

Adherence to Inhaled Corticosteroid Use and Local Adverse Events in Persistent Asthma

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Asthma is a common disease affecting approximately 20 million people in the United States.¹ Inhaled corticosteroids (ICSs) are recommended by US and international guidelines as the foundation of therapy for persistent asthma,^{2,3} as regular use of ICSs in patients with persistent asthma has been associated with improved health outcomes.^{4,5} Unfortunately, studies⁶⁻¹⁴ have shown that adherence to long-term ICS use in patients with asthma is lower than acceptable. Patients who do not adhere to the use of ICSs have worse outcomes.¹²⁻¹⁴ Colice and colleagues¹⁵ found that inconsistent use of ICSs in patients with mild persistent asthma was associated with higher direct healthcare costs.

Patients with asthma may not use ICSs regularly for various reasons. Boulet¹⁶ asked 603 patients with asthma to complete a questionnaire about their perception of ICSs. Most patients (59%) expressed fear of adverse effects with ICS use. These patients were mostly concerned about systemic effects of corticosteroids, but other authors have emphasized that adverse events related to ICS deposition in the upper airway (such as hoarseness and oropharyngeal candidiasis) might also affect adherence.^{17,18} To further explore the relationship between adherence to ICS use and ICS-related local adverse events (LAEs), this study was designed to (1) measure adherence to ICS therapy objectively by pharmaceutical claims data and subjectively by patient-report using a survey, (2) identify patient-reported LAEs using a validated questionnaire and physician-reported LAEs from medical record review, and (3) evaluate the association between LAEs and adherence to ICS therapy.

METHODS

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Data Sources
Study patients were associated with a multispecialty medical group practice organization located in central Massachusetts with more than 200 physicians and 20 medical centers. Patients were members of a mixed-model health maintenance organization serving central Mas-

sachusetts with an annual enrollment of approximately 170,000 members. All provided healthcare services are captured in automated data tables that reflect the type of service the patient received. Automated tables include pharmacy claims, outpatient

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Objectives: To measure adherence to inhaled corticosteroid (ICS) therapy using prescription claims and a patient survey, to identify local adverse events (LAEs) from the patient perspective and from medical records, and to evaluate the association between LAEs and adherence to ICS therapy.

Study Design: Survey administration and claims-based and medical record–abstracted data.

Methods: Patients aged 6 to 64 years with persistent asthma (defined using an established algorithm) and at least 2 ICS prescriptions were selected from a claims database (1999-2006) of a central Massachusetts medical group practice. Prescription claims were used to calculate the ICS medication possession ratio (MPR). A survey obtained information about patient-reported adherence to ICSs using the Morisky scale and a visual analog scale (VAS) and about LAEs using the validated Inhaled Corticosteroid Questionnaire. Medical records of survey respondents were abstracted for LAEs.

Results: Among 372 survey respondents, 2.7% met the claims-based measure of good adherence (MPR, $\geq 80\%$). Patient-reported adherence was much higher; 20.7% of patients were highly adherent based on the Morisky scale (score, 0) and 55.4% based on the VAS (score, $\geq 80\%$). Medical record review identified 27.2% of patients having at least 1 LAE within 1 year after the ICS index date, but 47.3% of patients reported being bothered at least “quite a lot” by LAEs. Multivariate analysis indicated that unpleasant taste was significantly related to lower adherence based on the Morisky scale ($P = .02$).

Conclusions: Patient-reported adherence and LAEs were higher than those measured from claims or medical records. Unpleasant taste seems to be associated with lower adherence based on the Morisky scale.

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For author information and disclosures, see end of text.

visits, inpatient and specialist visits, laboratory tests, and membership and were available from 1999 to 2006. Utilization of medical services is recorded in the data tables with date of service, associated diagnoses, performed procedures, and billed charges. The pharmacy file also includes pharmacy claims with prescribed medications identified by National Drug Code, date of prescription fill, days of supply, quantity, and billed charges. A set of deidentified data tables was used to identify the patients for this study. Patient survey administration and medical record abstraction (described herein) were also conducted. This research was approved by a local institutional review board.

