Adherence and persistence with fluticasone propionate/salmeterol combination therapy

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Background: Pharmacy database medication refill studies provide a panoramic view of medication-taking behavior in patients nationally.

Objective: To investigate fluticasone propionate/salmeterol combination (FSC) adherence, including the factors associated with refill adherence in a large national pharmacy database.

Methods: Adherence and persistence were documented for 12 months from date of initial FSC prescription in 5504 patients who filled their medication at a nationwide pharmacy chain.

Results: On average, patients filled enough medication to cover 22.2% of days. More than half the patients filled a 30-day prescription only once over the 1-year interval. Higher adherence levels were associated with being male, being older than 35 years, having a comorbid disorder, a having a copay of $1.01 to $10, previous β_2-agonist use, and a prescription for higher-dose FSC.

Conclusion: This pharmacy database study portrays medication adherence levels to be considerably lower than those reported in most clinical trials, suggests that most adults taking FSC obtain a single fill before abandoning their controller medication, and indicates a need for a reappraisal of current treatment guidelines and educational strategies for both providers and patients.

Clinical implications: For many patients, filling of a controller medication is markedly discrepant with practice guidelines. Reappraisal of both the guidelines and strategies to implement them is in order. (J Allergy Clin Immunol 2006;118:899-904.)

Key words: *Asthma, chronic obstructive pulmonary disease, adherence, persistence, fluticasone propionate, salmeterol, inhaled corticosteroid*

Abbreviations used
FSC: Fluticasone propionate/salmeterol combination
ICS: Inhaled corticosteroid

In all parts of the world and across chronic conditions, medication nonadherence contributes to treatment failure.[1] Full recognition of the fact that patients may take far less medication than their physicians prescribe came only after the development of microchip-equipped medication-tracking devices, allowing documentation of the actual times and dates during which patients interacted with their metered dose inhalers. These reports also revealed that patient self-reporting greatly overestimated adherence. One of the earliest studies to use electronic monitoring found that all 19 adults with asthma reported on diary cards using their controller medication on a majority of study days, yet examination of recorded data revealed that only half did so.[2] In a study of children with asthma, mothers reported giving almost 90% of the prescribed inhaled corticosteroid (ICS) to their children, whereas electronic monitoring revealed that only about half the medicine had been discharged from the inhaler.[3]

The enormity of the nonadherence problem is better recognized through studies examining pharmacy prescription databases, which provide a panoramic view of adherence behavior in much larger groups of patients than previously had been studied through clinical trials. Although examination of refill records cannot provide information about daily medication use, it does produce epidemiologic evidence of the degree to which patients accept and obtain controller medications. Such prescription database information also introduces the concept of *persistence* (continued refills of medication over time) as a complement to the commonly used term *adherence* (average daily medication obtained). Although the 2 measures are correlated, persistence typically accounts for behavior over a long period, whereas adherence is used to typify daily behavior over periods of time as short as 2 weeks.[4] These studies have the additional important advantage of reflecting patient behavior in a variety of clinical practice settings, in contrast with a clinical trial setting.

The unique contribution of pharmacy database studies is seen in the valuable information they reveal. For example, one study demonstrated that patients requiring antihypertensive medication were less likely to persist in refilling angiotensin II antagonist prescriptions than other treatments.[5] Another study showed that of patients receiving statin therapy, 32% discontinued treatment within 1 year;

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discontinuation was inversely related to an increase in the number of concurrent medications.[6] In a study of patients with asthma, pharmacy prescription records indicated that medication adherence with oral corticosteroids and ICSs increased only briefly after an emergency department visit.[7] Adherence to ICSs was shown to be approximately 50% in a large health maintenance organization, with a significant association between decreasing ICS refills and increasing OCS requirements and emergency department visits.[8] In another patient database study, the use of a fluticasone/salmeterol combination (FSC) in a single device improved the rate of refill persistence.[9] FSC contains the most frequently prescribed ICS in the United States along with a long-acting β_2 agonist. FSC is commonly prescribed for moderate to severe persistent asthma, and in some cases of chronic obstructive pulmonary disease. The objective of our study was to investigate FSC adherence patterns, including the factors associated with refill discontinuation, in a large national pharmacy database.

METHODS

Data in this retrospective cohort study of medication adherence and persistence were obtained from blind computerized pharmacy records of a national pharmacy chain, representing more than 1200 community pharmacies nationwide. Data contained prescription drug activity for all of the prescriptions filled at this national chain for each individual patient regardless of health care plan. Diagnosis information was not included in the database. A total of 5504 patients filled initial FSC prescription between April 1, 2003, and September 30, 2003. The index date was defined as the date on which a patient's first FSC prescription was filled.

