RESEARCH

Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids

JAMES CHAN, PharmD, PhD; RITA L. HUI, PharmD, MS; and MICHELE M. SPENCE, PhD

ABSTRACT

BACKGROUND: The addition of a long-acting beta-agonist (LABA) to an inhaled corticosteroid (ICS) for patients with moderate or severe persistent asthma improves outcomes such as pulmonary function, reduces exacerbations requiring oral steroids, and reduces use of rescue beta-agonists.

OBJECTIVE: To assess the key resource utilization outcomes of adding salmeterol, a LABA, to fluticasone, an ICS, either as a fixed-combination inhaler (fluticasone-salmeterol [FSA] or as a separate inhaler used concomitantly with the ICS beclomethasone (BSA).

METHODS: This is a retrospective, observational database study that extracted data from electronic medical and prescription records in which the prescription written was identical to the prescription dispensed. The sample included asthmatic patients aged 12 to 55 years who received a medium dose of an ICS (240-480 mcg of beclomethasone, 264-660 mcg of fluticasone, 600-1,200 mcg of budesonide, or 1,000-2,000 mcg of triamcinolone acetonide) between July 2001 and December 2002 and had salmeterol added to the regimen (index date). From this population of patients, the analytical cohort was derived to include 1,213 patients who received FSA and a matched cohort of 1,213 patients who received BSA. The primary endpoint was an asthma-related event (ARE), which was defined as (1) an emergency department (ED) visit or (2) hospital admission with a primary asthma diagnosis code (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 493.xx). The secondary endpoints were the (1) use of short-acting beta-agonist (SABA) equivalents, (2) percentage of patients who received 1 or more oral steroid prescriptions, (3) patterns of ICS use, and (4) refill rates of salmeterol. All data were collected for 6 months before and 6 months after the index date, defined as the first prescription dispensed to the patient that included salmeterol as an ingredient.

RESULTS: Outcomes were improved in both cohorts with no significant difference in the likelihood of an ARE, 60 patients (4.9%) for FSA and 90 patients (8.1%) for BSA (odds ratio [OR], 0.668; 95% confidence interval [CI], 0.443-1.008); $P=0.055$). FSA was associated with a reduction in AREs of 55% (10.9%-4.9%; $P<0.001$), and BSA with a reduction in AREs of 39% (13.3%-8.1%; $P<0.001$). FSA compared with BSA was associated with a greater reduction in SABA use (-0.66 canister equivalents over 6 months, $P<0.001$) and a lower likelihood of filling an oral steroid prescription, 35.8% of FSA patients compared with 38.0% of BSA patients (OR, 0.801; 95% CI, 0.662-0.970; $P=0.023$). For the 132 FSA patients (10.9%) and 162 BSA patients (13.4%) who had an ARE in the preperiod, those who received FSA in the postperiod had a 47% lower likelihood of a subsequent ARE, 17.4% of 132 patients compared with 27.8% of 162 BSA patients (OR, 0.527; 95% CI, 0.291-0.954; $P=0.034$). No ARE differences in subgroup analyses were noted for patients without an ARE in the preperiod or for patients using more than 6 canisters of SABA. More patients in the FSA group took daily doses of 400 mcg or more of ICS than those in the BSA group (32.0% compared with 10.0%, $P<0.001$). The average refill rate for salmeterol was 2.71 prescriptions (SD = 1.42) over 6 months for FSA compared with 2.38 (SD = 1.49) for BSA ($P<0.001$).

CONCLUSION: Overall, the addition of salmeterol as a fixed combination with fluticasone or with beclomethasone as separate inhalers was associated with a reduction in the ARE rate. Patients who received FSA were more likely to be exposed to a higher dose of ICS compared with those who received BSA. Differences in resource utilization may be attributed to how these drugs are prescribed and taken by patients in a real-practice (naturalistic) setting rather than to any inherent difference between the drugs (i.e., higher ICS dose rather than greater efficacy).