Sample Selection

The target sample size for this study was approximately 400 survey respondents. Because this is not a prospective clinical trial for estimating the effect of an intervention, we did not perform a formal power calculation. Because a study goal was to explore the relationship between symptoms of LAEs and adherence measures, we used regression analysis. With 400 observations, we substantially exceeded the informal rule in applied statistics that the sample size should be at least 10 times the number of regressors (ie, there are 20 regressors in the regression model, including 15 Inhaled Corticosteroid Questionnaire [ICQ] domain scores).¹⁹ In addition, although the domain scores of the ICQ are measured on a continuous scale, the literature suggests that a sizeable portion of patients would report 0 score in many domains.²⁰ Because it would be difficult to estimate the sample size required for an unknown and highly skewed distribution with floor effect, we used a conservative sample of 400 patients that would allow us to detect certain domains with statistical significance.

Potential survey candidates had an asthma diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 493) and at least 2 prescriptions for ICSs from January 1, 2000, to December 31, 2005. The patient index date was defined as the date of the first ICS prescription without a prescription for ICSs in the 6 months before the index date.

To ensure complete capture of medical and pharmacy utilization, patients in the study sample were required to have had continuous health coverage eligibility 6 months before and 1 year after the index date (follow-up period). Patients older than 64 years at the index date were excluded because information could not be obtained from Medicare sources. Patients younger than 6 years at the index date were excluded because there are different treatment guidelines for children younger than 6 years.

Patients with persistent asthma were identified from the database using a previously described categorization process that relies on medical and pharmacy utilization data 6

months before and 6 months after the index date.^{15,21} This approach uses the Health Plan Employer Data and Information Set criteria²² as a preliminary screen to identify patients with persistent asthma and criteria by Leidy and colleagues²³ in conjunction with established Global Initiative for Asthma guideline treatment recommendations³ to ensure that patients with mild intermittent asthma were not included and to allow severity categorization.

Surveys were initially mailed in February 2007. A second set of surveys was mailed to a different group of patients in May 2007 to ensure that the expected sample size was achieved. In each survey wave, patients were initially sent a letter introducing the study, followed by a letter with a more detailed study description, enclosed survey, and research authorization form. Reminder letters encouraging study participation were mailed to patients who did not return surveys within 2 weeks. The surveys were mailed first to patients with most recent ICS use. The mailed surveys contained questions about adherence measured using the Morisky scale and a visual analog scale (VAS), adverse effects measured using the validated ICQ,²⁴ and demographics. A parent or guardian was asked to complete the survey for patients aged 6 to 11 years.

Nurses reviewed medical records of survey respondents. They confirmed the diagnosis of asthma and the exclusion of patients with chronic obstructive pulmonary disease.

Adherence Measures

Claims-Based Adherence Measures. The medication possession ratio (MPR) was calculated during 1 year after the index ICS date as the sum of the days' supply of ICS (obtained from pharmacy claims) within 1 year after the ICS index date divided by 365 and multiplied by 100. The MPR is identical to the continuous multiple-interval measure of medication availability described by Steiner and Prochazka.²⁵ A cutoff of 80% has been previously used in categorizing patients with asthma as adherent and nonadherent.^{6,26}

Survey-Based Adherence Measures. The Morisky scale²⁷ was developed initially to assess adherence to medication use in patients with essential hypertension but has subsequently been used in other studies^{6,27} of asthma medication compliance. The adapted Morisky scale used in this study was composed of 4 yes (score, 1) and no (score, 0) questions related to the use of ICSs as prescribed by a patient's physician. Patients were not instructed to recall a specific period. Answering no indicated better adherence. The questions were as follows: (1) Do you ever forget to take your ICS medications? (2) Are you careless at times about taking your ICS medications? (3) When you feel better, do you sometimes stop taking your ICS medications? (4) Sometimes, if you feel worse when you take your ICS medications, do you stop taking them?

Patient adherence was classified into 3 categories based on responses to the Morisky scale.²⁶ These included high adherence (score, 0), medium adherence (score, 1-2), and low adherence (score, 3-4).

Patient-reported adherence was also measured in the survey using a VAS shown to have moderate concordance with adherence measures derived from pharmacy claims.²⁸ Patients were asked to put an “X” at the point along a 100-mm line showing their best guess about how much of their ICS they have taken during a 6-month period when they were using ICSs (range, 0%-100%). Based on the VAS score, patients were categorized into the following 3 adherence groups: low adherence (score, ≤50%), medium adherence (score, >50% to <80%), and high adherence (score, ≥80%).

Medical Record–Based Adherence Measures. Changes in prescriptions for ICSs (such as switching, discontinuation, new start, and dose changes) were abstracted from medical records, as well as information about the reason for change from previous therapy (eg, LAEs, systemic adverse effects, and formulation change). Data were abstracted starting with the ICS index date through 2007. The rate of ICS discontinuation within a year after the ICS index date is reported as a measure of medical record–based adherence, as well as the rate of ICS discontinuation because of an LAE.

