International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Cost-effectiveness of combination fluticasone propionate–salmeterol 250/50 µg versus salmeterol in severe COPD patients

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease
4 June 2010
Number of times this article has been viewed

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Objective: To estimate the cost-effectiveness of fluticasone propionate–salmeterol combination (FSC) compared to salmeterol for maintenance therapy in severe chronic obstructive pulmonary disease (COPD).

Study design: Pooled economic analysis.

Methods: We performed an economic analysis of pooled data from two randomized clinical trials (combined N = 1554) that evaluated the effect of maintenance therapy with FSC (250/50 µg twice daily) or salmeterol (50 µg twice daily) on exacerbation rates in patients with severe COPD. We calculated exacerbation rates and applied standardized costs to exacerbation-related health care utilization reported in the trials (office, urgent care, and emergency department visits; hospitalizations; and oral corticosteroids and antibiotics) to determine cost differences between FSC and salmeterol treatment outcomes.

Results: Annual rates of any exacerbation and moderate/severe exacerbation were lower in the FSC group than the salmeterol group (4.91 vs 5.78 and 1.32 vs 2.00 respectively, both $P < 0.05$). Total adjusted annual COPD related exacerbation and therapeutic costs were $4,842 (95% CI; $4,731–$4,952) in the FSC group and $5,066 (95% CI; $4,937–$5,195) in the salmeterol group.

Conclusions: FSC combination therapy is associated with reduced risk of any exacerbation and moderate/severe exacerbation, and incurs lower annual COPD-related health care costs compared to treatment with salmeterol. This analysis demonstrates that FSC therapy may be advantageous from both a clinical and cost-benefit standpoint for patients with severe COPD.

Keywords: COPD, cost-effectiveness analysis, economic, maintenance therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airway obstruction and inflammation that leads to chronic bronchitis and emphysema. It affects approximately 210 million people worldwide and leads to 3 million deaths annually.[1] In the United States, COPD affects 24 million adults and accounts for 8 million physician visits, 1.5 million emergency department (ED) visits, 726,000 hospitalizations, and 119,000 deaths annually.[2,3] The US economic burden of COPD in 2007 was $42.6 billion, including $26.7 billion in direct health care expenditures.[4]

Exacerbations are a primary concern in the clinical management of COPD and are associated with accelerated lung function decline, hospitalization or treatment in the ED, and an overall negative impact on quality of life.[5–7] Clinical studies suggest that fluticasone propionate–salmeterol combination (FSC) therapy for COPD has clinical efficacy benefits over salmeterol monotherapy, including lower rates of exacerbation

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and a reduced rate of decline in lung function;[5,8–14] other observational studies have found that FSC is more cost-effective than other therapies.[15–17] However, no direct cost comparisons of FSC and salmeterol have been made using exacerbation and health care event data from randomized controlled trials (RCTs), making it difficult to evaluate the cost-benefit of these therapies or make formulary decisions based on willingness-to-pay (WTP) thresholds.

The objective of this study was to estimate the cost-effectiveness of FSC compared to salmeterol for maintenance therapy in patients with severe COPD using data pooled from two RCTs that compared the effects of FSC and salmeterol on the annual rate of moderate/severe exacerbations in populations of severe COPD patients. Pooling data from trials is advantageous, particularly when the studies have similar protocols and patient-level data are available.[18] This approach reduces the likelihood of false negative results, aids exploration of heterogeneity across studies, and helps resolve conflicting findings. To our knowledge, this is the first economic analysis to use clinical trial efficacy data associated with FSC and salmeterol therapy to estimate cost differences in COPD maintenance therapy following 1 year of treatment.

Methods

Overview

We performed a post hoc economic evaluation using pooled data from two recent RCTs to assess the cost-effectiveness of FSC compared to salmeterol for COPD management. The data were from two double-blind, parallel-group trials (GlaxoSmithKline SCO40043 and SCO100250) in which patients with COPD were randomized to receive FSC 250/50 μg twice daily or salmeterol 50 μg via Diskus™ dry powder inhaler, twice daily for 52 weeks. The study methods have been described previously.[8,10] Patients were aged 40-years-old and older, had a cigarette smoking history of 10 pack-years or greater, a forced expiratory volume (FEV_1) of 50% of predicted normal value or less, and a history of one or more exacerbations in the prior year that required treatment with oral corticosteroids, antibiotics, or hospitalization. Patients with asthma, other significant lung disease, and certain other significant and uncontrolled disorders were excluded. Concurrent use of inhaled long-acting bronchodilators, ipratropium–albuterol combination products, inhaled corticosteroids and theophylline were not allowed, but albuterol could be used as needed. The planned study enrollment (N = 740 per trial) provided 90% power to detect a greater than 20% reduction in the rate of moderate/severe exacerbations in the FSC group compared to the salmeterol group at the 95% level of significance based on estimated exacerbation rates of 1.5 for FSC and 1.9 for salmeterol. The first trial (SCO40043, N = 776) included 391 patients in the FSC group and 385 patients in the salmeterol group, and the second trial (SCO100250, N = 778) included 385 patients in the FSC group and 393 patients in the salmeterol group; all patients were included in our analysis.