KEYWORDS: Drug therapy, Combination; Asthma; Adherence; Emergency services; Hospitalization; Fluticasone; Salmeterol; Beclomethasone

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Asthma is a clinical and public health problem and one of the most common chronic diseases worldwide.[1] Asthma-related hospital admissions and emergency department (ED) visits generally suggest poor disease control and/or inadequate treatment. They are also associated with subsequent readmissions.[2-5] In the United States, hospitalization with asthma as the primary diagnosis has remained relatively stable between 1980 and 2002.[6] Hospitalization with asthma as a secondary diagnosis, however, has increased in the same time period. In 2002, asthma accounted for about 2 million annual ED visits and a half-million hospitalizations.[7]

The inadequate management of asthma results in a significant economic burden on asthma patients as well as on society. Prescription and hospitalization costs are the largest contributors to direct health care costs, while the loss of work and productivity are the largest contributors to indirect health care costs.[1] The estimated cost impact due to asthma in 2000 was $14 billion in medical and indirect costs, with direct medical costs accounting for an estimated $9.4 billion.[8]

Inhaled corticosteroid (ICS) is the preferred treatment for mild, moderate, and severe persistent asthma. Use of ICS has been associated with reduced ED visits and admissions.[9-11] In patients with moderate or severe persistent asthma, the

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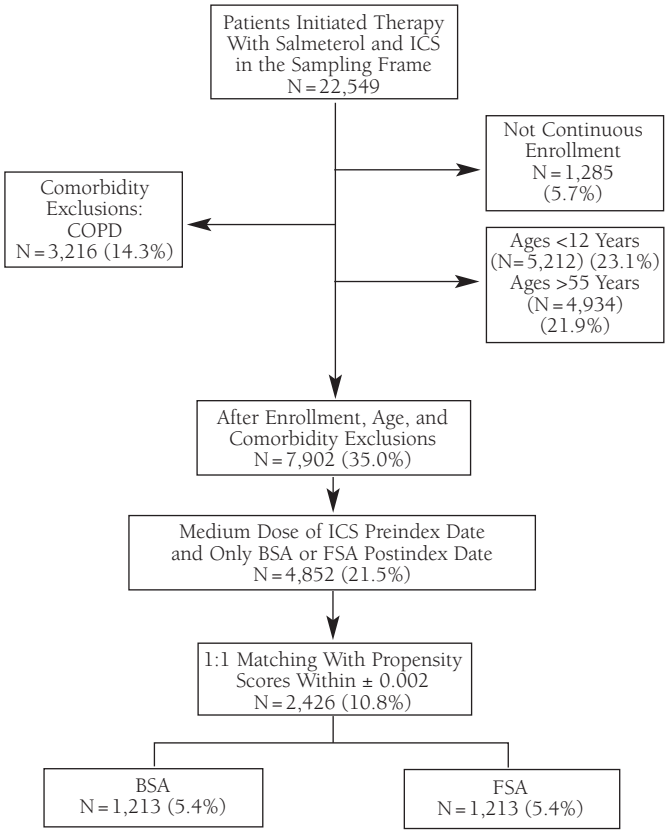
FIGURE 1 Flowchart for Asthma Patient Selection*



** 6 months of continuous enrollment was required before and after initiation of combination therapy.*
BSA = beclomethasone-salmeterol; COPD = chronic obstructive pulmonary disease; FSA = fluticasone-salmeterol; ICS = inhaled corticosteroid.

addition of an inhaled long-acting beta-agonist (LABA) to an ICS leads to improvement of pulmonary function, reduces exacerbations requiring the use of oral steroids, and reduces the use of short-acting beta-agonists (SABAs).[12] Improved refill persistence has been reported when the combination of fluticasone and salmeterol is administered in a fixed combination (Advair, henceforth referred to as FSA) compared with use of separate inhalers.[13] In addition to more convenient administration, the combination FSA product provides possible advantages with codeposition of the drugs in the airway.[14]

FSA has been compared with a number of other dual therapies, including fluticasone (Flovent) and salmeterol (Serevent) administered separately; fluticasone and montelukast; and formoterol and budesonide.[1,15] Nguyen et al. reported that in an inner-city population with a history of frequent ED visits, FSA reduced subsequent encounters (ED or hospitalization) by 33% compared with the usual care.[16] Prior ED visits and admissions, as well as use of SABAs and oral steroids, are the strongest predictors of visits and admissions.[5,11] These factors have been proposed in a risk stratification scheme for identifying patients at risk of experiencing emergency hospital care.[17] Most studies have compared clinical outcomes such as pulmonary function and symptoms in clinical trial settings.[1,15] However, the impact on health care resources, ED visits, or admissions has not been fully investigated. We sought to compare, in a real-practice (naturalistic) setting, the effects of the fixed-combination product of beclomethasone diproprionate and salmeterol on ED visits and hospitalization, as well as the subsequent use of SABAs and oral steroids. In addition, we assessed drug adherence and prescribing patterns of providers regarding these 2 drug regimens.