Local Adverse Events

Patient-Reported LAEs. The validated ICQ, which has 57 questions organized into 15 domains, addresses the extent to which patients are affected by LAEs and by systemic adverse effects related to the use of their ICSs (see [eAppendix Table](#) available at www.ajmc.com).²⁴ Question responses are based on a 7-point Likert-type scale with 0 indicating “not at all” and 6 indicating “a very great deal.” To allow comparisons among domains with different numbers of questions, the 15 domain scores for the ICQ are each transformed into a score ranging from 0 (no adverse effects) to 100 (affected a very great deal) using the following equation:

$$\frac{\text{Sum of Responses From Answered Items in Domain } X}{(\text{Number of Answered Items in Domain } X) \times 6} \times 100$$

The total overall score for all 15 domains of the ICQ is calculated as the sum of the domain scores divided by the number of domain scores calculated. In this study, separate scores were calculated for LAEs and for systemic adverse effects. In the ICQ validation study, patients were asked to recall their experience in the previous 14 days. Patients in this study were asked to respond to questions about the adverse effects related to the use of their ICS at any time.

Medical Record–Abstracted LAEs. Medical records of survey respondents were reviewed from the index date through 2007 for occurrences of the following LAEs: bad taste; hoarseness; throat pain; oral candidiasis; voice disturbance; application-site dryness; cough following inhalation; pharyngitis or acute pharyngitis; tongue burning, swelling, or pain; application-site burning, inflammation, or irritation; and other or nonspecified LAEs. If the medical records contained an indication that the LAEs were or were not related to ICS use, then the relationship of the LAE to ICS use was noted in the medical record abstraction. If a relationship to ICS use was not specified in the medical records, the relationship of these LAEs to ICS use was noted as “unknown.”

Statistical Analysis

Baseline characteristics of patients with persistent asthma who completed the survey were compared with those of patients with persistent asthma who were identified as candidates for the study but were not in the final study sample because they did not respond to the survey or because they did not receive surveys. Categorical variables were compared using χ^2 tests. Continuous variables such as age were compared using *t* tests. Kendall τ rank correlation was used to test for dependence across the 3 adherence measures. Descriptive statistics were used to describe adverse effects reported in surveys, abstracted from medical records, and identified in utilization data. The distributions of domain scores were compared descriptively across adherence groups using Wilcoxon rank sum tests. Ordinary least squares (OLS) regression analyses were used to evaluate the relationships between ICQ domain scores and self-reported adherence measured by the Morisky scale and VAS, adjusting for patient characteristics such as age, sex, and persistent asthma severity category. As a sensitivity analysis, an ordered probit model was used to evaluate the effect of ICQ domain scores on the Morisky scale. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

There were 1410 patients with persistent asthma identified who met the criteria for receiving the mailed survey and who had at least 2 fills for ICSs. To reach a target sample of approximately 400 survey respondents, 790 surveys were mailed in 2 waves. The response rate was approximately 50%, and 396 surveys were returned. The final sample consisted of 372 survey respondents who also returned research authorization forms allowing analysis of their deidentified medical utilization and pharmacy data. Baseline characteristics of identified

candidates for the survey who were not included in the final sample and those of patients in the final sample were similar (Table 1). Most patients were adults (age range, 18-64 years) and female and were categorized as having mild or moderate persistent asthma.

Although most patients in the final sample had ICS index dates between 2003 and 2005, most patients reported in the survey that they were current or recent ICS users. Sixty-eight percent of patients had used ICSs within the past month, and 79.0% of patients had used ICSs within the past 6 months.

Adherence Measures

The mean MPR during 1 year after the index date for the final sample was 30.4%, indicating that patients had on average 111 days' supply of ICSs for that year (Figure 1). The median MPR of 24.9% indicates that half of the patients in our final sample had a 90 days or less supply of ICSs for that year. When fully adherent patients were defined as those with an MPR of at least 80%, only 10 patients (2.7%) were considered adherent. Self-reported adherence, obtained using the Morisky scale, showed that 20.7% of patients believed that they were highly adherent to ICS therapy. Six percent of surveyed patients had a missing item response that prevented calculation of the Morisky scale score. More than half of the study sample (55.4%) reported a VAS score of 80% or higher for adherence, indicating that more than half of the patients reported using approximately 80% of their prescribed ICS in a 6-month period. One percent of surveyed patients did not report a VAS score.

