Poor disease control among insured users of high-dose combination therapy for asthma

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ABSTRACT

Adherence to asthma treatment may not completely prevent exacerbations. Clinical trial results indicate that many highly adherent asthma patients still have symptoms. Little is known about the level of control achieved by adherent patients outside clinical trials. This study was designed to evaluate the extent of asthma control among insured patients who were highly adherent to combination controller therapy. We used an administrative claims database for this cohort study of patients aged 12–64 years. Patients were newly treated with fluticasone, 500 micrograms/salmeterol, 50 micrograms, between January 1, 2003 and June 30, 2004. Patients were stratified according to adherence levels: low (<50%), moderate (50–74%), and high (≥75%). We compared rates of poor control. A logistic regression model was used to control for baseline differences. Among 3357 patients, the mean age was 40.5 ± 13.6 years, and 64.1% were women. Sixty-one percent had low adherence, 20% had moderate adherence, and 19% had high adherence. Highly adherent patients were older, and more used fluticasone, 250 micrograms/salmeterol, 50 micrograms, during the preindex period than the other groups. Even after starting high-dose fluticasone/salmeterol, many patients with low, moderate, and high adherence had indicators of poor symptom control (28.9% [587/2030], 30.6% [209/682], and 30.7% [198/645], respectively). Patients who were highly adherent and used additional controller medications had rates of poor control that ranged from 23.1 to 31.2%. After adjusting for age, gender, and baseline characteristics, results were similar. Many patients continue to have poor asthma control despite being adherent to high-dose combination therapy or using additional controller medications.

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Key words: Adherence, adherence levels, administrative claims, compliance, control, controller medications, fluticasone/salmeterol, high-dose combination therapy, moderate-to-severe persistent asthma, outcomes

Asthma affects 15–20 million individuals in the United States and costs >$15 billion/year to treat.[1] Updated guidelines from The National Heart, Lung, and Blood Institute focus on improving control of asthma symptoms through the stepwise use of prescription medications.[2] The Joint Council of Allergy, Asthma, and Immunology Practice Parameters Task Force published a practice parameter that also emphasized the importance of achieving control of asthma symptoms, in part through appropriate prescribing of "controller" medications.[3] Other aspects of asthma management that can encourage well-controlled asthma include adherence with avoidance measures and appropriate treatment of comorbid conditions (*e.g.*, chronic sinusitis and gastroesophageal reflux). Asthma control includes two components: impairment and future risk. Impairment comprises the frequency and intensity of symptoms and patients' current or recent physical limitations. Risk comprises potential for asthma exacerbations, decline in lung development or function, and medication-related adverse events.[2]

The implication of this focus on medication use to improve control is that if patients adhere to their treatment regimens, most will be able to control their symptoms. Because up to one-half of patients who are receiving long-term asthma treatment do not take medications appropriately, improving adherence has been the focus of many studies.[4–7] However, several investigators have shown that adherence to treatment may not completely prevent exacerbations.[8–10]

Little is known about the level of asthma control achieved by adherent patients outside the highly controlled setting of clinical trials. In this study, administrative claims were used to investigate the extent of asthma control achieved in practice among patients treated with high-dose combination inhaled corticosteroid (ICS)/long-acting β-agonist (LABA) inhalers who had varying

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levels of adherence to their medication regimens; these claims were specifically used to determine if good adherence led to adequate asthma control.

PATIENTS AND METHODS

Study Design and Data Source

This was a cohort study evaluating markers of poor asthma control among patients with varying levels of adherence to controller medications. Pharmacy and medical utilization claims from 2002 to 2005 were reviewed for commercially insured patients with asthma. The study was completed using a Health Insurance Portability and Accountability Act–compliant administrative claims database of 8–10 million covered lives and was exempt from review by a Human Subjects Committee. Claims included information on each physician visit, medical procedure, hospitalization, dispensed drug, and performed test. Member enrollment and benefit information as well as limited patient, provider, and hospital demographic information were also available. All major regions of the United States were represented.