Methods

Study Population and Design

This was a retrospective longitudinal analysis of data from administrative databases of the Kaiser Permanente (KP) Medical Care Program, located in California. KP is a prepaid integrated health care delivery system that provides comprehensive medical care, including prescription drugs, to more than 6 million members in California and 8 million members nationwide. The study population included all patients in the 2 health plans in northern and southern California who met the following criteria: (1) aged 12 to 55 years, (2) prescribed a medium dose of an ICS between July 2001 and December 2002, and (3) had salmeterol added to the regimen. The medium daily dose was defined as a prescribed (i.e., the directions to the patients for use as documented in the electronic prescription record) dose of 240-480 mcg of beclomethasone hydrofluoroalkane (HFA), 264-660 mcg of fluticasone, 600-1,200 mcg of budesonide, or 1,000-2,000 mcg of triamcinolone acetonide. The initiation date for salmeterol was defined as the index date. Patients were excluded if they were not continuously enrolled for 6 months before and after the index date or if they had a diagnosis of chronic obstructive pulmonary disease (COPD: *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 490.x, 491.x, 492.0, 942.8, 496, 506.4) during the 6 months before the index date. All data were collected for 6 months before and after the index date. This study was approved by the northern California and southern California Institutional Review Boards.

The study was designed as a pretest, posttest cohort analysis with 2 active groups derived from the original sample of patients who received 1 or more of 4 ICS drugs in the period prior to initiation of salmeterol (LABA). The fluticasone-salmeterol group (FSA) had salmeterol added as the combination product. The beclomethasone-salmeterol group (BSA) had salmeterol added to beclomethasone HFA and administered as separate inhalers. Only these 2 combinations of LABA and ICS were used in the analysis since beclomethasone was the plan's preferred ICS and FSA, although a nonformulary product, was available to our prescribers without prior authorization. Patients dispensed

FSA were charged 1 copayment and those dispensed BSA were charged 2 copayments for the 2 prescriptions (salmeterol and beclomethasone). Copayment per prescription varied depending on the patient's prescription drug coverage. However, the copayment was the same for each individual patient (e.g., $25 for FSA and 2 x $25 for BSA).

Subjects were matched using propensity scores,[18] which were based on a 1-to-1 match of scores within ± 0.002. Those scores that did not match were excluded from analysis. Propensity scores were based on age, gender, unscheduled office visits, ED visits, and hospitalizations for asthma-related events (AREs), asthma medication prescribed by a specialist (allergist, pulmonologist) in addition to the primary provider, and the use of anti-inflammatory drugs and SABA. The electronic records of 22,549 patients were accessed, and 2,426 (1,213 matched pairs) met inclusion criteria and were used in the analysis (Figure 1).

Determination of equivalent(s) canisters of ICS and SABA was done using the method similar to that of Glauber et al.,[19] which standardizes these medications on the basis of differences in potency and days supply of medication per pharmacy claim (Table 1). Patients who switched ICSs in the study period were also excluded from the analysis. However, patients who were dispensed other controllers (e.g., montelukast) were tracked and not excluded. For this analysis, the mcg equivalence was assumed for fluticasone and beclomethasone HFA based on the relative clinical effectiveness reported by Fairfax.[20] Both medications appear equivalent at 400 mcg per day. At higher doses, 800 mcg of beclomethasone HFA and 1,000 mcg per day of fluticasone appear equivalent. Three subgroup analyses were done: (1) patients with prior ED visits or admissions, (2) patients without prior ED visits or admissions, and (3) patients using 6 or more canister equivalent(s) of inhaled beta-agonist. The 3 subgroups were used to determine if differences in outcomes were related to the level of asthma control.