Physician-acknowledged switching or discontinuation

that was recorded in medical records was evaluated. Thirty-two percent of patients switched or discontinued asthma controller medications.

Local Adverse Events by the ICQ and Noted in Medical Records

Wide variations in responses to individual questions for the ICQ were noted (eAppendix Figure 1 available at www.ajmc.com). For example, most patients reported at least a little hoarseness (52.4%) and at least a little bad taste (65.3%), but fewer patients (21.8%) described even a little problem with oral thrush. Also remarkable is that a consistent but small group of patients (range, 3.2% for oral thrush to 9.4% for hoarseness to 11.8% for bad taste) reported at least "quite a lot" of problems with at least 1 LAE. Overall, 47.3% of patients reported ever being bothered by an LAE related to the use of their ICS medication at least "quite a lot."

Comparison of scores across domains showed that a few patients reported being affected (score, >60) by LAEs and by systemic effects (Figure 2). Among LAEs, the individual domains that most affected a substantial minority of patients were thirst, taste, oropharynx problems, voice problems, and dental deterioration.

Medical record abstraction revealed that 27.2% of patients had at least 1 LAE within 1 year after the ICS index date (Table 2). The most commonly reported LAE was pharyngitis (17.2%), but this condition was never recorded in medical records as being directly related to ICS use. Inhalation corticosteroid-related LAEs were noted in 5.6% of patients, and LAEs with unknown relation to ICSs were recorded in medical records of 14.0% of patients. The most commonly reported LAEs

after pharyngitis were throat pain (5.4%) and hoarseness (4.8%). Hoarseness and oral candidiasis were the LAEs most often recorded as being related to ICS use; hoarseness was related to ICS use in 44.4% of patients with at least 1 recorded hoarseness adverse effect, and oral candidiasis was related to ICS use in 66.7% of patients with at least 1 recorded oral candidiasis adverse effect.

■ **Table 1.** Comparison of Baseline Characteristics of Survey Candidates and Final Sample

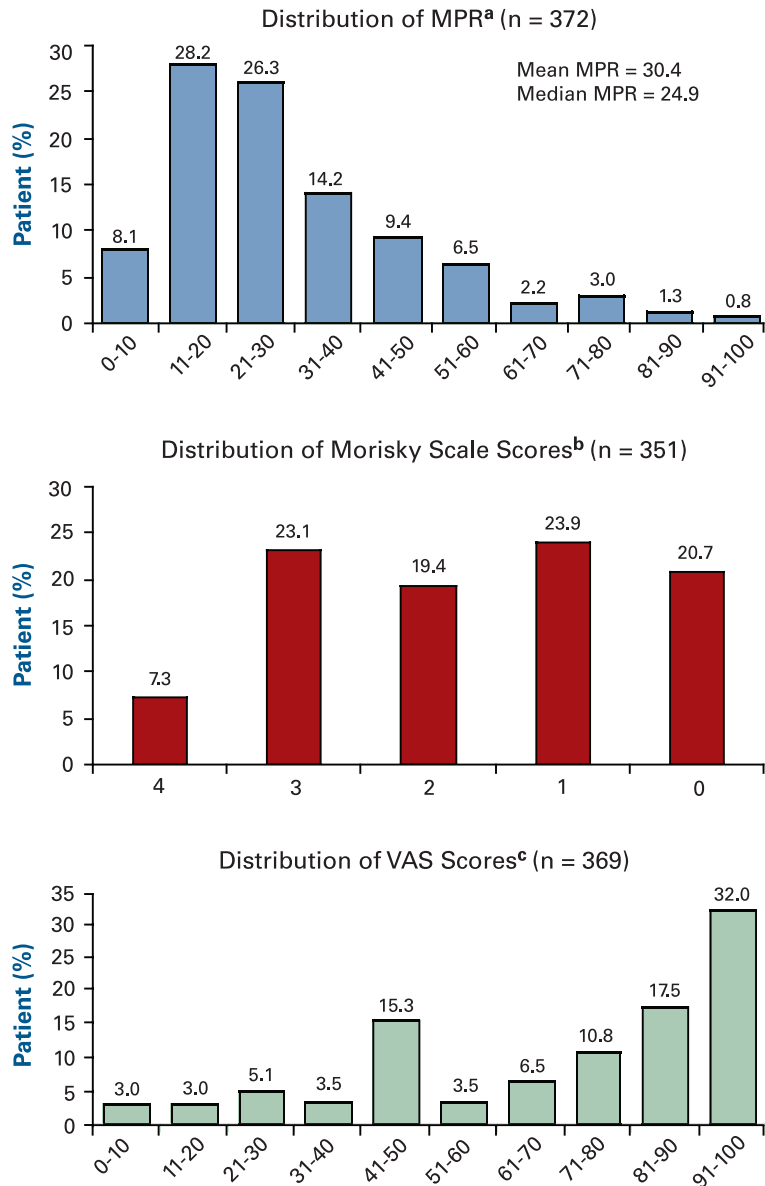
Characteristic	Patients in the Final Sample (n = 372)	Patients Identified as Candidates for the Survey but Not in the Final Sample (n = 1038)	P
Age, mean (SD), y	36.9 (17.3)	35.2 (18.1)	.13
Age group, y, No. (%)			.10
6-11	37 (9.9)	145 (14.0)	
12-17	46 (12.4)	140 (13.5)	
18-64	289 (77.7)	753 (72.5)	
Female sex, No. (%)	231 (62.1)	595 (57.3)	.11
Persistent asthma severity category, No. (%)			.13
Mild	156 (41.9)	397 (38.2)	
Moderate	153 (41.1)	415 (40.0)	
Severe	63 (16.9)	226 (21.8)	

