Comparison of Prevalence, Cost, and Outcomes of a Combination of Salmeterol and Fluticasone Therapy to Common Asthma Treatments

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Objectives: To compare a combination of salmeterol and fluticasone with common asthma pharmacologic regimens used in real-world clinical practice, and to evaluate the associated costs and outcomes of care.

Study Design: Cross-sectional examination of medical and pharmacy claims.

Methods: The study population included 33,939 adult asthmatics (at least 12 years of age) continuously enrolled in 1 of 4 participating health plans for the 6-month study period. Every subject was in 1 of 10 different pharmacotherapy treatment groups. Univariate and multivariate analyses were used to compare the rates and costs of pharmaceutical prescriptions and medical care services between patients on salmeterol plus fluticasone and patients with other pharmacologic therapies.

Results: About 60.4% of the patients were on single controllers; the balance was on short-acting β_2-agonists alone (23%) or double controllers (16.8%). The average overall cost of asthma care was approximately $228 per patient over the 6 months of the study. Pharmaceutical cost was the major cost driver, which was significantly lower for single-controller (mean = $134) than for double-controller therapies (mean = $325). However, total costs were $50-$200 lower ($P < .029$) for patients on salmeterol plus fluticasone and inhaled steroids plus mast cell stabilizing agents than for those on other double controllers.

Conclusions: Single-controller regimens and short-acting β-agonists were less costly than double-controller regimens. Within the double-controller groups, salmeterol plus fluticasone appeared to be less costly than other double controllers, except inhaled steroids plus mast cell stabilizing agents.

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Asthma remains one of the most prevalent conditions—and one of the most important causes of preventable morbidity and mortality—in the United States. In 1999, an estimated 17 million Americans suffered from asthma[1]; collectively, asthmatics account for more than 1.8 million emergency department (ED) visits,[2] almost 500,000 inpatient admissions,[2] and an estimated $3.6 billion in direct medical costs annually.[3] Equally important, data suggest that the indirect costs of asthma (including the costs of lost time at work that these ED visits and inpatient stays represent) are nearly as large—in excess of $2.6 billion in 1990[3] and estimated to be rising.[4]

There is good evidence that high-quality care for patients with asthma leads to better outcomes, and that those better outcomes may be achieved at a lower cost.[5-7] Care directed at control of symptoms and progression of the underlying disease process can reduce rates of medication use for symptom relief, rates of ED presentation, and rates of inpatient utilization. These improvements, in turn, may mean both lower medical expenditures for asthma care and higher-functioning asthmatics. Thus, "investments" in the control of asthma may pay off considerably, both directly and indirectly.

The importance of pharmacologic therapy in the control of asthma has been well established, and current guidelines (eg, those of the National Asthma Education Program [NAEP][8]) emphasize the critical need for appropriate medication to manage acute

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symptoms and to establish longer-term control. The importance of long-term control—and of the timely and adequate use of long-term controller medication in patients with persistent disease—is especially well understood. What is not nearly so well understood is the relative effectiveness of various controller medications, particularly the effectiveness of those agents in settings outside of randomized controlled clinical trials. Whereas data from clinical trials are extremely valuable for establishing theoretical limits to the efficacy of a medication, those trials may overstate the actual effectiveness of some agents in everyday practice.

The objective of the present study was to examine the relative effectiveness of common therapeutic regimens for patients with asthma in real-world practice. In particular, we compared a combination of salmeterol and fluticasone with asthma pharmacologic regimens that are common in clinical practice, and evaluated the associated cost and outcomes of care.

··· METHODS ···

The study population was identified using medical claims and pharmacy databases. Selection criteria included identification as an asthmatic and assignment to a treatment group based on the number and type of prescriptions filled during the 6-month study. The pool from which the study population of asthmatics was drawn included all individuals at least 12 years of age as of January 31, 1999, who had been continuously enrolled in 1 of 4 participating, geographically dispersed health plans during the study period.

The 4 plans were wholly owned subsidiaries under Health Net, Inc. (formerly Foundation Health Systems, Inc.). Health Net, Inc. is one of the nation's largest publicly traded managed healthcare companies, and provides health benefits to approximately 5.3 million individuals in 16 states through group, individual, Medicare risk, Medicaid, and TRICARE programs. Health Net's subsidiaries offer managed healthcare services through their contracted providers or provider groups, but payment methods are different between the West Coast plan, in which most members have capitated contracts, and the other 3 plans, in which most participants have fee-for-service arrangements. Membership size differed considerably between the 4 health plans studied. The largest one was the plan on the West Coast, which covered more than 2 million members, followed by the Northeast plan with more than 1 million members, while the other 2 plans had a combined membership of more than 1 million in 1999.