Patients were presumed to be new to therapy if they had no history of any respiratory medication (mAbs, leukotriene receptor antagonists, inhaled steroids, long-acting β_2-agonists, xanthine derivatives) use (except for β_2 agonists) within 6 months before the index date. Patients with an FSC prescription but no prescribed refills in the index script and β_2-agonist use in the 12-month period were excluded from the sample. Patients' adherence and persistence were evaluated for 1 year after the index date.

In the database population, 93.9% of all patients had a 30-day supply for the index fill, and 95.9% of all patients had a prescribed daily dose of 200 μg (100 μg fluticasone/50 μg salmeterol, twice a day) or 500 μg (250 μg fluticasone/50 μg salmeterol, twice a day) for the index fill. To make the sample more homogenous and facilitate interpretation, the study cohort was restricted to patients with a 30-day index supply of a daily dose of 200 μg or 500 μg. The number of refills prescribed was an independent predictor of adherence. The analyses were adjusted for this variable.

Statistical analysis

The analysis strategy encompassed both adherence and persistence. Both measures are presented because average daily refill pick-up and duration of refill pick-up provide different perspectives on patient medication refill behavior. For example, patients who obtained medication consistently for 6 months and then stopped refilling would present with the same level of adherence over the 1-year period as patients who picked up half their medication every day for 12 months, yet the implications of these behaviors for disease control are likely quite different. Finally, although persistence is a direct measure of frequency of refilling, adherence carries a supposition that filled medication is being taken. Given that some patients may not use all of the medicine filled, adherence estimates are conservative, and actual nonadherence is likely even a greater problem than reflected in these data.

Adherence

Cumulative drug obtained (total days supply) during the 1-year follow-up period was used as the measure of adherence. This outcome represents an example of count data. The distribution of counts is discrete and limited to nonnegative values, and as a result is skewed to the right. Such data are usually well described by a negative binomial distribution. Consequently, the multivariate generalized linear model with a negative binomial distribution and log-link function[10] was used to determine the significant predictors for the adherence outcome. Total days supply obtained was divided by the number of days in the evaluation period and multiplied by 100 to obtain the proportion of medication obtained, or percentage adherence.

Persistence

Persistence was expressed as the proportion of patients who continued FSC treatment for 1 year. A persistence value of 0.1 would mean that 10% of the patients continued treatment for 1 year and that 90% discontinued treatment. Kaplan-Meier estimates of survival (persistence) curves[10] were used to assess the time to discontinuation and to calculate the 1-year rate of discontinuation. Patients were regarded as discontinued if they had a gap of 90 days or more between 2 consecutive refills, switched to another drug, or completely stopped therapy during the evaluation period. Time to therapy discontinuation was calculated as the number of days from the index date to the date the FSC supply was exhausted preceding the gap of more than 90 days. Patients who did not discontinue FSC 365 days after the index date were censored. The multivariate Cox proportional hazard model[11] was used to identify significant predictors of persistence. Proportional hazard assumptions were tested and met for each covariate in the final model.

Covariates

The following covariates were included in all regression models: age, gender, region, copay amount, index daily dose, number of refills prescribed for the index script, presence of β_2-agonist prescription in the 6-month preindex period, and number of prescriptions for comorbid conditions obtained during the 6-month preindex period. Patient age was calculated as of the index prescription fill date. Because of a strong nonlinear relationship between the adherence outcome and continuous predictors, for modeling purposes, age and copay amount were transformed into categorical variables on the basis of the following group definitions age, <12, 13-20, 21-35, 36-55, 56-70, >70; and copay amount, <$1, $1.01-$10.00, $10.01-$20.00, $20.01-$100.00, >$100.00. Descriptive statistics were used to determine the frequencies of various baseline patient characteristics. A 2-sided P value of <0.05 was considered to indicate statistical significance. All analyses were performed by using the MS Windows–based SAS v 9.13 software system (SAS Institute, Cary, NC).

