterol-containing medications were prescribed in accordance with labelling for adults and children with asthma, and there was no evidence that prescribing salmeterol or SFC resulted in worsening of asthma requiring increased prescriptions of asthma medications in the year subsequent to initiation.

Conclusions

Overall, this study suggests appropriate prescribing of salmeterol-containing medications, as per asthma treatment guidelines from 2003 to 2006, in an initiation cohort in the UK. Salmeterol was prescribed consistently with an ICS as add-on controller for the majority of patients in the initiation cohort. There was no evidence that prescribing of LABA-containing medications resulted in worsening asthma in this population-based cohort study. Salmeterol-containing medications were prescribed to patients following treatment patterns consistent with worsening of asthma (e.g. increased use of SABA, systemic corticosteroids). Following the initiation of salmeterol-containing medications, we observed a subsequent decrease in the use of all asthma medications to levels observed prior to worsening.

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