Patient Selection

Identified patients were 12–64 years old and were newly treated with fluticasone, 500 μg/salmeterol, 50 μg, during a 18-month identification period (January 1, 2003, through June 30, 2004). This was the only combination ICS/LABA inhaler marketed in the United States during the study. New use of fluticasone, 500 μg/salmeterol, 50 μg, served to identify a group with somewhat similar disease severity because at that dosage it is used to treat moderate-to-severe persistent asthma.[2,11] For the same reason, patients who were receiving high-dose combination therapy had to have evidence of controller use in the year before the index date. That is, we excluded those whose first identified controller was high-dose combination therapy because these patients may have differed systematically in their disease severity from our target population.

Other methods of identifying moderate-to-severe asthma patients required clinical data not in the database or were confounded by the outcomes of interest (use of services and additional controller medications). The date of the first claim for fluticasone, 500 μg/salmeterol, 50 μg, during this period was the index date, and the year following this date was defined as the study year. Patients who had any pharmacy claims for this dosage during the year before the index date were excluded. Patients had to be enrolled in their health plans continuously for 1 year before and 1 year after the index date.

Asthma diagnosis was confirmed by one or more medical claims with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for asthma (493.xx) and at least one preindex claim for an asthma controller medication other than fluticasone, 500 μg/salmeterol, 50 μg (*e.g.*, ICSs, LABA inhalers, and leukotriene receptor antagonists [LTRAs]). Medications were identified using National Drug Codes. Patients were excluded if they had any claims with ICD-9-CM codes for chronic obstructive pulmonary disease (491.xx, 492.xx, or 496.xx) or if they had claims with a National Drug Code or Health Care Common Procedure Coding System J code[12] for omalizumab, because patients who used this medication may have had more severe disease.

Descriptive Variables

Baseline variables (measured in the preindex year) included demographic characteristics, asthma medication use, and asthma-related medical use. There were no indicators of socioeconomic status or race/ethnicity available. To describe concomitant controller medication use, we used six nonexclusive categories: fluticasone, 250 μg/salmeterol, 50 μg; fluticasone, 100 μg/salmeterol, 50 μg; ICSs plus LABAs as separate inhalers; ICSs plus LTRAs; ICSs only; and other controller medications (LTRAs or LABAs alone or in combination, but without ICSs or fluticasone/salmeterol).

Outcome and Stratification Variables

The main outcome measure was poor disease control in the postindex year, defined as one or more claims for emergency department (ED) visits or hospitalizations where asthma was the first diagnosis, six or more pharmacy claims for short-acting β-agonists (SABAs), or two or more pharmacy claims for oral corticosteroids (OCSs). These outcomes have been used in a variety of studies as markers of poor control and correlate with patient-centered measures of disease.[13–17] Clinical indicators of disease severity or control such as decreased peak expiratory flow rate or forced expiratory volume in 1 second were not available.

Patients were grouped according to fluticasone, 500 μg/salmeterol, 50 μg, adherence levels in the postindex year. Using a published approach, the "days' supply" was used to determine adherence.[18] Total therapy days for each patient were determined by summing the days' supply for all fluticasone, 500 μg/salmeterol, 50 μg, fills, truncating fills beyond the end of the study year. Adherence was calculated as the percentage of total therapy days divided by 365. For example, if the sum of the days' supply for all fluticasone, 500 μg/salmeterol, 50 μg, fills was 365 and the time frame of interest was 365 days, adherence equaled 100%. Each patient's adherence was categorized using the designations low (<50%), moderate (50–74%), and high (≥75%).[19]

Analysis

We reported descriptive statistics for baseline characteristics and compared the proportion of patients with poor control in each of the adherence cohorts. A subset of patients used controller medications other than fluticasone/salmeterol during the postindex period, which may have affected disease control. We reported proportions of patients with poor control among the subset who used additional controllers and stratified these by adherence. For continuous variables, values are presented as means with standard deviations (SDs). For categorical variables, numbers of patients with metrics of interest are accompanied by percentages. To compare outcomes between the adherence groups, Pearson's chi-squared test was used for categorical variables and the *F* test was used for continuous variables.

Patient characteristics differed across cohorts, so a logistic regression model was used to adjust for baseline differences. The model adjusted for the following variables from the preindex period: age (as a continuous variable) and gender, any asthma-related ED visit, any asthma-related hospitalization, two or more OCS fills, and six or more SABA fills (as dichotomous variables). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported for logistic regression results. All reported *p* values are two-sided with a 0.05 significance level. All data transformations and statistical analyses were done using SAS Version 9.1 (SAS Institute, Cary, NC).