Association Between Adherence and Adverse Effects

On average, the MPR of 30.5% during 1 year after the index date among patients with at least 1 LAE recorded in the medical records (excluding pharyngitis) was not significantly different than the MPR of 31.0% in patients without LAEs. Of 35 patients with physician-acknowledged switching or discontinuation from index ICS therapy within 1 year who also had an LAE, 16 patients (45.7%) switched or discontinued therapy because of an LAE (data not shown).

A trend was noted for patients with low adherence on the Morisky scale to report more often being affected by an LAE on the ICQ (eAppendix Figure 2 available at www.ajmc.com). In univariate analysis, a comparison of ICQ domain scores for individual LAEs by patient-reported adherence category based on the Morisky scale indicated that patients with low adherence were significantly more affected by voice problems, unpleasant taste, and itching in the mouth than patients with high adherence (Table 3). Patients with medium adherence were affected significantly more by unpleasant taste and itching in the mouth compared with patients with high adherence. Multivariate analysis evaluating the effect of ICQ domain scores on the continuous Morisky scale score indicated that a higher ICQ summary score for any LAE was significantly related to lower adherence (OLS coefficient [SE], 0.0112 [0.0042]; $P = .008$; data not shown). Among individual ICQ domains, only unpleasant taste was related to lower adherence (OLS coefficient [SE], 0.0125

Figure 1. Adherence Measured by Pharmacy Claims (Medication Possession Ratio [MPR]) and by Patient-Reported Measures (Morisky Scale and Visual Analog Scale [VAS])