TABLE 1 Canister-Equivalent Conversion Factors

	Quantity	Canister Equivalents
Short-Acting Beta-Agonists		
Albuterol 90 mcg	17 g	1
Albuterol 90 mcg HFA	6.7 g	1
Albuterol 0.083% solution	3 mL	0.02
Albuterol 0.5% solution	20 mL	0.8
Metaproterenol 0.6% solution	2.5 mL	0.02
Metaproterenol 650 mcg	14 g	1
Inhaled Corticosteroids		
Beclomethasone 40 mcg	7.3 g	0.83
Beclomethasone 80 mcg	7.3 g	1.67
Fluticasone 44 mcg	10.6 g	0.8
Fluticasone 110 mcg	12 g	2
Fluticasone 220 mcg	12 g	4
Fluticasone 100 mcg (in FSA)	60 doses	1
Fluticasone 250 mcg (in FSA)	60 doses	2.5
Fluticasone 500 mcg (in FSA)	60 doses	5
Budesonide 200 mcg	200 doses	6.67

FSA = fluticasone and salmeterol in combination product; HFA = hydrofluoroalkane.

Measurement

The primary endpoint was an ARE, which was defined as an ED visit or hospital admission for an asthma-related event (ICD-9-CM code 493.xx). The secondary endpoints were the (1) use of SABA, (2) percentage of patients with 1 or more oral steroid pharmacy claims, (3) prescribing and patient consumption patterns of ICS, and (4) refill rate of salmeterol. The data were all based on pharmacy claim records from the KP electronic prescription system.

Statistical Analysis

Patient characteristics were compared using *t* tests or the Wilcoxon rank sum test for continuous variables and chi-square tests or the McNemar test and Cochran's *Q* test for categorical variables. Conditional logistic regression analysis was used to compare the incidence of AREs and the likelihood of filling at least 1 prescription for an oral steroid between the matched data in the 2 groups (FSA and BSA). Subgroup analyses were conducted with unconditional logistic regression because these subjects were no longer matched and analyzed as different cohorts. Change in SABA use was analyzed using analysis of covariance (ANCOVA). To adjust for differences in practice between northern and southern California regions, a dummy variable was created and used as a covariate in all the analyses. Other covariates used in the models were age, gender, prior ED visits, admissions, oral steroid use, beta-agonist use, ICS use, and medication prescribed by an allergist or pulmonologist. All *P* values were 2-sided. Statistical significance was defined as $P < 0.05$. SAS statistical software version 9.12 was used for data analysis (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics of the study cohorts are summarized in Table 2. The electronic records of 22,549 subjects were screened and 2,426 met the inclusion criteria, 1,213 in each group. There were no statistical differences between the 2 groups in terms of baseline demographics or clinical characteristics. There were no statistical differences in the number of prescriptions dispensed or the estimated duration of therapy for other controllers (e.g., montelukast) between groups both preindex and postindex date (data not shown).

Changes in the primary and secondary endpoint measures,

TABLE 2 Baseline Characteristics of the Study Population 6 Months Preindex* Date

Characteristic	FSA N = 1,213	BSA N = 1,213	*P* Value
Age, mean [SD]	36.1 [13.8]	37.1 [12.7]	0.063
Sex (% female:% male)	61:39	59:41	0.349
SABA, mean [SD]	3.89 [4.47]	4.10 [4.76]	0.247
Anti-inflammatory (AI) equivalents†, mean [SD]	5.16 [6.87]	4.79 [6.91]	0.182
AI ratio‡, mean [SD]	0.429 [0.366]	0.401 [0.357]	0.074
ED visits with a diagnosis code for asthma (ICD-9-CM code 493.xx), mean [SD]	0.127 [0.471]	0.158 [0.522]	0.125
% (no.) of patients with a hospital admission with an ICD-9-CM diagnosis code of 493.xx	10.9 (132)	13.3 (162)	0.062
Specialist (allergist, pulmonologist) pharmacy claims, mean [SD]	1.56 [2.47]	1.52 [3.10]	0.674
% (no.) of patients with oral steroid prescriptions	41.3 (501)	43.1 (523)	0.366

** The index date is the first date of a pharmacy claim for salmeterol in combination (FSA) or separate inhaler.*
† Anti-inflammatory (AI) equivalents is the sum of the canister equivalent(s) of inhaled corticosteroids (ICSs) in the 6-month preindex period.
‡ AI ratio is AI equivalents divided by the sum of AI equivalents and SABA canister equivalents.
BSA = beclomethasone and separate salmeterol; ED = emergency department; FSA = fluticasone and salmeterol in combination product; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SABA = short-acting beta-agonist.