RESULTS

We identified 17,405 patients treated with high-dose fluticasone/salmeterol. After excluding those with chronic obstructive pulmonary disease, users of omalizumab, and those without continuous enrollment during the study year and the prior year, we had 6959 patients. We further excluded 2492 patients who were continuing, rather than new, users of fluticasone, 500 μg/salmeterol, 50 μg, and 578 patients who were not 12–65 years old. An additional 1110 patients had not used asthma controller medications in the year before beginning high-dose combination therapy and were excluded, leaving 3357 patients in the final study group (Fig. 1).

Study patients had a mean age of 40.5 ± 13.6 years and 64.1% were women ($n = 2151$). Patients used a variety of medication regimens before starting fluticasone, 500 μg/salmeterol, 50 μg. The most common were fluticasone, 250 μg/salmeterol, 50 μg, used by 50.3% ($n = 1688$), and ICSs alone, used by 14.0% ($n = 470$). During the preindex period, 37.1% ($n = 1245$) had poor disease control. Sixteen percent ($n = 536$) had two or more OCS fills, 13.5% ($n = 453$) had six or more SABA fills, 12.4% ($n = 416$) had an asthma-related ED visit, and 8.2% ($n = 274$) had an asthma-related hospitalization (Table 1).

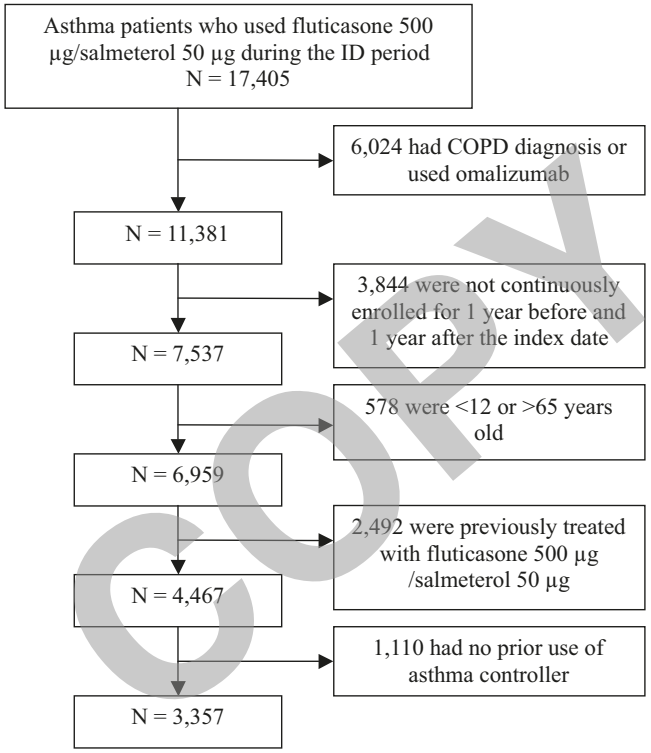

Figure 1. *Selection of asthma patients who used fluticasone, 500 μg/salmeterol, 50 μg, during the identification (ID) period.*

During the preindex period, 60.5% ($n = 2030$) of patients had low adherence, 20.3% ($n = 682$) had moderate adherence, and 19.2% ($n = 645$) had high adherence. The low-adherence group had a mean age of 38.8 years, the moderate-adherence group had a mean age of 42.3 years, and the high-adherence group had a mean age of 44.0 years. A higher proportion of patients in the low-adherence group were women, and more patients in the low-adherence group used ICSs only before initiating combination therapy. Evidence of poor control in the preindex year was highest in the moderate-adherence group (Table 1).

Before adjustment for baseline differences, 29.6% of patients (994/3357) met at least one criterion for poor control in the postindex period, compared with 37.1% ($n = 1245$) in the preindex period, an absolute decrease of 7.5% ($p < 0.0001$; not shown). In an unadjusted analysis, an equal number of patients in all adherence cohorts had some evidence of poor control (Table 2). Highly adherent patients had fewer asthma-related hospitalizations than the other two groups ($p = 0.004$). The other components of poor control were similar across groups.