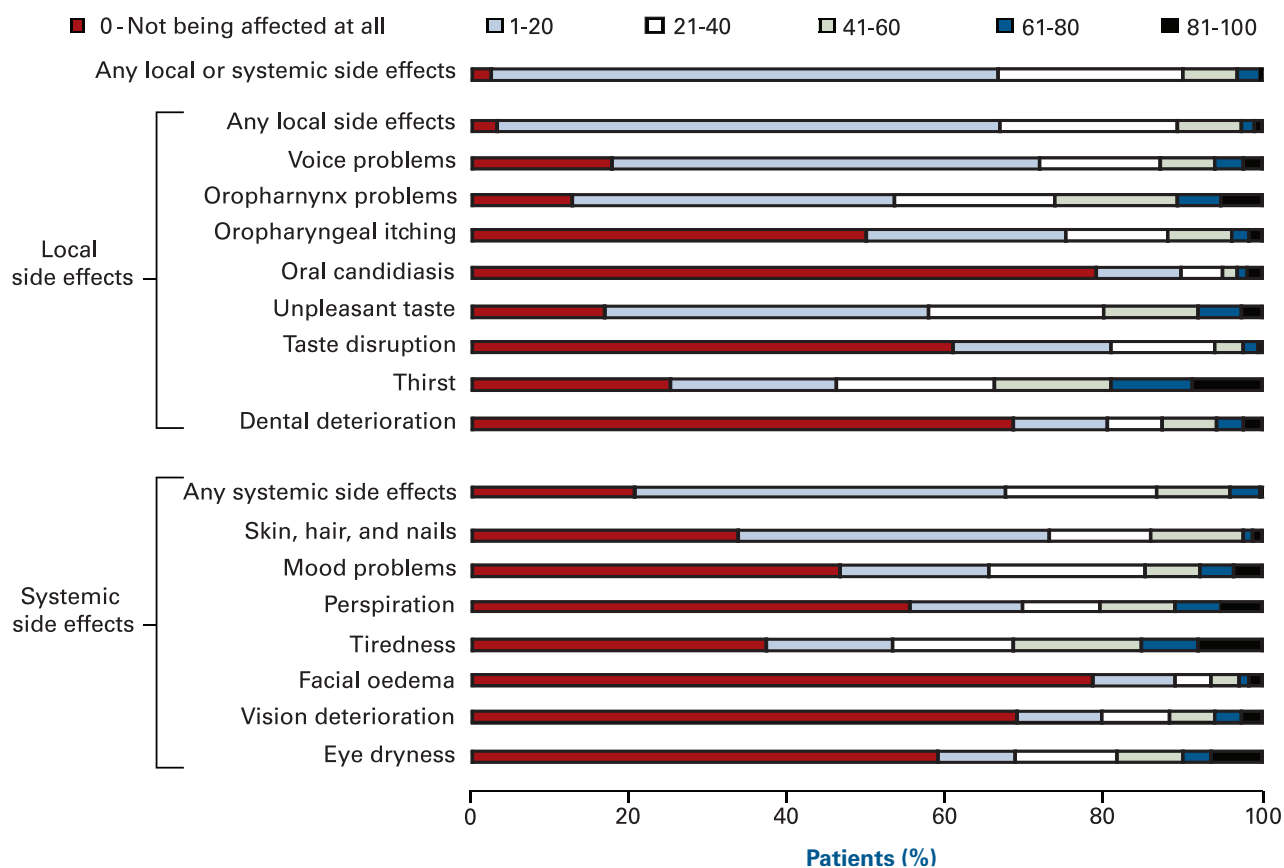


^aAdherence by the MPR ranges from 0% (no days' supply of inhaled corticosteroids [ICSs] during 1 year after the ICS index date) to 100% (365 days' supply of ICS during 1 year after the ICS index date).
^bAdherence by the Morisky scale score ranges from 0 (highly adherent) to 4 (nonadherent).
^cAdherence by the VAS score ranges from 0% (no ICS medication used during the 6 months a patient was taking ICS) to 100% (perfect compliance or all ICS medication used during the 6 months a patient was taking ICS).

[0.0052]; $P = .02$; data not shown). Sensitivity analysis using ordered probit models supported the findings from OLS analysis.

Trends were not apparent in the relationship between adherence by VAS and by LAE reporting on the ICQ. No significant differences were found in descriptive comparisons of individual ICQ domain scores for LAEs across self-report-

■ **Figure 2.** Distribution of Inhaled Corticosteroid Questionnaire Domain Scores for Local Adverse Events



The domain scores range from 0 ("not at all affected") to 100 ("affected a very great deal").

ed adherence groups based on VAS scores. In multivariate analysis, increase in dental deterioration (OLS coefficient [SE], 0.161 [0.080]; $P = .04$) and tiredness (OLS coefficient [SE], 0.176 [0.088]; $P = .047$) were significantly related to increased adherence (higher VAS scores).

DISCUSSION

In this survey of patients with persistent asthma, patient-reported adherence to ICS therapy was moderate to high on the Morisky scale and on the VAS. However, pharmacy claims data suggest that adherence was actually poor. Patients reported being affected more frequently by LAEs related to ICS use than was noted in the medical records by their physicians. However, no clear association was found between LAEs and low-to-medium adherence to ICS use.

Our finding that patients reported being more adherent to ICS use than could be supported by pharmacy prescription refills suggests substantial underuse of ICSs. Others have

made a similar observation. In a systematic review of the medical literature about adherence to ICS use assessed by electronic counters, Cochrane and colleagues⁹ reported that patients underused their prescribed ICSs on 24% to 69% of days. A study²⁹ of 48,751 patients with asthma aged 6 to 55 years showed that only 33.8% were adherent to newly initiated ICS therapy. The MPR of 30.4% for ICSs in our study fits within the 8% to 50% range of MPRs calculated from information in previous studies^{6,30,31} assessing prescription refills of ICSs. Better adherence to ICS use, which would improve asthma care and outcomes, can be achieved with simpler and less frequent dosing regimens³² and with intense educational efforts, but whether improved adherence can be maintained during the long term is unclear.³³