6-month postindex date, are shown in Table 3. The FSA group had a reduction in AREs of 55.0% (10.9%-4.9%; $P < 0.001$), and the BSA group had a reduction of 39.1% (13.3%-8.1%; $P < 0.001$). The adjusted odds ratio (OR) for an ARE was not statistically different for FSA compared with BSA (OR, 0.668; 95% CI, 0.443-1.008; $P = 0.055$). There was a 13.3% reduction in oral steroid dispensing for the FSA group (41.3%-35.8%; $P = 0.002$) and an 11.9% reduction (43.1%-38.0%; $P = 0.002$) for the BSA group. Patients treated with FSA were about 20% less likely to fill a prescription for an oral steroid. The change in the adjusted mean (least square mean) for inhaled SABA use was -1.05 canister equivalent(s) for FSA and -0.39 canister equivalent(s) for BSA. This represented a 27.0% reduction for FSA and 9.5% reduction for BSA; both were statistically significant reductions ($P < 0.001$). The adjusted difference between FSA and BSA was -0.66 canisters equivalent(s) ($P < 0.001$) in favor of FSA.

The subgroup analysis is shown in Table 4 and Table 5. No statistical difference was observed in AREs for patients with no prior AREs (OR, 0.730; 95% CI, 0.470-1.135; $P = 0.163$). AREs were observed in 3.4% of FSA patients and in 5.0% of BSA patients. No statistical difference was observed in the reduction of oral steroid dispensing (a relative 4.2% reduction for FSA, from 35.5% of patients to 34.0% of patients, and a relative 5.3% reduction for BSA, from 35.9% to 34.0%). Significant changes in adjusted beta-agonist use were observed for each regimen compared with baseline: -0.95 canister equivalent(s) for FSA (26% decrease) and -0.33 canister equivalent(s) for BSA (9% decrease) ($P < 0.001$). The adjusted difference between treatments was -0.62 canister equivalent(s) in favor of FSA over BSA ($P < 0.001$).

In patients who had previous AREs, a significant difference was observed (OR, 0.527; 95% CI, 0.291-0.954; $P = 0.03$) for FSA compared with BSA. Both regimens significantly reduced oral steroid dispensings (43.6% and 29.5%, respectively) ($P < 0.001$). Those treated with FSA were about 52% less likely to fill an oral steroid prescription (OR, 0.482; 95% CI, 0.293-0.793; $P = 0.004$). The adjusted change in inhaled SABA use was -1.76 for FSA ($P < 0.01$) and -0.85 for BSA ($P = 0.009$). An adjusted difference of -0.91 canister equivalent(s) was observed in favor of FSA but did not reach statistical significance.

In the 6-month baseline period, 665 patients used 6 or more canister equivalent(s) of SABA. The median use in each group was 9, with an interquartile range of 7-12. Both groups significantly reduced their beta-agonist use: -3.52 canister equivalent(s) for FSA and -2.71 for BSA in the post-6-month period ($P < 0.001$). The difference between groups in reduction of use was -0.81 canister equivalent(s) ($P = 0.026$) in favor of FSA.

In the postperiod, 50% of patients on BSA continued with a medium dose of inhaled steroid compared with 47% for the FSA group. Thirty-four percent of BSA subjects were prescribed a lower dose compared with 2% for the FSA group. Conversely, 33% of patients in the FSA group filled prescriptions for a higher dose compared with 2% for BSA. Thirty-two percent of patients on FSA appeared to take 400 mcg or higher compared with 10% for BSA. Twenty-six percent of patients in the BSA group adhered to the dose prescribed compared with 31% for the FSA group. Fifty-one percent of patients on BSA took a lower dose than prescribed compared with 45% for FSA patients. These were all significant at $P < 0.001$. The mean number of equivalent prescriptions filled for salmeterol was 2.71 per 6 months for FSA compared with 2.38 for BSA ($P < 0.001$).