The primary outcome measure of the trials was the annual rate of moderate/severe COPD exacerbation. Secondary outcomes were time to first moderate/severe COPD exacerbation, annual rate of moderate/severe COPD exacerbation requiring treatment with oral corticosteroids, and pre-dose AM FEV_1. Individually, the trials reported similar results, including an approximately 30% lower annual rate of exacerbations in the FSC group than the salmeterol group ($P < 0.001$).[8,10] Secondary outcomes also favored FSC therapy over salmeterol. Adverse event profiles of the groups were similar with the exception of a higher incidence of known local inhaled corticosteroids (ICS)-related side effects (candidiasis and dysphonia) and pneumonia in the FSC group, although percentages of study subjects experiencing these effects in the clinical trials were very low. The percentage of patients experiencing candidiasis in the FSC group was 4% in SCO40043 compared to 2% in the salmeterol group, and in SCO100250 it was 6% compared to <1%; for dysphonia the percentages were 4% compared to <1% in SCO40043 and 5% compared to 1% in SCO100250. Percentages of patients having pneumonia were 7% in the FSC group compared to 4% in the salmeterol group in SCO40043 and 7% compared to 2% in SCO100250.

In the clinical trials, a COPD exacerbation was defined as a worsening of two or more major symptoms (dyspnea, sputum purulence, and sputum volume) and one minor symptom (cough/wheeze, fever, sore throat, and cold). A moderate/severe exacerbation was defined as worsening symptoms requiring treatment with oral corticosteroids, antibiotics, or hospitalization, and a mild exacerbation was one that did not require these interventions. For our economic analysis, we evaluated moderate and severe exacerbations together as well as separately. A moderate exacerbation was defined as worsening symptoms that required an office, urgent care, (UC) or ED visit, and treatment with oral corticosteroids or antibiotics. A severe exacerbation was defined as worsening symptoms that required hospitalization. Exacerbation categories were not mutually exclusive; a patient could have one or more types of exacerbation. The exacerbation counts, level of severity, and related health care

events used in this analysis were based on the clinical trial investigator reports.

Costing methods

The costs assigned to exacerbation-related health care are shown in Table 1. The studies were not designed with the intention of performing economic analyses and therefore we were unable to utilize actual costs incurred in managing and treating COPD. Instead we approximated costs using estimates obtained through prior research. While information was gathered in the clinical trials concerning exacerbation recovery time (length of hospital stay and length of oral corticosteroid and antibiotic treatments), the distributions for recovery times showed tremendous variation, with the potential for outliers to severely bias comparison results. In associating costs with exacerbation events, we have associated estimated costs for average length experiences.

COPD-related hospitalizations and ED visits have been used in prior studies as evidence of an exacerbation, and were the primary endpoints of the clinical trials used in this analysis.[8,10] Costs for COPD-related hospitalizations and ED visits were derived from a study by Stanford et al.[7] Assigned costs for hospitalizations assume an average length of stay. Stanford et al found that COPD patients admitted to the hospital from the ED had an average length of stay of 5 days, or 8.4 days if ICU care was required. We also calculated the costs of exacerbation-related office and UC visits using costs derived from a study by Nurmagambetov et al.[19]

Costs of study drugs (FSC and salmeterol) and courses of oral corticosteroids and antibiotics to treat exacerbations were derived from the 2007 Wholesale Acquisition Cost (WAC) in the *Drug Topics Red Book*®.[20] To assign an average cost to a course of antibiotic or oral corticosteroid therapy, the number of drug therapy events that occurred during the trials and the associated drug costs were summed, and a weighted average daily cost for each treatment was calculated. Antibiotic treatment of an exacerbation was assumed to require a 7-day regimen and oral corticosteroid treatment a 10-day regimen, regardless of the days of antibiotic or oral corticosteroid use captured in the trial reports. The costs were thus calculated to be $113.72 for an antibiotic course and $2.77 for an oral corticosteroid course.