RESULTS

A total of 5504 patients were included in the study. Of these patients, 2349 (42.7%) were prescribed the 200 μg dose, and 3155 (57.3%) were prescribed the 500 μg dose. The distribution of patient demographic characteristics is seen in Table I. Patients' ages ranged from 5 to 96 years (mean ± SD, 54.0 ± 22.0), and 60.2% of the patients

TABLE I. Demographic and other baseline characteristics of the 200 and 500 dose cohorts

	Daily dose		
	200 μg N = 2349	500 μg N = 3155	All patients N = 5504
	N (%)		
Age (y)			
≤12	218 (9.3)	55 (1.7)	273 (5.0)
13-20	277 (11.8)	146 (4.6)	423 (7.7)
21-35	213 (9.1)	230 (7.3)	443 (8.1)
36-55	597 (25.4)	820 (26.0)	1417 (25.7)
56-70	33 (22.7)	944 (29.9)	1477 (26.8)
71+	511 (21.7)	960 (30.5)	1471 (26.7)
Sex			
Female	1406 (59.9)	1907 (60.4)	3313 (60.2)
Male	943 (40.1)	1248 (39.6)	2191 (39.8)
Region*			
Northeastern	259 (11.0)	318 (10.1)	577 (10.5)
Midwestern	830 (35.3)	1229 (38.9)	2059 (37.4)
Southern	938 (40.0)	1219 (38.7)	2157 (39.2)
Western	322 (13.7)	389 (12.3)	711 (12.9)
Previous β_2-agonist			
No	2125 (90.5)	2877 (91.2)	5002 (90.9)
Yes	224 (9.5)	278 (8.8)	502 (9.1)
Refills prescribed			
1	284 (12.1)	344 (10.9)	628 (11.4)
2	332 (14.1)	400 (12.7)	732 (13.3)
3	484 (20.7)	619 (19.6)	1103 (20.0)
4-5	494 (21.0)	693 (22.0)	1187 (21.6)
6+	755 (32.1)	1099 (34.8)	1854 (33.7)
Copay			
≤$1	416 (17.7)	522 (16.6)	938 (17.0)
$1-$10	398 (16.9)	673 (21.3)	1071 (19.5)
$10-$20	635 (27.0)	734 (23.3)	1369 (24.9)
$20-$100	645 (27.5)	805 (25.5)	1450 (26.3)
$100+	255 (10.9)	421 (13.3)	676 (12.3)
Other drugs†			
0	1440 (61.3)	1703 (54.0)	3143 (57.1)
1	278 (11.8)	417 (13.2)	695 (12.6)
2+	631 (26.9)	1035 (32.8)	1666 (30.3)

*Northeastern states include Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; midwestern states include Iowa, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, North Dakota, Ohio, South Dakota, and Wisconsin; southern states include Alabama, Arkanasas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, D.C., and West Virginia; and western states include Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming.
†Number of nonasthma medications obtained during the 6-month preindex period.

were female. Pharmacy databases do not include information on patient race. In this study, race was estimated on the basis of zip codes from US Census data. Of the patients included in this study, 94% came from zip codes that were predominantly white, and 3% came from zip codes that were predominantly black. When included in the models, probable race did not alter findings and was not a significant predictor of adherence or persistence.

TABLE II. Mean days supply at 12 months by risk factors

Parameter	Value	N	Mean (SD) days	% Adherence
Age (y)	≤12	273	69.0 (60.3)	18.9
	13-20	423	57.9 (50.7)	15.8
	21-35	443	58.2 (55.2)	15.9
	36-55	1417	75.5 (73.0)	20.7
	56-70	1477	88.9 (85.5)	24.4
	>70	1471	94.2 (88.7)	25.8
Sex	Female	3313	78.3 (75.1)	21.4
	Male	2191	85.2 (84.0)	23.3
Region*	Northeastern	577	85.9 (83.8)	23.5
	Midwestern	2059	84.5 (82.3)	23.1
	Southern	2157	77.1 (74.8)	21.1
	Western	711	78.9 (78.9)	21.6
Previous β_2-agonist	No	5002	80.4 (78.5)	22.0
	Yes	502	87.5 (81.8)	24.0
Refills prescribed	1	628	58.6 (55.8)	16.0
	2	732	69.9 (67.0)	19.2
	3	1103	79.2 (76.1)	21.7
	4-5	1187	90.8 (85.6)	24.9
	6+	1854	87.8 (84.7)	24.1
Copay	≤$1	938	78.9 (76.3)	21.6
	$1-$10	1071	89.5 (84.4)	24.5
	$10-$20	1369	78.5 (75.3)	21.5
	$20-$100	1450	78.1 (77.7)	21.4
	>$100	676	82.0 (81.9)	22.5
Other drugs	0	3143	74.7 (74.0)	20.5
	1	695	82.6 (78.7)	22.6
	2+	1666	92.4 (86.1)	25.3
Daily dose	200 μg	2349	77.1 (74.4)	21.1
	500 μg	3155	83.9 (81.9)	23.0

*Northeastern states include Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; midwestern states include Iowa, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, North Dakota, Ohio, South Dakota, and Wisconsin; southern states include Alabama, Arkanasas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, D.C., and West Virginia; and western states include Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming.