Inhaled corticosteroids are known to cause various upper airway adverse effects. The most often reported LAEs related to ICS use are oropharyngeal candidiasis, dysphonia, pharyngitis, glossitis, tongue hypertrophy, and dental erosions.^{18,20,34,35} Although the mechanisms by which ICSs cause these LAEs are not entirely clear, these adverse effects

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seem related to deposition of the ICS in the oropharynx and larynx. Local adverse event rates may vary by ICS dose, device, and potency.^{18,20,34,35} Moreover, patient use of a device may affect the rate of LAEs. For example, patients may have used a spacer device or were taught the “swish and spit” method to remove excess medication from deposition in the oral mucosa. Physicians tend to perceive ICS-related LAEs as less of a problem than patients. In a Delphi panel evaluation of the effect of ICS-related LAEs, physicians estimated that only 3% to 6% of their patients with asthma using ICSs specifically sought care for these problems.³⁶

However, when questioned directly about this issue, patients reported being frequently bothered by LAEs.^{24,37} In response to a questionnaire, 58% of patients with asthma using ICSs described voice and throat problems.³⁷ The present study, using a validated questionnaire, confirmed that most patients

were bothered by LAEs but that these complaints were infrequently noted by physicians in the medical records. Presumably, patients had to be bothered “quite a lot” before physicians recognized their concern. Unpleasant taste was reported in our questionnaire as a concern for many patients

Table 2. Patients With at Least 1 Local Adverse Event (LAE) Abstracted From Medical Records Within 1 Year After Inhaled Corticosteroid (ICS) Index Date

Variable	All Patients, No. (%) (N = 372)		
	Patients With ≥1 LAE	Patients With ≥1 LAE Related to ICS Use	Patients With ≥1 LAE With Unknown Relation to ICSs
Any LAE	101 (27.2)	21 (5.6)	52 (14.0)
Any LAE, excluding pharyngitis	37 (9.9)	21 (5.6)	30 (8.1)
Hoarseness	18 (4.8)	8 (2.2)	10 (2.7)
Application-site burning, inflammation, irritation	3 (0.8)	2 (0.5)	1 (0.3)
Application-site dryness	0	0	0
Cough following inhalation	0	0	0
Oral candidiasis	6 (1.6)	4 (1.1)	2 (0.5)
Pharyngitis or acute pharyngitis	64 (17.2)	0	31 (8.3)
Throat pain	20 (5.4)	3 (0.8)	14 (3.8)
Voice disturbance	7 (1.9)	1 (0.3)	6 (1.6)
Bad taste	3 (0.8)	2 (0.5)	1 (0.3)
Tongue burning, swelling, or pain	0	0	0
Other or unspecified	9 (2.4)	4 (1.1)	3 (0.8)

Table 3. Inhaled Corticosteroid Questionnaire Local Adverse Event (LAE) Domain Scores by Adherence Measured Using the Morisky Scale^a

Variable	Low Adherence (n = 113) [1]		Medium Adherence (n = 161) [2]		High Adherence (n = 77) [3]		P		
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	[2]-[1]	[3]-[1]	[3]-[2]
LAE score	17.9 (17.1)	13.0	18.1 (15.7)	13.7	14.2 (15.2)	10.2	.52	.14	.03
Voice problems	18.1 (21.9)	10.0	17.4 (20.4)	8.9	13.1 (18.4)	5.6	.77	.04	.05
Oropharynx problems	26.2 (25.6)	16.7	26.6 (25.7)	16.7	20.9 (20.3)	18.5	.94	.27	.22
Oropharyngeal itching	24.0 (22.9)	16.7	23.6 (21.9)	19.0	16.9 (19.6)	9.5	.98	.03	.02
Oral candidiasis	9.3 (16.7)	0	9.5 (15.3)	0	7.4 (15.8)	0	.37	.19	.49
Unpleasant taste	30.4 (28.1)	25.0	33.3 (28.9)	29.2	28.5 (30.1)	16.7	.99	.01	.01
Taste disruption	15.4 (20.0)	8.3	15.4 (20.7)	8.3	9.2 (14.5)	0	.38	.37	.08
Thirst	8.0 (17.6)	0	6.1 (16.3)	0	6.3 (18.7)	0	.42	.45	.12
Dental deterioration	10.1 (19.4)	0	12.9 (22.3)	0	10.4 (21.3)	0	.22	.98	.27

^aThe Morisky scale score could be calculated for 351 of the 372 patients responding to the survey. Twenty-one patients provided either incomplete or no response to the Morisky scale questions.