Table 1 Unit costs used in the calculation of exacerbation costs

Input	Cost in US dollars
Moderate exacerbation	
Office visit	96.00[a,b]
Urgent care visit	96.00[a,b]
Emergency department visit	656.00[a,c]
Antibiotic course, 7-day regimen	113.71[d]
Corticosteroid course, 10-day regimen	2.77[d]
Severe exacerbation	
Standard hospitalization	6890.93[a,c]
Intensive care unit admission	12,375.41[a,c]
Treatment drug costs	
Fluticasone/salmeterol 250/50 μg twice daily, 30-day supply	164.64[d]
Salmeterol 50 μg twice daily, 30-day supply	109.16[d]

Notes: [a]Costs were inflated to 2007 dollars using the Consumer Price Index. [b]Nurmagambetov et al.[19] [c]Stanford et al.[7] [d]2007 Drug Topic Redbook Annual.[20]

Information on concomitant COPD and non-COPD medication utilization by study participants was available at a summary level by therapy group for each study. However, information was only available for the number and percentage of participants having any use of specific medications. For example, in SCO40043 76% of the FSC patients and 86% of the salmeterol patients had some use of COPD concomitant medications, and 96% of FSC patients and 95% of salmeterol patients had some use of non-COPD concomitant medications. However, it was unknown which individuals used specific medications and in what quantity. Because of the varying lengths of time patients were followed in the clinical trials and because the focus of our analysis is on exacerbation costs and therapeutic costs, we chose not to include cost estimates for concomitant medications in our analysis.

Statistical analysis

The statistical analyses included descriptive, bivariate, and multivariate analyses. Frequencies for categorical variables and measures of central tendencies for linear data were calculated for patient characteristics, exacerbation events, exacerbation-related health care utilization, and associated health care costs.

Annual rates were calculated for any and moderate/severe exacerbation events and Wilcoxon rank sum tests were performed to assess differences between treatment groups. Mean annualized rates of any and moderate/severe exacerbations by treatment group were also calculated using a generalized linear model with a negative binomial distribution and log link, controlling for treatment, investigator, COPD reversibility stratum (based on FEV_1 response to albuterol at baseline screening), baseline disease severity, and time on treatment. In addition, mean annual rates for exacerbation-related health care utilization (office, UC and ED visits, hospitalizations, and pharmacy) were estimated using similar negative binomial models. Relative risks for the FSC treatment group were calculated using model β coefficients.

All patients in the study incurred pharmacy costs; not all patients incurred costs associated with medical care. In multivariate analyses, predicted values for annual total medical costs were calculated using the generalized linear model described above, but with a gamma distribution. For the predicted values, bootstrapped confidence intervals were calculated for the difference between means using the percentile method with 1000 samples. All analyses were conducted with SAS version 9.1.3 for Windows (SAS Institute, Cary, NC).

Results

Patient characteristics

Baseline characteristics of patients in the pooled FSC and salmeterol groups are shown in Table 2. Randomization to treatment groups within the individual clinical trials successfully balanced the observable covariates, and this carried over to the pooled groups. Both the pooled FSC and salmeterol groups had a mean age of 65 years, were 55% male, and had a mean duration of diagnosed COPD of approximately 8 years. Patients were also similar in terms of race, geographic region, body mass index, smoking status, pack-year history, COPD type (emphysema, chronic bronchitis, or both), and lung function.