A subgroup of patients in each adherence group used additional controller medications besides high-dose fluticasone/salmeterol. In the high-adherence group, 63.1% used LTRAs, 44.0% used ICSs, and

Table 1 **Baseline characteristics of 3357 insured asthma patients by adherence level**

	Adherence* Level			All Adherence Levels $n = 3357$
	<50%	50–74%	≥75%	
	No. of Patients (%)			
	$n = 2,030$ (60.5%)	$n = 682$ (20.3%)	$n = 645$ (19.2%)	
Mean age, yr (SD)	38.8 (14.0)	42.3 (12.7)	44.0 (12.5)	40.5 (13.6)
Age (yr)				
12–24	402 (19.8)	76 (11.1)	55 (8.5)	533 (15.9)
25–34	306 (15.1)	92 (13.5)	83 (12.9)	481 (14.3)
35–44	509 (25.1)	185 (27.1)	164 (25.4)	858 (25.6)
45–54	533 (26.3)	209 (30.6)	201 (31.2)	943 (28.1)
55–64	280 (13.8)	120 (17.6)	142 (22.0)	542 (16.1)
Gender—female	1339 (66.0)	414 (60.7)	398 (61.7)	2151 (64.1)
Preindex medication use				
Fluticasone/salmeterol, 100/50 μg	199 (9.8)	60 (8.8)	44 (6.8)	303 (9.0)
Fluticasone/salmeterol, 250/50 μg	957 (47.1)	362 (53.1)	369 (57.2)	1688 (50.3)
ICS + LABA	80 (3.9)	53 (7.8)	47 (7.3)	180 (5.4)
ICS + LTRA	118 (5.8)	45 (6.6)	35 (5.4)	198 (5.9)
ICS only	340 (16.7)	79 (11.6)	51 (7.9)	470 (14.0)
Other controllers	336 (16.6)	83 (12.2)	99 (15.3)	518 (15.4)
Preindex poor disease control				
Any poor control indicator	731 (36.0)	273 (40.0)	241 (37.4)	1245 (37.1)
≥2 OCS fills	320 (15.8)	107 (15.7)	109 (16.9)	536 (16.0)
≥6 SABA fills	228 (11.2)	115 (16.9)	110 (17.1)	453 (13.5)
Asthma-related ED visits	269 (13.3)	86 (12.6)	61 (9.5)	416 (12.4)
Asthma-related hospitalizations	170 (8.4)	60 (8.8)	44 (6.8)	274 (8.2)

**Defined as days' supply for all fluticasone, 500 μg/salmeterol 50 μg, fills/365.*
ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β-agonist.

Table 2 **Unadjusted proportion of insured asthma patients with poor disease control by adherence level***

Postindex Poor Disease Control	Adherence Level			*p* Value	All Adherence Levels $n \geq 3357$
	<50%*	50–74%	≥75%		
	No. of Patients (%)				
	$n = 2,030$ (60.5%)	$n = 682$ (20.3%)	$n = 645$ (19.2%)		
Any poor control indicator	587 (28.9)	209 (30.6)	198 (30.7)	0.553	994 (29.6)
≥2 OCS fills	237 (11.7)	90 (13.2)	95 (14.7)	0.108	422 (12.6)
≥6 SABA fills	205 (10.1)	61 (8.9)	79 (12.2)	0.129	345 (10.3)
Asthma-related ED visits	186 (9.2)	64 (9.4)	50 (7.8)	0.495	300 (8.9)
Asthma-related hospitalizations	145 (7.1)	48 (7.0)	23 (3.6)	0.004	216 (6.4)

**Patients may have had more than one poor control indicator.*
ED = emergency department; OCS = oral corticosteroid; SABA = short-acting β-agonist.

2.0% used LABAs. Among these highly adherent fluticasone/salmeterol users who used additional controller medications, many still had at least one indicator of poor control. The pattern of persistent lack of control despite the use of high-dose fluticasone/salmeterol and additional control medications

was consistent across all adherence groups: about one-third of all patients who used additional controller medications had at least one indicator of poor control (Table 3).