The formulary structures for the 4 plans were similar, although the covered drugs differ somewhat. All the drugs on the recommended list, or formulary, had equal coverage, except that generic substitutes were mandatory if they were available. **Table 1** details how each of the drugs involved in this study was covered under the 4 plans during the study period.

Data from the plans on the West Coast and in the Northeast were from November 1998 through April 1999, and data from plans in the mid-Atlantic states and the Southeast were from July 1998 through December 1998. The time of the two 6-month periods did not correspond exactly because of a lack of data, but were assumed to be close enough to permit comparison and preclude secular trends in patient care.

Inclusion Criteria

Asthmatic subjects were identified through use of common asthma agents falling into the following classes of drugs: short-acting β_2-agonists, corticosteroids (CS), long-acting bronchodilators (LAB), methylxanthines, leukotriene modifiers (LM), and mast cell stabilizing agents (MCS). Table 1 depicts the class and generic names of all the asthma agents used to identify asthmatic subjects in this study. Only oral and inhaled preparations were included. Asthmatic subjects were identified as having a record of 1 or more of the following:

1. At least 1 medical claim with the *International Classification of Diseases, Ninth Revision, Clinical Modification*[9] (ICD-9-CM) code 493 (extrinsic asthma, allergic asthma, atopic asthma, occupational asthma)
2. At least 2 prescriptions for short-acting β_2-agonists, CS, LAB, LM, or MCS
3. At least 3 prescriptions for theophylline or other methylxanthines
4. At least 1 prescription for a CS preparation and at least 1 prescription for salmeterol.

Treatment groups comprised combinations of the above classes of drugs, and were created based on what the data and clinical experience suggested were the most common single- and double-controller regimens, as shown in **Table 2**. Patients in any of the single- or double-controller groups may also have been on concomitant short-acting β_2-agonist therapy.

Concurrently, we were interested in examining the role of the long-acting bronchodilator salmeterol in combination with fluticasone propionate, because the use of salmeterol and fluticasone in asthmatic patients not previously treated with CS has been found to be more effective than fluticasone or salmeterol alone for symptom control,[10] and more effective than budesonide alone for managing moderate to severe asthma.[11] The superior effects of double agents in comparison with single agents are not limited to salmeterol plus fluticasone. For example, it has been demonstrated that combining salmeterol with another corticosteroid, such as beclomethasone, is superior to high-dose beclomethasone alone in improving peak expiratory flows.[12] Nevertheless, several recent studies have focused specifically on comparing the combination of salmeterol and fluticasone with the combination of salmeterol and other inhaled CS,[13-17] although few studies have investigated the impact of the treatment combination on health services utilization and costs.

Exclusion Criteria

Patients with claims indicating treatment for chronic obstructive pulmonary disease (ICD-9-CM codes 490-492, 494-496, 500-519, and 748.4) during the study period were excluded. We also excluded from our analyses medication treatment groups with fewer than 0.5% of all patients because of their relative unimportance quantitatively. The

Table 1. Drug Names, Dosage Form, and Coverage in the 4 Health Plans

Treatment Class and Generic Name	Dosage Form	Formulary			
		West	Northeast	Mid-Atlantic	Southeast
Short-Acting β_2-Agonists					
Albuterol	Inhaled, Oral	Y	Y	Y	Y
Bitolterol mesylate	Inhaled	N	Y	N	Y
Ipratropium bromide;	Inhaled	Y	Y	Y	Y
Ipratropium bromide + albuterol		N	Y	N	N
Isoproterenol	Inhaled	N	Y	N	Y
Metaproterenol	Inhaled, Oral	Y	Y	N	Y
Pirbuterol	Inhaled	Y	Y	N	Y
Terbutaline sulfate	Inhaled, Oral	Y	Y	Y	Y
Corticosteroids					
Beclomethasone dipropionate	Inhaled	Y	Y	Y	Y
Budesonide	Inhaled	N	Y	Y	Y
Flunisolide	Inhaled	N	Y	N	Y
Fluticasone propionate	Inhaled	Y	Y	Y	Y
Triamcinolone acetonide	Inhaled, Oral	Y	Y	Y	Y
Long-Acting Bronchodilator					
Salmeterol xinafoate	Inhaled	Y	Y	Y	Y
Methylxanthines					
Dyphylline	Oral	N	Y	N	N
Theophylline	Oral	Y	Y	Y	Y
Theophylline + ephedrine + hydroxyzine	Oral	N	Y	N	N
Leukotriene Modifiers					
Montelukast	Oral	Y	Y	Y	N
Zafirlukast	Oral	N	Y	Y	N
Zileuton	Oral	N	Y	N	N
Mast Cell Stabilizers					
Cromolyn sodium	Inhaled, Oral	Y	Y	Y	Y
Nedocromil sodium	Inhaled	Y	Y	Y	Y