Table 2 Patient characteristics in the pooled clinical trials sample

	FSC group (N = 776)	SAL group (N = 778)
Clinical trial SCO40043	391 (50.4)	385 (49.5)
Clinical trial SCO100250	385 (49.6)	393 (50.5)
Age, mean (SD)	65.1 (9.1)	65.1 (9.0)
Male, mean (SD)	424 (54.6)	424 (54.5)
Race, N (%)		
Black	33 (4.3)	40 (5.1)
Caucasian	728 (93.8)	729 (93.7)
Other	15 (1.9)	9 (1.2)
Body mass index, mean (SD)	27.5 (6.2)	27.4 (7.0)
Smoking status, N (%)		
Current smoker	320 (41.3)[a]	317 (40.7)
Former smoker	455 (58.7)[a]	461 (59.3)
Pack-years, mean (SD)	58.1 (31.8)	55.3 (26.7)
COPD duration, mean (SD)	8.2 (7.6)	8.1 (7.4)
COPD type, N (%)		
Chronic bronchitis	219 (28.2)	242 (31.1)
Emphysema	360 (46.4)	333 (42.9)[a]
Both	197 (25.4)	202 (26.0)
FEV_1% predicted, mean (SD)	33.4 (10.8)	33.3 (10.3)
FEV_1/FVC, mean (SD)	0.45 (0.1)	0.45 (0.1)
Region, N (%)		
Canada	93 (12.0)	94 (12.1)
Mid-Atlantic	147 (18.9)	136 (17.5)
Midwest	96 (12.4)	91 (11.7)
North	82 (10.6)	80 (10.3)
Northeast	96 (12.4)	93 (12.0)
South	69 (8.9)	78 (10.0)
Southeast	98 (12.6)	101 (13.0)
West	95 (12.2)	105 (13.5)

Notes: [a]Data missing for one patient; denominator is one less than total sample N
Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume; FVC, forced vital capacity.

Exacerbation rates and costs, unadjusted

Unadjusted exacerbation rates are presented in Table 3. A small percentage of patients in both groups, approximately 13%, had no exacerbations during the 52-week clinical trials. The percentage of patients in the FSC group who had a moderate/severe exacerbation was lower in the FSC group than the salmeterol group (53.9% vs 59.5%). The FSC group had a slightly higher percentage of patients with one to three (43.7% vs 42.8%) and four to six exacerbations (21.3% vs 20.7%), and a slightly lower percentage with seven to nine exacerbations (13.5% vs 15.7%). More than 8% of patients in each group had ten or more exacerbations. The cumulative effect was significantly lower annualized rates of any exacerbation (4.91 vs 5.78, $P < 0.05$) and moderate/severe exacerbation (1.32 vs 2.00, $P < 0.05$) in the FSC group. On average, patients in the FSC group had more days on treatment than patients in the salmeterol group (305.0 vs 274.4).

Unadjusted patient costs are presented in Table 4. While mean total costs of the FSC group, unadjusted for differing number of days on treatment, were $465 higher than costs in the salmeterol group ($2778 vs $2313, $P < 0.05$), the FSC group's unadjusted mean annualized total costs were $304 lower ($4,291 vs $4,596, $P < 0.05$), or 93% of the salmeterol group's costs.

Exacerbation rates and costs, adjusted

Mean adjusted annual rates for exacerbation events for each treatment group are shown in Table 5. The adjusted rates for any exacerbation and moderate/severe exacerbation are slightly lower than the unadjusted rates shown in Table 3. The adjusted annual rate of any exacerbation was 4.76 in the FSC group and 5.67 in the salmeterol group ($P < 0.001$); the adjusted annual rate of moderate/severe exacerbations was 1.10 in the FSC group and 1.58 in the salmeterol group ($P < 0.001$). Compared to salmeterol therapy, the relative risk for FSC therapy is 0.84 for any exacerbation and 0.70 for moderate/severe exacerbation (both $P < 0.001$). FSC

Table 3 Exacerbations (unadjusted) in patients receiving fluticasone propionate/salmeterol versus salmeterol therapy

	FSC group (N = 776)[a,b]	SAL group (N = 778)[a,b]
Patients with any exacerbation (mild, moderate, severe)	678 (87.4)	681 (87.5)
Patients with a moderate exacerbation	418 (53.9)	463 (59.5)
Patients with severe exacerbation	83 (10.7)	99 (12.7)
Patients with moderate/severe exacerbation	419 (54.0)	464 (59.6)
Treated with antibiotic	378 (48.7)	402 (51.7)
Treated with oral corticosteroid	311 (40.1)	363 (46.7)
Treated with hospitalization	83 (10.7)	99 (12.7)
Annual rate of any exacerbation per 100 patients, mean (SD)	4.91 (4.11)	5.78 (4.43)[c]
Annual rate of moderate/severe exacerbation per 100 patients, mean (SD)	1.32 (2.05)	2.00 (2.95)[c]
Days on treatment, mean (SD)	305.0 (110.6)	274.4 (132.7)
Number of exacerbations		
Patients with 0 exacerbations	98 (12.6)	97 (12.5)
Patients with 1–3 exacerbations	339 (43.7)	333 (42.8)
Patients with 4–6 exacerbations	165 (21.3)	161 (20.7)
Patients with 7–9 exacerbations	105 (13.5)	122 (15.7)
Patients with ≥10 exacerbations	69 (8.9)	65 (8.4)

Notes: [a]Exacerbation events and days on treatment are derived from data reported to US Food and Drug Administration in GlaxoSmithKline-sponsored clinical trials SCO40043 and SCO100250.[8,10] Exacerbation categories are not mutually exclusive. [b]Figures provided are N (%) unless otherwise indicated. [c]$P < 0.05$ for difference between rates, Wilcoxon rank sum test.

Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg.

therapy was also associated with lower relative risk for most components of exacerbation-related health care costs, with the exception of ED/UC visits ($P = 0.080$).

The percentages of patients using specific components of exacerbation-related health care are shown in Table 6. There was a significant difference between groups in use of total medical services (44.1% of FSC group vs 50.3% of salmeterol group, $P < 0.05$), but not for subcomponents of medical services. Mean predicted adjusted annual health care costs for COPD-related exacerbation events are shown in Table 7. Estimated annual total exacerbation and therapeutic costs were $4,842 (CI $4,731–$4,952) for the FSC group and $5,066 (CI $4,937–$5,195) for the salmeterol group. These adjusted cost estimates, while slightly different in absolute

Table 4 Unadjusted healthcare costs associated with COPD exacerbations in patients treated with fluticasone propionate/salmeterol versus salmeterol: pooled clinical trials data

Cost component	Cost in US dollars		
	FSC group, mean/median (SD) (N = 776)	SAL group, mean/median (SD) (N = 778)	Mean cost difference (FSC–SAL)
Exacerbation-related costs			
Total cost, any exacerbation (mild, moderate, severe)	1127/114 (2906)	1351/116 (3225)	–224[a]
Total cost, moderate exacerbation	243/114 (352)	301/116 (436)	–58[a]
UC visit	3.34/0 (21)	2.22/0 (16)	1.12
ED visit	75/0 (225)	107/0 (314)	–32
Office visits	73/0 (118)	89/0 (145)	–16
Antibiotic	90/0 (117)	101/0 (128)	–10
Oral corticosteroid	1.73/0 (3)	2.21/0 (3)	–0.48[a]
Total cost, severe exacerbation	884/0 (2683)	1050/0 (2938)	–166
Hospitalization	613/0 (2113)	859/0 (2532)	–246
ICU	271/0 (1813)	191/0 (1526)	80
Study medication costs	1651/2002 (643)	962/1307 (501)	689[a]
Total cost	2778/2024 (2919)	2313/1328 (3224)	465[a]
Total annualized cost	4291/2101 (11,027)	4596/1469 (13,042)	–304[a]

Notes: [a]$P < 0.05$, Wilcoxon rank sum test.

Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg; UC, urgent care; ER, emergency department; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

Table 5 Mean annual exacerbation rates and relative risks for maintenance therapy with fluticasone propionate/salmeterol versus salmeterol therapy

Exacerbation-related event	FSC Annualized adjusted exacerbation rates[a]	SAL Annualized adjusted exacerbation rates[a]	RR, FSC	*P*-value for RR[b]
Any exacerbation (mild, moderate, severe)	4.76	5.67	0.84	<0.001
Moderate/severe exacerbation	1.10	1.58	0.70	<0.001
Any medical service	1.30	2.11	0.62	<0.001
Office visit	1.63	2.15	0.76	<0.001
UC/ED visit	0.33	0.43	0.76	0.080
Hospitalization	0.12	0.18	0.69	0.017
Pharmacy				
Antibiotic course	0.93	1.20	0.78	<0.001
Oral corticosteroid course	0.74	1.17	0.64	<0.001

Notes: [a]Mean annual event rate from negative binomial regression models adjusting for treatment, investigator, COPD reversibility stratum, baseline COPD severity and time on treatment. [b]*P*-value based on χ^2 test.
Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg; RR, relative risk; UC, urgent care; ED, emergency department; COPD, chronic obstructive pulmonary disease.

value from unadjusted costs (Table 4), reflect a similar relationship between the two treatment groups.