Take-away Points

Poor adherence to the use of inhaled corticosteroids (ICSs) in asthma is a well-recognized problem, but whether adverse effects contribute to poor adherence to ICS use is unclear. To evaluate the association between adverse effects and adherence to ICS therapy, this study used pharmacy-based and patient-reported measures of adherence, as well as adverse effects noted in medical records and reported by patients.

- Patient-reported adherence was higher than claims-based adherence.
- Patients reported being bothered by adverse events more often than recorded in medical records.
- Unpleasant taste seems to be associated with lower adherence based on the Morisky scale.

but is not described as an adverse effect of ICSs in the medical literature.^{18,20,34,35}

A unique aspect of this analysis was the evaluation of the relationship between adherence and LAEs. No significant differences were found between the MPRs of patients with at least 1 LAE within 1 year after the ICS index date versus patients without any LAEs during that period. Descriptive analysis of the validated ICQ domain scores by self-reported adherence based on the Morisky scale indicated that individual LAEs, particularly voice problems, unpleasant taste, and itching of the mouth, might have been related to low-to-medium adherence. However, on multivariate analysis only the relationship between unpleasant taste and the Morisky scale score was statistically significant. These findings were not replicated with the VAS. Insufficient sample size may also explain why some specific ICQ domains were not found to be statistically significant. Although these analyses do not clearly relate LAEs to the underuse of ICSs, they raise concerns that more careful attention should be placed on LAEs, especially taste, related to ICS use.

Limitations of this study must be acknowledged. Patients with persistent asthma were identified from an administrative claims database rather than from symptom and lung function assessment.² Previous work supports this approach and indicates that medication use can be a useful surrogate measurement of quality of care for persistent asthma.^{15,21,38} A common concern with survey administration and analysis is that the respondents might be different from the overall population of interest. For example, patients who experience LAEs related to ICS use may be more likely to respond to a questionnaire evaluating this issue. This possibility cannot be completely excluded, but the baseline characteristics of the patients identified as candidates for the survey and not included in the final study sample were comparable to those of patients who responded to the survey. Recall bias is a limitation of surveys in general. The claims-based adherence and LAEs abstracted from medical record data were reported during 1 year following the patients' index dates, while patient-reported adherence and adverse effects were based on the survey completed in 2007.

We did not have information about patients' ICS dosage, device use, or educational level that would affect the rate of LAEs. Moreover, this study assessed only the relationship between patient-reported LAEs and patient-reported adherence. Considering the differences in patient-reported and claims-based adherence, it would be informative to evaluate the effect of patient-reported LAEs on a more ob-

jective measure of adherence. Because of lags in claims data availability, calculation of claims-based adherence at the time of survey completion was not possible. Furthermore, the ICQ, Morisky score, and VAS, to our knowledge, have not been validated in children.

As with any retrospective analysis, the results should be viewed cautiously and primarily as a foundation for future studies. A prospective study of patients newly initiated to a regimen of ICSs that includes the ICQ and adherence measures would be a logical next step based on the results of this study. A prospective study designed to carefully evaluate the relationship between LAEs and adherence should be large enough to consider such factors as patient age and sex, ICS dosage, and ICS device. Future research could also focus on the effect of LAEs on patient costs over time.

CONCLUSIONS

This survey has demonstrated that patients report higher adherence with the use of ICSs than is supported by pharmacy records. Patients also more frequently report LAEs related to ICS use than is reflected in the medical records. An association between low-to-medium adherence and LAEs related to ICS use was not clearly found, although unpleasant taste was related to a measure of adherence and to the underuse of ICSs. A large prospective study taking into account patient sex, ICS dosage, and ICS device would provide better evidence about the relationship between LAEs and adherence.

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Inhaled Corticosteroid Use and Local Adverse Events in Persistent Asthma

Authorship Information: Concept and design (JII, HGB, APY, BS, TV, SE, RAR, GLC); acquisition of data (HGB, APY, SE, RAR); analysis and interpretation of data (JII, HGB, MH, APY, BS, SE); drafting of the manuscript (JII, HGB, MH, APY, BS, TV, SE, GLC); critical revision of the manuscript for important intellectual content (JII, HGB, MH, APY, BS, TV, RAR, GLC); statistical analysis (JII, MH, APY, GLC); provision of study materials or patients (JII, BS); obtaining funding (JII, HGB, BS); administrative, technical, or logistic support (JII, HGB, RAR); and supervision (JII, HGB, TV, RAR).

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