Discussion

The addition of salmeterol either to fluticasone as a combination product or individually to beclomethasone improved outcomes in asthmatic patients overall. However, the greater benefit was achieved in patients who were previously poorly controlled (i.e., had previous ED visits or hospitalizations for an asthma-related reason). After the addition of salmeterol, beclomethasone was

TABLE 3 Outcome Measures After the Addition of Salmeterol to Beclomethasone (BSA) Versus the Combination Fluticasone and Salmeterol Product (FSA) 6 Months Postindex Date

Outcome Measures	FSA	BSA	Difference or Odds Ratio	*P* Value
% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma	4.9 (60)	8.1 (98)	0.668 (0.443-0.008)*	0.055
% (no.) of patients who received oral steroids	35.8 (434)	38.0 (461)	0.801 (0.662-0.970)†	0.023
Adjusted change in SABA	-1.05	-0.39	-0.66‡	<0.001
% (no.) of patients who consumed a daily dose of ICS of ≥400 mcg	32.0 (388)	10.0 (121)	N/A	<0.001
Mean [SD] refills for salmeterol separately or as FSA	2.71 [1.41]	2.38 [1.49]	N/A	<0.001§

** Odds ratio adjusted for baseline asthma-related event and geographic region.*
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ Least squares difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.
§ t test.
ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICS = inhaled corticosteroid; SABA = short-acting beta-agonist.

TABLE 4 Outcome Measures After the Addition of Salmeterol to Beclomethasone (BSA) Versus the Combination Fluticasone and Salmeterol Product (FSA) in Patients With No Prior ED Visits or Admissions 6 Months Postindex Date

	FSA (N = 1,081)		BSA (N = 1,051)		Difference or Odds Ratio	
Outcome Measures	Preindex	Postindex	Preindex	Postindex	(95% CI)	*P* Value
% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma	0 (0)	3.4 (37)	0 (0)	5.0 (53)	0.730 (0.470-1.135)*	0.163
% (no.) of patients who received oral steroids†	35.5 (384)	34.0 (368)	35.9 (377)	34.0 (357)	0.861 (0.711-1.042)†	0.124
SABA use‡	3.66	2.76	3.74	3.31	-0.62§	<0.001

** Odds ratio adjusted for baseline asthma-related event and geographic region.*
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ No statistical difference between values at baseline.
§ Least squares mean difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.
CI = confidence interval; ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SABA = short-acting beta-agonist.

prescribed at a lower dose than fluticasone. The availability of the various dosage strengths may help explain the observed usage pattern. FSA is supplied commercially as 100 mcg, 250 mcg, and 500 mcg of fluticasone per diskus. These are generally dosed twice daily. In contrast, beclomethasone is supplied as 40 mcg and 80 mcg per puff. Using the 80-mcg strength, a dose of 480 mcg requires 6 puffs, and 640 mcg requires 8 puffs. Adherence was statistically better with FSA than BSA. This makes it easier for prescribers to prescribe a higher dose and for patients to adhere to a higher dose. It was not feasible to compare equipotent doses of BSA and FSA within the context of this analysis because of disproportionate distribution of doses with similar potency. Therefore, these findings, representing naturalistic or real-practice settings with attention to both the prescribers' and patients' perspective, suggest that patients prescribed FSA are more likely to take a higher dose and because of this, those patients with poor control may achieve greater benefit. Thus, the observed differences may be related to the way the drugs are available and used rather than to any inherent differences between them.

TABLE 5 *Outcome Measures After the Addition of Salmeterol to Beclomethasone (BSA) Versus the Combination Fluticasone and Salmeterol Product (FSA) in Patients With Prior ED Visits or Admissions 6 Months Postindex Date*

Outcome Measures	FSA (N = 132)		BSA (N = 162)		Difference or Odds Ratio (95% CI)	*P* Value
	Preindex	Postindex	Preindex	Postindex		
% (no.) of patients with ED visits or hospital admission with ICD-9-CM code 493.xx for asthma	100 (132)	17.4 (23)	100 (162)	27.8 (45)	0.527 (0.291-0.954)*	0.034
% (no.) of patients who received oral steroids†	88.6 (117)	50.0 (66)	90.1 (146)	64.2 (104)	0.482 (0.293-0.793)†	0.004
SABA use‡	5.74	4.17	6.46	5.29	-0.91§	0.06

** Odds ratio adjusted for asthma-related event and geographic region.*
† Odds ratio adjusted for baseline oral steroid use and geographic region.
‡ No statistical difference between values at baseline.
§ Least squares mean difference between FSA and BSA adjusted for baseline beta-agonist use and geographic region.
CI = confidence interval; ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; SABA = short-acting beta agonist.