Discussion

To our knowledge, this is the first economic evaluation to use efficacy data from randomized controlled clinical trials to estimate cost differences associated with FSC or salmeterol therapy for COPD treatment. The pooled clinical trial data showed that 87% of patients experienced some type of exacerbation, and exacerbation rates were lower in patients treated with FSC versus salmeterol. The economic evaluation demonstrates corollary cost benefits. On an annualized basis, maintenance therapy with FSC incurred significantly lower total health care costs than salmeterol, with reductions in medical costs more than offsetting the higher FSC pharmacy cost. In fact, annualized adjusted total pharmacy costs for FSC patients were lower than for salmeterol patients. Unadjusted annual total exacerbation and therapeutic costs associated with FSC were approximately 93% of those associated with salmeterol therapy. Predicted total costs associated with FSC after adjusting for treatment, investigator, COPD reversibility stratum, baseline disease severity and time on treatment, were 96% of those associated with salmeterol therapy. While cost-effectiveness ratios are often calculated in economic evaluations of clinical trials, in this case it was not necessary since both exacerbation-related medical and pharmacy costs were lower for FSC than for salmeterol therapy.

Retrospective studies of health care utilization have found that FSC is more cost-effective than ipratropium.[9,15,19] In addition, a cost-benefit study reported lifetime treatment with FSC or salmeterol was cost-effective compared to no treatment. Earnshaw et al calculated the incremental costs of FSC 500/50 therapy to be $33,865 per quality-adjusted-life-year-gained (QALY), substantially less than the $50,000 per QALY that is a benchmark against which many public health and medical interventions are evaluated.[21] Thus, both observational approaches and evaluation of actual clinical trial data confirm the effectiveness and cost benefit of FSC.

Exacerbation treatment is a large part of the cost of treating COPD patients, with ED visits and hospitalizations accounting for 70% of all COPD care.[22] In this economic analysis of clinical trial data, exacerbation costs were a lower percentage of costs. Several factors account for this, among them, selection bias of clinical trial participants, and the higher use of therapeutic medications (and thus higher medication costs). Exacerbation costs on an unadjusted basis were 64% ($1,262/$2,778) of total analyzed costs for the FSC group and 55% ($1,262/$2,313) for the salmeterol group.

Table 6 Patients incurring exacerbation-related healthcare costs with fluticasone propionate/salmeterol versus salmeterol therapy[a]

	FSC, N (%) (N = 776)	SAL, N (%) (N = 778)
Medical services	342 (44.1)	391 (50.3)[a]
Office visit	303 (39.0)	338 (43.4)[b]
UC/ED visit	98 (12.6)	104 (13.4)[b]
Hospitalization	83 (10.7)	99 (12.7)[b]
Pharmacy	776 (100)	778 (100)[b]

Notes: [a]$P < 0.05$, χ^2 test. [b]Differences between groups not significant at 0.05 level, χ^2 test.
Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg; ED, emergency department; UC, urgent care.

Table 7 Estimated annual health care costs associated with maintenance therapy with fluticasone propionate/salmeterol versus salmeterol

Cost component	Mean cost in US dollars[a]		
	FSC group, mean (95% CI)	SAL group, mean (95% CI)	Difference, FSC–SAL (95% CI[b])
Medical services	2699 (2612, 2786)	3959 (3820, 4098)	–1260 (–1454, –1068)
Office visit	102 (100, 104)	164 (161, 168)	–62 (–67, –57)
UC/ED visit	179 (174, 185)	317 (307, 327)	–138 (–152, –124)
Hospitalization	2492 (2403, 2580)	3455 (3324, 3587)	–964 (–1146, –778)
Pharmacy	1972 (1949, 1996)	1316 (1296, 1336)	657 (620, 694)
Total costs	4842 (4731, 4952)	5066 (4937, 5195)	–224 (–424, –31)

Notes: [a]Predicted mean annual costs from gamma regression models (including zero cost observations) adjusting for treatment, investigator, COPD reversibility stratum, baseline COPD severity, and time on treatment. [b]Bootstrapped 95% confidence intervals for difference between means.
Abbreviations: FSC, fluticasone propionate/salmeterol 250 μg/50 μg; SAL, salmeterol 50 μg; CI, confidence intervals; COPD, chronic obstructive pulmonary disease.