Adherence

Adherence averaged 22.2% across all 5504 patients. Adherence data across different patient and medication characteristics are summarized in Table II. The relationship of percent medication obtained to the covariates was evaluated within the generalized linear model. Age, sex, copay, number of prescriptions for comorbid conditions in the preindex period, previous β_2-agonist prescription presence, and number of refills prescribed were each significant within this model.

Patient characteristics

Younger patients filled fewer days of medication than did older patients. Patients between 13 and 35 years of age filled the least medication compared with the groups older than

TABLE III. Results of generalized linear model for cumulative drug consumption

Parameter	Level	Estimate	SE	*P* value
Intercept		4.413	0.050	<.001
Age (y)	≤12	−0.290	0.055	<.001
	13-20	−0.490	0.047	<.001
	21-35	−0.461	0.044	<.001
	36-55	−0.221	0.031	<.001
	56-70	−0.072	0.029	.014
	>70	0.000		
Sex	Female	−0.099	0.022	<.001
	Male	0.000		
Region*	Midwestern	0.047	0.034	.166
	Northeastern	0.081	0.043	.062
	Southern	−0.041	0.033	.220
	Western	0.000		
Previous β_2-agonist	1	0.159	0.036	<.001
	0	0.000	0.000	
Refills prescribed		0.024	0.003	<.001
Copay	<$1	0.134	0.041	.001
	$1.1-$10	0.161	0.039	<.001
	$10.1-$20	0.113	0.038	.003
	$20.1-$100	0.082	0.037	.029
	>$100	0.000		
Other drugs	0	−0.093	0.025	<.001
	1	−0.073	0.035	.037
	2+	0.000		
Daily dose	200 μg	−0.020	0.022	.355
	500 μg	0.000		

*Northeastern states include Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; midwestern states include Iowa, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, North Dakota, Ohio, South Dakota, and Wisconsin; southern states include Alabama, Arkanasas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, D.C., and West Virginia; and western states include Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming.

36 years. Male patients obtained slightly more medication than female patients. Patients from western states obtained the least medication, whereas those from northeastern states obtained the most medication (Tables II and III).

Medication characteristics

The lower-dose fluticasone/salmeterol combination (200 μg) was associated with fewer days supply of medication obtained over a period of 12 months than the higher dose (500 μg; Table II). Patients with copays in the $1.01 to $10 range had higher adherence compared with patients in other copay categories. Patients with copays in the $20 to $100 range had the lowest adherence. The presence of a β_2-agonist prescription in the 6-month period before initiation of an FSC prescription was associated with a greater day supply of medication obtained. Finally, patients obtained a greater number of days supply of FSC when also receiving prescriptions for comorbid conditions (Tables II and III).

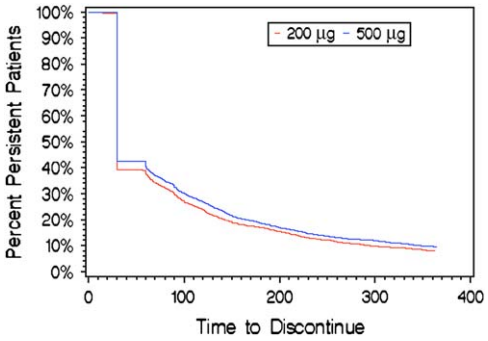

FIG 1. Kaplan-Meier survival curves for discontinuation related to dose. Patients were regarded as discontinued if they had a gap of 90 days or more without sufficient medication. Patients on FSC 500 μg were more persistent than those on 200 μg.