Our findings suggest that higher doses of inhaled steroids may lead to a decrease in ED visits and hospital admissions. This is consistent with the findings of Schatz et al.[9] These investigators found a trend toward decreased ED visits and admissions with increased use of inhaled canisters. This differs from the findings of Sin and Man who reported that low-dose therapy appears to be as effective as high-dose inhaled steroid therapy.[10] The authors, however, concluded that further studies are needed to determine the optimal dosing regimen for inhaled steroids.

On the basis of the results presented, it may be cost effective to stratify patients by level of risk for ED visits or admissions similar to that described by Schatz et al.[17] The scheme to identify these at-risk patients is based on previous ED visits, admissions, any use of oral steroids, and use of >14 canisters of beta-agonist based on administrative data. From the perspective of the health care provider, ED visits or admissions are most costly to the health plan. FSA provides a more cost-effective regimen to manage patients with prior ED visits or admissions. For those with better control, FSA dose not show a robust difference in outcome.

FSA was more effective than BSA in reducing beta-agonist use in patients who were high users (6 or more canisters per 6 months). No statistically significant difference was seen in ED visits or admissions between treatment groups. It is possible that the follow-up period of 6 months may be too short to detect a difference. Studies have generally related treatment patterns over 12 months for AREs.[9,11,17] However, the Salmeterol Multicenter Asthma Research Trial (SMART) was for 28 weeks and a recent meta-analysis used 6-month endpoints.[21,22]

Similarly, the 6-month preperiod may not have been adequate to define the patient's past history. Lastly, since the 6-month period was used both preaddition and postaddition of salmeterol, seasonality may be a confounding factor. However, this factor is expected to affect both groups similarly, thus minimizing its impact.

Limitations

Our study is observational in nature and relies on data from administrative databases. Channeling bias or confounding by indication is an inherent problem in this type of study. We attempted to minimize this effect by matching patients using propensity scores and conditional logistic regression comparing matched pairs. However, we cannot be completely certain that we have adjusted fully for channeling bias. The baseline characteristics of the study population suggest no significant dissimilarities.

For the subgroup analysis, unconditional logistic regression was used, as the subgroups were not matched by propensity scores. In this case, potential confounders or effect modifiers were adjusted using logistic regression to minimize the influence of these factors. We may have underestimated the use of oral steroids because patients may have prefilled steroid prescriptions on hand in case of flare-ups. We did not collect asthma-related deaths as an endpoint, although this has been widely discussed in the literature[21-24]; a larger study with a different design and inclusion criteria should be used to assess this endpoint. Finally, these findings are from an integrated managed care organization in California and may not be generalizable to other practice settings.

Conclusion

The addition of salmeterol to either beclomethasone as a separate inhaler or to fluticasone as a combination product improves clinical outcomes in asthmatic patients with no significant differences between the groups in the primary outcome of asthma-related ED visits or hospital admissions. Patients with prior ED visits or admissions for AREs showed a better primary outcome with FSA compared with BSA. For those patients with no prior ED visits or admissions (i.e., apparent lower asthma severity or better control), outcomes were not significantly different between the 2 regimens. Patients who received FSA were more likely to be exposed to a higher dose of inhaled steroid compared with those who received BSA. Differences between FSA and BSA may be attributed to the way these drugs are used in a naturalistic setting rather than to any inherent difference between drugs.

What is already known about this subject

- Previous studies on health care utilization have compared combination fluticasone (ICS) and salmeterol (LABA) with fluticasone and salmeterol separately or with fluticasone and montelukast (leukotriene inhibitor).
- Data are lacking on effects of combination fluticasone and salmeterol compared with separate inhalers of beclomethasone (ICS) and salmeterol.

What this study adds

- Both combination fluticasone/salmeterol and separate inhalers of beclomethasone and salmeterol reduce asthma-related ED visits and hospital admissions.
- Patients with recent ED visits or admissions (presumably with poorer control) show a greater reduction on combination fluticasone/salmeterol therapy, albeit at a higher equivalent steroid dose.

DISCLOSURES

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