Y = drug was covered in the formulary; N = drug was not covered in the formulary.

largest excluded group (those on the combination of salmeterol plus xanthines; n = 171) was 40% smaller than the smallest included group (those on salmeterol plus leukotriene receptor antagonists [LRA]; n = 270), so there was a natural distinction between the size of the included and excluded groups. Patients with claims for 3 or more asthma drugs were excluded owing to their small numbers and because our methods did not permit us to ascertain whether they were on 3 concurrent medications or whether they had switched medications or regimens during the course of the study. Additionally, we excluded a relatively small group of individuals (accounting for 2.5% of the population) who were on infrequent, typically multidrug combination therapies we classified as "other." Because we created the treatment groups based on the most common combinations found in pharmacy claims data and made the above exclusions, the treatment groups for which analyses are presented do not represent every possible combination of the asthma drugs included in the study.

Outcomes Measurement

Asthma-related costs and medical service utilization were identified in outpatient, inpatient, ED, and pharmacy claims databases. Costs were defined as actual insurance-paid claims for any of the medications listed in Table 1 or services with ICD-9-CM code 493. Pharmacotherapy regimens were based on all separate, although not necessarily unique, pharmacy claims during the study period. For each treatment group, total asthma-related utilization and costs during the 6-month study period were evaluated in the following domains:

- Pharmacologic cost and utilization (number and cost of all prescriptions filled)
- Outpatient cost and utilization (visits per 1000 patients and associated cost)
- ED cost and utilization (visits per 1000 patients and associated cost)
- Inpatient hospital cost and utilization (admissions per 1000 patients and number of days per 1000 patients)
- Total cost (sum of above costs)

Table 2. Characteristics of the Study Cohort, by Medication Treatment Group

Treatment Group*	Number (%)	Age, years (Mean ± SD)	Sex (% Male)	Presence of Comorbidities† (%)
No Controllers				
Short-acting β_2-agonists	7762 (22.9%)	39.5 ± 19.2‡	42.8‡	36.6
Single Controllers				
Corticosteroids (CS)	17,243 (50.8%)	46.3 ± 16.0‡	40.8‡	44.4‡
Long-acting bronchodilators/xanthines	2282 (6.7%)	50.8 ±18.3‡	37.5	47.4‡
Leukotriene receptor antagonists (LRA)	961 (2.8%)	42.0 ± 17.4‡	38.0	45.3‡
Group total	20,486 (60.4%)	46.6 ± 16.4	40.3	44.8
Double Controllers				
CS (excluding fluticasone) + salmeterol	2511 (7.4%)	45.3 ± 17.0‡	39.0	41.3
CS + LRA	826 (2.4%)	43.6 ± 16.4	33.8	45.6‡
CS + xanthines	629 (1.9%)	54.1 ± 15.7‡	40.1	54.7‡
CS + mast cell stabilizing agents	488 (1.4%)	35.0 ± 17.7‡	37.7	33.4‡
Salmeterol + fluticasone	967 (2.9%)	43.8 ± 16.0	37.0	39.7
Salmeterol + LRA	270 (0.8%)	44.6 ± 16.4	34.4	44.8
Group total	5691 (16.8%)	44.8 ± 17.2	37.7	42.7
Grand Total	33,939	44.7 ± 17.4	40.4	42.5

*Patients in the single- and double-controller treatment groups may also have used short-acting β_2-agonists.
†Comorbidities include 1 or more of the following: cardiovascular disease, congestive heart failure, depression, diabetes, emphysema, hyperlipidemia, hypertension, or other respiratory conditions.
‡$P<.05$.
§$P<.01$.