Persistence

Fig 1 includes a Kaplan-Meier survival curve for FSC 200 μg and 500 μg where discontinuation of medication refill is the outcome event. Of the 5504 patients receiving an initial fill for FSC, 58.9% never filled the prescription again over a 12-month period. By the year's end, only 8.8% of patients had continued to refill their prescription. Persistence was associated with age, sex, copay, number of prescriptions for comorbid conditions, and previous β_2-agonist prescription presence in the preindex period, previous β_2-agonist prescription presence, and number of refills prescribed, although in each instance differences were small (Table IV). Older patients were more persistent than younger ones. Patients 13 to 20 years old had a hazard ratio of 1.473 or a 47.3% greater risk to discontinue in the 12-month interval than adults older than 70 years. Women had a 9.2% higher risk of discontinuation than men. Patients on FSC 500 μg appeared to be more persistent than those on 200 μg, but the difference was not statistically significant (Table IV; Fig 1). Patients who had not filled a prescription for a β_2 agonist in the previous 6 months were 12.5% more likely to discontinue their FSC therapy than patients who had filled a β_2-agonist prescription in the previous 6 months (Table IV). Persistence was greater as the number of prescribed refills increased, with the rate of 1.9% per refill. Persistence was slightly greater when the copay was between $1.01 and $10 and decreased at higher copay and copay $1 or under. Persistence with FSC medications increased when patients were also receiving prescriptions for comorbid conditions. The administrative database cannot establish that all patients had received prescription renewals sufficient to carry them through the 12-month study evaluation period. An assumption was made that patients included in the 1-year persistence analysis had a chronic disease requiring continuous daily treatment. If this assumption were not true, then qualitatively different persistency curves would be expected for patients with high and low numbers of refills prescribed. The proportional hazard model indicates that persistence gradually improved as the number of prescribed refills increased, but the persistence curves for

those with more than 6 refills had an indistinguishable shape compared with those of patients with index prescription of 6 or fewer refills, with the curve for the group with high refills prescribed slightly shifted upward (data not shown).

DISCUSSION

In this study, adult patients on a new prescription for FSC obtained remarkably little of their controller medication. On average, the adherence rate to FSC therapy was only 8.8% over the 1-year period, and the majority of patients filled their prescription only once. The discrepancy between current FSC therapy guidelines and patient behavior is enormous and indicates a need for careful re-evaluation of treatment strategies. Efforts to educate patients and providers about the importance of daily controller medication have been substantial. The National Asthma Education and Prevention Program, created within the National Heart, Lung, and Blood Institute, has dedicated a decade of research to improving the adherence of physicians and patients to these guidelines.[11] The data presented here suggest that most patients are not using controller medications consistently with these guidelines.

Several medication and patient characteristics appear to influence medication refill behavior. Results emerging from both data analytic strategies, characterizing adherence and persistence, were similar. However, none of these variables accounted for much variance in refill behavior, and all groups remained largely nonadherent. The association seen here between lower medication cost and greater adherence has also been observed in patients with diabetes[12] and cardiac diseases.[13,14] Older patients and male patients were slightly more likely to fill an FSC prescription. Although no clinical data were available, indirect evidence suggests that patients with more severe symptoms may have been more adherent. Patients on higher-dose FSC, with a previous β_2-agonist prescription, or with comorbid conditions filled more medication, likely a reflection of experiencing more troubling symptoms and perceiving greater need for a controller medication. The fact that many patients prefer to take controller medication only during symptomatic periods is well established.[15] Similarly, patients without a recent β_2-agonist history and those with fewer available refills may represent patients with less severity and less motivation to take controller medication. The fact that a large number of patients who did not receive a recent β_2-agonist prescription were placed directly on a combination ICS/long-acting β_2-agonist should raise additional concern about physician adherence to treatment guidelines. One explanation could be that the group of patients on FSC without a recent β_2-agonist history might have included some patients with acute bronchitis and not chronic asthma or chronic obstructive pulmonary disease. However, this is unlikely, because patients with a single-use FSC prescription and patients with β_2-agonist monotherapy were removed from the analysis.

TABLE IV. Results of proportional hazard model for 1-year risk of discontinuation

Parameter	Level	Hazard ratio	Hazard ratio LCL	Hazard ratio UCL	*P* value
Age (y)	≤12	1.278	1.111	1.470	.001
	13-20	1.473	1.307	1.660	<.001
	21-35	1.451	1.295	1.625	<.001
	36-55	1.204	1.113	1.303	<.001
	56-70	1.057	0.981	1.140	.144
	>70	0.000			
Sex	F	1.092	1.034	1.154	.002
	M	0.000			
Region*	Midwestern	0.964	0.884	1.050	.398
	Northeastern	0.924	0.826	1.032	.161
	Southern	1.033	0.948	1.125	.457
	Western	0.000			
Previous β_2-agonist	Yes	0.875	0.798	0.961	.005
	No	0.000			
Refills prescribed		0.981	0.973	0.988	<.001
Copay	≤$1	0.898	0.809	0.997	.044
	$1-$10	0.871	0.789	0.962	.006
	$10-$20	0.914	0.828	1.008	.072
	$20-$100	0.935	0.849	1.029	.169
	>$100	0.000			
Other drugs	0	1.080	1.012	1.152	.020
	1	1.062	0.971	1.161	.191
	2+	0.000			
Daily dose	200 μg	1.017	0.963	1.075	.542
	500 μg	0.000			