There were baseline differences between adherence cohorts, so a logistic regression model was used to adjust for age, gender, and preindex evidence of poor control (asthma-related ED visits and hospitalizations, six or more SABA fills, and two or more OCS fills). Adjusted results were consistent with unadjusted ones. The OR for any evidence of poor control was 1.0 for the comparison of the low- to high-adherence group (95% CI, 0.8, 1.2) and for the comparison of the moderate to high group (95% CI, 0.8, 1.3). For each comparison, the lower adherence group had twice the odds of an asthma-related hospitalization as the higher group (Table 4).

DISCUSSION

The burden of asthma on affected individuals and society is enormous and rightly commands the attention of health professionals and policy makers.[20–26] Despite clinical care guidelines for asthma, many patients' asthma remains poorly controlled and adverse outcomes are common. This study showed that nearly one-third of asthma patients highly adherent to high-dose fluticasone/salmeterol therapy still had evidence of poor control. Even among the subset of highly adherent patients who used additional controller medication, rates of poor control were high.

Outcomes differed across adherence groups, with higher hospitalization rates for asthma in both adjusted and unadjusted analyses for patients who were not highly adherent to their medication. Use of controller medications has been shown to reduce use of health care services[27,28]; however, our study showed that poor control, as reflected in overreliance on "reliever" medications (SABAs and/or OCSs), is not infrequent in patients receiving combination controller therapy (including high-dose ICSs) despite patterns of medication adherence.

We found no other studies in a typical care setting examining rates of poor control among adherent patients, but adherence is usually high in randomized controlled trials (RCTs), and RCTs have shown rates of poor control similar to ours. One such study compared the efficacy of fluticasone propionate and salmeterol/fluticasone in achieving totally and well-controlled asthma.[8] Among 3421 uncontrolled asthma patients studied, treatment was stepped up until total control was achieved or until the patient was receiving the maximum 1000-μg/day dose of corticosteroids. At the conclusion of the 1-year trial, 41% of patients in one group and 29% in the other still did not have well-controlled asthma.

Findings were similar in an RCT of combination therapy with budesonide/formoterol, where 48–57% of the patients still had at least one asthma exacerbation during a 12-week period despite up to 90 days of treatment.[9] The continued evidence of poor control despite adherence to treatment does not appear to be restricted to patients with moderate-to-severe asthma. In a trial of a variety of treatment regimens for patients with mild persistent asthma, adherence was 90–100%, but after 16 weeks of therapy as many as one-third of patients had at least one indicator of poor control.[8]

There are many reasons why highly adherent patients may not experience complete control. Therapy may be prescribed at inadequate doses, and adherence with an inappropriate regimen should not be expected to control disease. Medications may be given with poor instructions, or patients may not understand proper use (leading to poor technique or inappropriate use).[11] It is also possible that the highly adherent patients we studied who were treated with high-dose combination therapy actually needed more aggressive treatment with additional medications or other nonmedication interventions.

Despite optimal medication adherence, poor control may persist because of a variety of factors including (but not limited to) lack of aeroallergen avoidance, presence of comorbid conditions or psychosocial issues, or an erroneous diagnosis of asthma.[3] The current findings provide further support for the The National Heart, Lung, and Blood Institute guideline, which suggests that asthma patients, even highly adherent ones, should be aggressively managed if they show evidence of poor control.

Our study examined a large population in a naturalistic setting; we used logistic regression to control for baseline differences among groups, but the study had limitations. One definition of adherence is "the extent to which … behavior … corresponds with … recommendations from a health care provider,"[29] and claims data provide no direct evidence of physicians' recommendations. We used the approach of measuring days of medication supplied as a proxy for prescription information. If a patient filled their prescription but did not use their medication, they would be counted as adherent. It would be difficult for patients to be more adherent than was estimated in this study (they would have to purchase medication without requesting reimbursement or use medication samples frequently). There is no reason to suspect that these behaviors would occur at different rates among the various adherence groups. Studies have found that although prescription claims are imperfect, they generally reflect actual medication use[30–32] and are adequate for computing adherence.[33]

Administrative claims lack clinical information needed to group patients with asthma by symptom

Table 3 **Unadjusted poor disease control among insured asthma patients using high-dose fluticasone/salmeterol and other controllers***