The fundamental premise underlying these analyses posits that care for asthmatic patients can be considered to be directed toward 1 or another of 2 complementary objectives: long-term control of the underlying pathophysiology of the disease, and the remediation of acute symptoms in individuals whose disease is not sufficiently controlled. Long-term control is primarily outpatient care, comprising medication and routine outpatient visitation for monitoring, medication adjustment, and planned adjustments to therapy. Remediation of acute symptoms is primarily inpatient care, comprising ED visitation and hospitalization. Whereas remediation of acute symptoms is often used to measure treatment success/failure, the costs associated with long-term control were found to be the main cost driver in the data used for this study. Drugs associated with long-term control were therefore the focus of this study, although remediation of acute symptoms was analyzed to elucidate asthma treatment efficacy and to help us more fully understand the underlying cost structure for patients in different groups.

To validate the claims data and establish that asthma-related services were identified accurately, we compared claims data and medical record data estimates of rates of asthma-related office visits, ED visits, inpatient stays, and inpatient days. Rates of concordance were high for ED visits, inpatient stays, and inpatient days (rates of exact agreement were 94%, 98.1%, and 97.4%, respectively). Rates of concordance between estimates of outpatient visits for asthma were much lower. However, because outpatient visit was not a key outcome in our analysis, we did not adjust for this factor.

All outcomes were evaluated using data from all 4 participating health plans, except outcomes that depended on outpatient cost data. Outpatient care in the western region plan was capitated, so there were no cost data from this plan. As a result, estimates of those statistics that required outpatient cost data are based on data from the other 3 regional plans.

Statistical Analysis

Univariate analyses were used to examine the differences in age, sex, and comorbidities among patients in different treatment groups. Multivariate analyses including linear and logistic regressions were adopted to estimate the impact of different treatments on costs or utilization, controlling for age, sex, residential region, and comorbidities. Whereas the multiple linear regression coefficients were not reported because of space limitations, the statistical significance results presented for the differences in mean costs and utilization rates are those from the multivariate analyses. Statistical testing was conducted for each treatment group compared to the salmeterol plus fluticasone group. All statistical analyses were performed using SAS version 6.12 (SAS Institute, Cary, NC).

··· RESULTS ···

Characteristics of the Treatment Groups

The 10 treatment groups included in the analyses comprised 33,939 patients. Table 2 describes the distribution of these patients across those groups. The mean age of the population was 44.7 years (range 12-102 years), and there were significantly more women than men (59.6% and 40.4%, respectively). Nearly half (49.0%) were enrolled in health plans on the West Coast, 32.2% were in the Northeast, 15.1% were in the mid-Atlantic states, and 3.7% were in the Southeast. About 43% of patients had at least 1 comorbid condition; the most common comorbidity was depression (affecting approximately 20% of patients; data not shown).

More than half (60.4%) of the patients were on a single-controller regimen; the rest were on short-acting β_2-agonists alone (22.9%) or double-controller regimens (16.8%). The vast majority of patients on a single controller were on a regimen that included CS, and virtually all patients on 2 controllers were on a preparation containing CS.

As shown in Table 2, the differences of average age were significant between the salmeterol plus fluticasone group and many other groups. Patients on short-acting β_2-agonists alone, on a single-controller LRA, and on CS plus MCS were younger. However, total costs were $50-$200 lower for patients ($P < .029$), and patients on single-controller CS or LAB, CS plus salmeterol, or CS plus xanthines were older ($P < .019$), than those on salmeterol plus fluticasone. However, there was little difference in sex across the treatment groups. Only patients on short-acting β_2-agonists alone and those on a single-controller CS were more likely to be male than the salmeterol plus fluticasone group ($P < .021$). All the single-controller groups and those on CS plus LRA or CS plus xanthines were more likely, whereas patients on CS plus MCS were less likely, to have a comorbid condition than patients in the salmeterol plus fluticasone group.

Costs

Table 3 summarizes the asthma-related medical costs per patient by treatment group. The average cost of asthma care for all patients was approximately $228 during the 6 months of study. Most of that expense ($147, or about 64%) was drug cost, whereas most of the remainder ($50, or about 22%) was for outpatient care. Emergency department and inpatient care together accounted for just over 8% of the total.