Tied to the large economic burden of exacerbation costs are tremendous quality of life issues. As Stanford et al point out, failure to prevent or treat acute exacerbations on an outpatient basis means patients return to the hospital repeatedly during their remaining years.[7] The Towards a Revolution in COPD Health (TORCH) survival study and other studies have shown that once an exacerbation occurs there is a decline in both lung function and quality of life.[5,6] Most recently, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study showed that improving maintenance therapy results in not just fewer exacerbations and hospitalizations, but significantly improved quality of life.[23] The prevention and treatment of exacerbations is therefore a singularly important goal of COPD management and a key component of clinical practice guidelines.[24,25]

Since both cost and quality of life issues are crucial to consider when evaluating a therapy's cost-effectiveness or determining a WTP threshold, the lower exacerbation rates and lower total health care costs associated with FSC compared to salmeterol therapy seen in this study, which occurred despite higher FSC drug costs, provide important information for decision-makers. This evaluation represents an initial foray into evaluating the costs associated with exacerbations and the economic benefits associated with a particular drug therapy, and further studies are needed to confirm these benefits. Typically, when an active treatment has substantial clinical advantages over the comparator but comes at a higher drug cost, cost-effectiveness (cost-utility) analyses using QALYs are considered. This provides outcomes in a metric of cost per QALY, or cost per exacerbation avoided. In this study, however, FSC was associated with significantly lower COPD-related exacerbation and therapeutic medical, pharmacy, and total costs compared to salmeterol after adjusting and annualizing costs.

This analysis has several advantages. The data used were from two year-long, well-controlled RCTs with identical protocols and definitions of exacerbations. We calculated not only predicted costs for the pooled sample (using multivariate regression with a log link and gamma distribution), but an adjusted exacerbation rate, lending additional rigor to the analysis. In addition, we calculated annualized exacerbation rates and costs to account for differential study withdrawal and lengths of follow-up. We controlled for the possibility that outliers might bias results towards one group by considering event-level health care utilization rather than person-level. We counted a hospitalization as a single event regardless of the length of stay and applied a standardized cost figure, since length of stay can be affected by additional complications that are unrelated to COPD or treatment arm. These methods give the study design strong internal validity. To a great extent, biases and limitations that routinely exist in the analysis of observational retrospective studies were avoided in this analysis.

Results from our analyses are only relevant to severe COPD patients and for patients using FSC and salmeterol. Other COPD medications such as tiotropium were not included as therapeutic agents in the trials. A limitation of this study is that we did not have access to actual health care charges, but assigned proxy unit costs to relevant health care utilization events based on cost estimates identified in prior research. Thus, the costs reported in this evaluation may be higher or lower than actual costs. This is a commonly encountered limitation in costing studies, particularly those using clinical trial data; however, we do not expect significant differences between our estimated costs and actual costs. We included protocol-driven office visits in the estimation of outpatient costs, and these occurred at a frequency during the

clinical trials that may not reflect the usual pattern of care in COPD. This may have led to overestimated costs, since fewer visits might have occurred if the trial had not taken place. This potential overestimation, however, probably affects both treatment groups equally. If the effect is unequal, cost overestimation is more likely to have occurred in the FSC group, since salmeterol patients experienced more exacerbations and some protocol-driven office visits would have substituted for visits that would have occurred if the trial had not taken place.

Conclusion

Compared to salmeterol monotherapy, FSC combination therapy provides significant clinical benefit through a reduction in exacerbations. This benefit is achieved at a relatively small additional drug cost and an overall savings in total COPD-related exacerbation and therapeutic health care costs. Because there is substantial room for improvement in the current management of COPD patients, the cost-benefit information provided by this analysis may be beneficial in evaluating COPD maintenance therapies against willingness-to-pay thresholds. Given the large impact of COPD exacerbations on patient quality of life, lung function, and the subsequent course of the disease, optimizing maintenance therapy in patients with severe COPD could have a large impact on patients' lives. Conversely, suboptimal management may not only adversely affect clinical outcomes, but increase the cost of care.

Acknowledgments

We thank Judith Hurley MS, who received payment from GlaxoSmithKline for medical writing services, and Susan Berry MSW, of Lovelace Respiratory Research Institute, for editorial assistance.

Financial disclosures

Dr Dalal is an employee of GlaxoSmithKline. Dr Blanchette and Dr St Charles have received research support from and served as consultants to: GlaxoSmithKline, AstraZeneca LP, Sepracor, Viostat, Wyeth, Schering-Plough, Premier, and NovoNordisk. Mr Petersen and Mrs Roberts have received research support from GlaxoSmithKline, AstraZeneca LP, Premier, and Wyeth. Ms Manavi-Zieverink is an employee of INC Research.

Funding

Financial support for this study was provided by GlaxoSmithKline.

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