LCL, Lower confidence limit; *UCL,* upper confidence limit.
*Northeastern states include Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont; midwestern states include Iowa, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, North Dakota, Ohio, South Dakota, and Wisconsin; southern states include Alabama, Arkanasas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, Washington, D.C., and West Virginia; and western states include Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, and Wyoming.

Limitations in this study necessitate caution when generalizing findings but also suggest the importance of additional large studies. Pharmacy prescription data provide an estimate of adherence, but may overestimate adherence when patients obtain but do not use medication, or when they refill medication that has been lost or has expired. Some patients assumed to have discontinued may have been stepped down from FSC or changed to another medication. The deidentified database came from a large national retail pharmacy chain and therefore could not be linked to clinical information in patient records and does not allow us to include other variables, including socioeconomic characteristics and coinsurance. Although the selected chain is nationwide and reasonably representative of the population, refill behavior within this chain may not represent that in all pharmacy chains. Some patients may have obtained subsequent prescriptions from other pharmacy chains, although evidence exists to suggest that this

practice is limited to less than 0.5% of patients transferring out of an individual chain (unpublished data, Adheris Inc., November 2005-January 2006).[16] Although refill renewals cannot be verified from this pharmacy database, it is assumed that healthcare providers continued to renew prescriptions once the initial allotted refills were obtained. This assumption is supported by the finding that persistence patterns were similar for those patients whose initial FSC prescription included higher and lower numbers of refills.

In summary, patients were more likely to continue filling their FSC controller medication if they were older and male with lower medication copays, another chronic medical condition, and moderate-to-severe symptoms. Even when these adherence-positive factors were present, remarkably little controller medication was filled and available to meet a daily medication treatment plan. It remains unclear whether this deficit is attributable to physician nonadherence to treatment guidelines or patient nonadherence to their physicians' instructions, but these results suggest that reappraisal of both the guidelines and strategies to implement them is in order.

REFERENCES

1. WHO. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
2. Spector S, Kinsman R, Mawhinney H, Siegel SC, Rachelefsky GS, Katz RM, et al. Compliance of patients with asthma with an experimental aerosolized medication: implications for controlled clinical trials. J Allergy Clin Immunol 1986;77:65-70.
3. Bender B, Wamboldt FS, O'Connor SL, Rand C, Szefler S, Milgrom H, et al. Measurement of children's asthma medication adherence by self report, mother report, canister weight, and Doser CT. Ann Allergy Asthma Immunol 2000;85:416-21.
4. Krishnan J, Riekert K, McCoy J, Stewart D, Rand C. Corticosteroid use after hospital discharge among high-risk adults with asthma. Am J Respir Crit Care Med 2004;170:1281-5.
5. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther 1998;20:671-81.
6. Grant RW, O'Leary KM, Weilburg JB, Singer DE, Meigs JB. Impact of concurrent medication use on statin adherence and refill persistence. Arch Intern Med 2004;164:2343-8.
7. Stempel DA, Roberts CS, Stanford RH. Treatment patterns in the months prior to and after asthma-related emergency department visit. Chest 2004; 126:75-80.
8. Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. J Allergy Clin Immunol 2004;114: 1288-93.
9. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. J Allergy Clin Immunol 2004;113:245-51.
10. McCullagh P, Nelder JA. Generalized linear models. London: Chapman and Hall; 1989.
11. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer-Verlag; 1997.
12. Apter A, Boston R, George M, Norfleet AL, Tenhave T, Coyne JC, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. J Allergy Clin Immunol 2003; 111:1219-26.
13. Bauman LJ, Wright E, Leickly FE, Crain E, Kruszon-Moran D, Wade SL, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. Pediatrics 2002;110:1-7.
14. Beausoleil J, Weldon D, McGeady S. B2Agonist metered dose inhaler overuse: psychological and demographic profiles. Pediatrics 1997;99:40-3.
15. Barr R, Somers S, Speizer F, Camargo CJ. Patient factors and medication guideline adherence among older women with asthma. Arch Intern Med 2002;162:1761-8.
16. Mail-order prescriptions again show strongest growth. Drug Benefit Trends 2003;15:4.