Total asthma-related costs varied with the number of controller medications. Total costs were lowest for the short-acting β_2-agonist group ($125), higher for those on single controllers ($194), and highest for those on double-controller regimens ($460). Costs also varied significantly within a category: The average cost ranged from $173 to $353 for those on single-controller regimens, and from $360 to $561 for those on double-controller regimens. The primary driver of cost difference between the groups was drug cost, ranging from $51 for those in the short-acting β_2-agonist group to more than $380 in the LRA-containing combination therapy groups. The magnitude of differences between treatment groups was smaller for outpatient, ED, and inpatient costs.

Total asthma care cost (in 6 months) rose predictably with intensity of therapy. The lowest total cost of care was for the group of patients on short-acting β_2-agonists ($125), followed by those on single-controller regimens ($194). The highest total costs were for patients on double controllers ($460). Within the category of double controllers, the total asthma care costs for patients on salmeterol plus flu-

Table 3. Average Asthma-Related Costs in a 6-Month Period, by Medication Treatment Group

	Costs, $						
Treatment Group*	Pharmacy	Outpatient	Pharmacy + Outpatient	Emergency Department	Inpatient	Inpatient + Emergency Department	Total§
No Controllers							
Short-acting β_2-agonists	51.48 ± 62.81†	46.97 ± 129.77†	102.89 ± 143.36†	11.57 ± 92.16	8.48 ± 217.76	20.05 ± 241.49	124.98 ± 315.70†
Single Controllers							
Corticosteroids (CS)	127.60 ± 102.27†	28.72 ± 111.02†	164.20 ± 156.36†	3.17 ± 50.79‡	4.60 ± 130.69	7.77 ± 146.40‡	173.44 ± 236.96†
Long-acting bronchodilators/xanthines	145.75 ± 115.70†	68.96 ± 162.56	217.60 ± 204.76†	11.88 ± 100.75	25.04 ± 439.63	36.92 ± 450.37	245.88 ± 358.96†
Leukotriene receptor antagonists (LRA)	214.34 ± 141.69†	91.44 ± 195.46	301.74 ± 233.25†	10.95 ± 67.07	40.52 ± 503.58	51.47 ± 514.65	353.27 ± 537.27†
Group average	133.69 ± 107.64	37.56 ± 126.63	179.44 ± 172.58	4.54 ± 59.44	8.72 ± 221.20	13.26 ± 232.98	193.68 ± 288.96
Double Controllers							
CS (excluding fluticasone) + salmeterol	352.21 ± 216.96†	87.26 ± 181.18	452.92 ± 298.41†	10.66 ± 91.01	16.02 ±228.47	26.67 ± 259.02	460.30 ± 444.98†
CS + LRA	385.72 ± 253.42†	121.80 ± 219.05†	500.79 ± 336.51†	10.48 ± 77.45	36.07 ± 406.54	46.56 ± 420.36	560.84 ± 627.42†
CS + xanthines	316.58 ± 240.64‡	89.73 ± 227.35	419.64 ± 353.99†	6.97 ± 85.44	61.16 ± 734.11†	68.13 ± 747.29†	455.24 ± 744.05‡
CS + mast cell stabilizing agents (MCS)	261.03 ± 202.71†	83.77 ± 207.98	352.10 ± 277.22	4.02 ± 40.79	0 ± 0	4.02 ± 40.79	359.72 ± 297.72
Salmeterol + fluticasone	297.07 ± 211.34	80.58 ± 197.66	381.61 ± 301.34	8.94 ± 76.18	20.93 ± 256.02	29.87 ± 271.32	408.63 ± 401.90
Salmeterol + LRA	382.79 ± 196.46†	118.37 ± 179.59†	488.81 ± 298.28†	22.72 ± 98.54†	32.31 ± 247.50	55.03 ± 294.81	537.08 ± 392.01†
Group average	325.48 ± 224.89	92.83 ± 198.67	424.47 ± 312.59	9.94 ± 83.03	24.06 ± 343.01	34.01 ± 361.38	460.13 ± 496.04
Global Average	147.05 ± 154.63	50.01 ± 145.06	208.41 ± 228.44	7.05 ± 72.35	11.43 ± 247.03	18.49 ± 262.65	228.41 ± 361.52

Statistical significance results are from multivariate regressions controlling for age, sex, region, and comorbidities.
*Patients in the single- and double-controller treatment groups may also have used short-acting β_2-agonists.
†$P<.01$.
‡$P<.05$.
§Due to missing data, the total is not necessarily an exact sum of subcategories.

ticasone ($409) were $50 to $150 lower ($P < .029$) than costs for all other double-controller regimens—with the exception of those on the combination of CS plus MCS ($360). The cost difference between salmeterol plus fluticasone group and CS plus MCS group was not statistically different.