	Adherence Level											
	<50%			50–74%			≥75%			All		
	Additional Controller Medication											
	ICSs (n = 755)	LABAs (n = 12)	LTRAs (n = 1044)	ICSs (n = 296)	LABAs (n = 16)	LTRAs (n = 394)	ICSs (n = 284)	LABAs (n = 13)	LTRAs (n = 407)	ICSs (n = 1335)	LABAs (n = 141)	LTRAs (n = 1845)
Any poor control indicator	229 (30.3)	43 (38.4)	355 (34.0)	101 (34.1)	5 (31.3)	137 (34.8)	81 (28.5)	3 (23.1)	127 (31.2)	411 (30.8)	51 (36.2)	619 (33.6)
≥2 OCS fills	109 (14.4)	26 (23.2)	158 (15.1)	52 (17.6)	4 (25.0)	62 (15.7)	43 (15.1)	1 (7.7)	64 (15.7)	204 (15.3)	31 (22.0)	284 (15.4)
≥6 SABA fills	59 (7.8)	13 (11.6)	125 (12.0)	18 (6.1)	0 (0.0)	34 (8.6)	29 (10.2)	0 (0.0)	50 (12.3)	106 (7.9)	13 (9.2)	209 (11.3)
Asthma-related ED visits	71 (9.4)	12 (10.7)	99 (9.5)	39 (13.2)	3 (18.8)	45 (11.4)	22 (7.7)	0 (0.0)	37 (9.1)	132 (9.9)	15 (10.6)	181 (9.8)
Asthma-related hospitalizations	56 (7.4)	7 (6.3)	93 (8.9)	23 (7.8)	1 (6.3)	34 (8.6)	12 (4.2)	2 (15.4)	13 (3.2)	91 (6.8)	10 (7.1)	140 (7.6)

**Patients may have used more than one type of additional controller medication.*
ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β-agonist.

Table 4 **Adjusted* odds ratios (OR) of poor disease control among insured asthma patients by adherence level**

	Adherence Level	
	<50% vs ≥75% OR (95% CI)	**50–74% vs ≥75% OR (95% CI)**
Poor disease control		
Any poor control indicator	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)
≥2 OCS fills	0.8 (0.6, 1.1)	0.9 (0.7, 1.3)
≥6 SABA fills	1.1 (0.8, 1.6)	0.6 (0.4, 0.9)
Asthma-related ED visits	0.9 (0.7, 1.3)	1.1 (0.7, 1.6)
Asthma-related hospitalizations	2.1 (1.3, 3.4)	2.0 (1.2, 3.4)

**Logistic regression model was used to adjust for age, gender, and the following preindex characteristics: asthma-related ED visits and hospitalizations, ≥2 OCS fills, and ≥6 SABA fills.*
CI = confidence interval; OCS = oral corticosteroid; SABA = short-acting β-agonist.

severity. To reduce the effect of varying severity levels on our findings, we focused on new users of high-dose combination therapy and, specifically, those for whom this high-dose therapy was not the first controller used. We controlled for evidence of poor disease control at baseline. We could not measure severity directly, and if more severely affected patients adhered more closely with therapy, the association of adherence with control could have been confounded. According to a recent comprehensive review, the evidence that adherence varies with illness severity is limited.[34]

Other problems inherent to automated claims data may have affected our findings. We were not able to measure drug sampling, which may have led to misclassification bias with respect to categorizing patients as having low rates of adherence and/or having low rates of reliance on SABAs. Coding errors may also have affected data integrity. Our study examined patients with commercial insurance and excluded children <12 years of age and adults >65 years of age. Our findings, therefore, may not reflect patterns of care among the uninsured, those with Medicaid or Medicare, or those receiving care in the Department of Veterans.

CONCLUSION

In a claims analysis, nearly one-third of asthma patients who were highly adherent to high-dose combination ICS/LABA therapy still had evidence of poor control, as measured by the need for hospitalization or ED utilization and/or the more frequent requirement for the use of "reliever" medications (SABAs and/or OCSs). Even among those highly adherent patients who used additional controller medication, rates of poor control were high. Patients with asthma, even highly adherent ones, should be aggressively managed if they show evidence of poor control.

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