The primary driver of cost was the pharmaceuticals, even after adjusting for age, sex, region, and comorbidities. Drug costs were significantly lower for those on short-acting β_2-agonists only and single-controller regimens, and significantly higher for those on other double-controller therapies. Compared with the salmeterol plus fluticasone group, for example, average pharmaceutical costs were more than $200 lower for patients on short-acting β_2-agonist only ($P < .001$), but between $20 and $89 higher for patients on other double-controller regimens ($P < .013$) except CS plus MCS. These differences appeared to drive the differences in total cost.

The average outpatient costs in the 6-month study period were about $50 and varied depending on the treatment groups. The lowest outpatient costs were found in the group with single controllers ($38), followed by the short-acting or no-controller group ($47), whereas the highest outpatient cost belonged to the group with double controllers ($93). Within the double-controller group, the salmeterol plus fluticasone group was associated with the lowest outpatient costs ($81), significantly lower ($P < .006$) than the costs for the group of CS plus LRA ($122) and the group of salmeterol plus LRA ($118), but similar to the costs of the other 3 groups—salmeterol plus CS ($87), CS plus xanthines ($90), and CS plus MCS ($84).

In terms of ED and inpatient costs, the differences across the treatment groups were usually small and had no statistical significance, with 3 exceptions: 1) The ED costs of the single controller, CS ($3), were significantly lower ($P < .034$); 2) the ED costs of the salmeterol plus LRA group ($23) were higher ($P < .091$) than the ED costs of the salmeterol plus fluticasone group; and 3) the inpatient costs of the CS plus xanthines group were higher ($P < .002$) than the inpatient costs of the salmeterol plus fluticasone group.

Utilization of Services

Table 4 describes the nature of the asthma-related care delivered to the study population over the 6 months studied. On average, asthmatic patients received 4.3 prescriptions for asthma medications. The rate of filling prescriptions per patient increased predictably as the intensity of the therapy increased, from about 3 for those on no controllers to almost 4 for those on single controllers and nearly 8 for those on double controllers. There was considerable variation within the double-controller group, with rates of prescription ranging from about 6.3 per person for those on salmeterol plus fluticasone to more than 10 per person for those on CS plus xanthines.

On average, the rate of outpatient visits for asthma care was 574 per 1000 patients during the 6-month study. Rates of outpatient visit varied less, both between and within groups. Patients on single or no controllers averaged 430 and 600 outpatient visits per 1000, respectively, whereas patients on double controllers averaged 1008 visits per 1000. The rates of outpatient visit were significantly lower for patients on salmeterol plus fluticasone (839 visits per 1000) or CS plus MCS (860 visits per 1000) than for those on any double controllers (from 970 to 1430 visits per 1000, $P < .017$), although the difference between these 2 groups was not significant.

Rates of ED visits and inpatient use for the care of asthma were low. For every 1000 patients, an average of 19 ED visits, 3.7 hospitalizations, and 10 hospital days to treat asthma were recorded during the 6-month study. As a group, patients treated with short-acting β_2-agonists alone had the highest rate of ED visits, 32 per 1000, whereas patients on single controllers as a group had the lowest rate, 12 per 1000. Rates of hospital use were comparable among patients on no or single controllers, and higher among those on double controllers. The rate of ED visits for patients treated with the combination of CS plus MCS were consistently lower than the rates for any of the other groups. Moreover, hospitalization rates in this group were zero; they were nonzero in all other groups. Rates of ED visit, hospitalization, and hospital days for patients on salmeterol plus fluticasone were around the middle level among the 6 groups of double controllers, and the differences of rates were not statistically significant in most of the comparisons.

··· DISCUSSION ···

The management of asthma continues to be a major issue in the United States, as prevalence of the disease rises, new therapeutic alternatives become available, and gaps in the application of current knowledge to current practice become more evident. We believe that a better understanding of current practice—and assessment of the real-world effectiveness of variations in practice—can help to improve asthma management.

This study probed the impact of different pharmacotherapies on the utilization and costs of medical services, and analyzed the costs of the drug or drug combinations. Drug cost analysis has often been ignored in the literature. Many researchers have studied the economic impact of alternative therapeutic treatments, separating the drug cost from the medical cost,[11,18] a method that does not indicate whether a more costly drug saves on the total cost or just the medical care cost. By merging the drug and medical cost data, this study found that more costly drugs or drug combinations do not necessarily decrease the total costs.

By identifying the prescriptions used during a 6-month period in a population of managed care enrollees with asthma, we found that, although many pharmaceutical regimens are used to treat asthma in adults, more than 80% of asthmatics were on 1 of the 10 most common regimens. Not surprisingly, most patients in the study were prescribed CS, either alone or in combination with other medications. A significant number of asthmatic patients were prescribed short-acting β_2-agonist therapy alone. We presume that additional agents would be added to inhaled steroids if patients responded incompletely to inhaled steroids alone. Per-person total costs were $125 and $194 for patients in the categories of no controllers and single controllers, respectively, totals that were far below that for patients in the category of double controllers ($460). In addition, patients on single controllers had only 430 visits per 1000 population during the 6 months, far fewer than any other treatment group, including the no-controller group (600 visits). These results suggest that single controllers probably comprise the most cost-effective treatment for the right patients. Nonetheless, the higher rates of ED use and hospitalization in most treatment groups of single or no controllers, in combination with published reports suggesting that many asthmatics who should be using inhaled anti-inflammatory agents are not,[19-21] suggest the potential that some of these patients are undertreated.

This study identified 6 common double-controller combinations, 5 of which were combinations of steroids and other agents, and one that was a combination of LRA plus salmeterol. The drug costs for these treatment combinations varied significantly. Among the 6 double-controller combinations, 2 (flu-

Table 4. Average Asthma-Related Utilization During a 6-Month Period, by Medication Treatment Group

Treatment Group*	Prescriptions Filled (n)	Outpatient Visits (per 1000)	Emergency Department Visits (per 1000)	Inpatient Admission (per 1000)
No Controllers				
Short-acting β_2-agonists	3.1 ± 2.4†	600 ± 1260†	32 ± 191	2.7 ± 52.2‡
Single Controllers				
Corticosteroids (CS)	3.5 ± 2.5†	350 ± 1080†	8 ± 104‡	1.7 ± 41.3†
Long-acting bronchodilators/xanthines	6.0 ± 4.1†	820 ± 1320	31 ± 193‡	7.2 ± 96.9
Leukotriene receptor antagonists (LRA)	5.3 ± 3.5†	1020 ± 1700†	37 ± 200	8.5 ± 92.0
Group average	3.9 ± 2.9	430 ± 1170	12 ± 124	2.7 ± 54.0
Double Controllers				
CS (excluding fluticasone) + salmeterol	7.4 ± 4.3†	970 ± 1590‡	23 ± 169	6.3 ± 79.4
CS + LRA	8.4 ± 4.7†	1250 ± 1840†	26 ± 169	8.4 ± 91.1
CS + xanthines	10.4 ± 5.8†	1090 ± 1780†	20 ± 179	16.2 ± 167
CS + mast cell stabilizing agents	6.4.± 4.3	860 ± 1700	13 ± 135	0 ± 0†
Salmeterol + fluticasone	6.3 ± 3.9	839 ± 1735	22 ± 159	9.3 ± 96.1
Salmeterol + LRA	8.8 ± 4.7‡	1430 ± 1980†	85 ± 338†	17.9 ± 133
Group average	7.7 ± 4.7	1008 ± 1712	25 ± 178	8.3 ± 97.2
Global Average	4.3 ± 3.5	574 ± 1319	19 ± 151	3.7 ± 63.7

Statistical significance results are from multivariate regressions controlling for age, sex,region, and comorbidities.
*Patients in the single- and double-controller treatment groups may also have been using short-acting β_2-agonists.
†$P<.01$.
‡$P<.05$.

ticasone plus salmeterol, CS plus MCS) were associated with significantly lower costs. Adjusting for group composition, direct medical costs for patients on these drugs were $50 to $200 lower per person during the 6 months of the study than comparable costs for patients on other double controllers. These figures represent a significant proportion of the total cost for asthma care—from 20% to 40%, depending on the specific group. These cost differences are due at least in part to differences in expenditures for pharmaceuticals; drug costs are lower for these 2 drug combinations than for any of the other 4.

The 2 treatment groups (fluticasone plus salmeterol, CS plus MCS) also had lower outpatient costs than other double-controller groups, probably because of lower rates of physician visits in these 2 groups (far below 900 visits per 1000 patients) than the rates in other groups (970-1430 visits per 1000 patients). Although some asthmatic patients will require more services that are intensive no matter how high the quality of care they receive, in many cases a visit to the physician's office is a signal that efforts to control the disease have been inadequate. To the extent that this is so, these costs (and the services that underlie them) are undesirable because they are indications of care marked by inadequate control.

Because pharmacy and outpatient care are the main cost drivers (91% of the total costs), savings on pharmacy and outpatient services associated with fluticasone plus salmeterol or CS plus MCS were reflected in total treatment costs for those combinations, which were $50 to $200 lower than for treatment with other double controllers. The cost analyses above suggest that these 2 double-controller combinations controlled the overall costs significantly better than did other regimens, suggesting differences in treatment effectiveness and efficiency.

Further, this variation suggests that there are important differences in outcomes, consideration of which could lead to improvements in care for many asthmatic patients. This finding forces consideration of the meaning of the lower costs, and lower rates of service use, for outpatient care associated with the combinations of salmeterol plus fluticasone and CS plus MCS. These treatment combinations suggest better outcomes—and therefore significantly higher value. These combinations can be provided not only without additional expenditures for the routine care (pharmaceutical and outpatient monitoring) needed to accomplish disease control, but with further reductions in those costs as well compared with other double controllers.

It is possible, of course, that the differences in cost and use that we observed were signals not of better outcome but of lower pretreatment disease severity. However, there is no reason a priori to believe that physicians would be inclined to assign lower-risk patients to the salmeterol plus fluticasone or CS plus MCS group. It is also unlikely that physicians would opt to treat lower-risk patients with one specific CS plus salmeterol combination (ie, salmeterol plus fluticasone) and to treat higher-risk patients with others. There are also empirical reasons to believe that we have not merely observed the effects of otherwise invisible differences in case mix. Although patients in the CS plus MCS group were significantly younger—and had fewer comorbidities—than those in the other double-controller groups, this was not true for those on the combination of salmeterol and fluticasone.

Preliminary research has indicated that combining salmeterol and an inhaled CS such as fluticasone or beclomethasone has advantages for symptom control in comparison with using a single inhaled corticosteroid,[22-24] but no efforts have been made to compare alternative combinations, ie, salmeterol plus fluticasone with salmeterol plus azmacort or budesonide or other CS. This study compared the cost of the combination of salmeterol plus fluticasone with those of salmeterol combined with other CS. The results revealed that treatment with salmeterol plus fluticasone costs less than treatment with salmeterol plus other steroids. Further studies are needed to compare the effects on costs and utilization of the combination of salmeterol plus fluticasone with salmeterol plus other individual CS such as azmacort or budesonide.

Our data provide only a 6-month snapshot of patient care in a managed care environment, and carry some other limitations as well. For example, African Americans appear to have higher asthma prevalence[25] and mortality,[26] and racial disparity exists in primary care access.[27] Unfortunately, we were unable to control for this potential confounding factor in this study, because race/ethnicity information was not available in the claims data. Moreover, no clinical information on asthma severity or duration was available except for comorbidities, nor were outcomes data other than those measured by healthcare utilization. In terms of medication usage, we used the number of prescriptions filled but could not assess drug compliance. This lack of information could limit our conclusions because differences in compliance could have influenced drug effectiveness. Further, the asthma med-

ications available to prescribing physicians could have been restricted to those available on a health plan's formulary.

These preliminary results show that different drug regimens are associated with measurable differences in outcomes, taken as a comprehensive view of a patient's pharmaceutical, outpatient, inpatient, and emergency service utilization. These differences represent a real public health impact, given the pervasiveness of asthma, its large medical and social costs, and considering that the indirect costs associated with asthma may be nearly as large as the direct costs.[3] Consideration of these indirect elements of value might even justify the incremental expenditures that might be incurred by moving patients from single-controller regimens (which are typically associated with lower total treatment costs) to one or the other of the double-controller regimens. These findings should certainly add enthusiasm for selecting the combination of fluticasone plus salmeterol or CS plus MCS when a patient continues to be symptomatic on a single-controller regimen or on another double-controller combination.

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