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Predictors of Asthma Medication Nonadherence

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Abstract

Objective—To describe asthma medication adherence behavior and to identify predictors of inhaled corticosteroid (ICS) under use and inhaled beta-agonist (IBA) overuse.

Methods—Self-reported medication adherence, spirometry, various measures of socioeconomic status, and blood for IgE measurement were collected on 158 subjects from a larger cohort of adults with asthma and rhinitis, who were prescribed an ICS, IBA, or both.

Results—There was a positive association between ICS under use and higher forced expiratory volume in one second percent (FEV₁%) predicted ($p=.01$) and a negative association with lower income ($p=0.04$). IBA overuse was positively associated with greater perceived severity of asthma ($p=0.004$) and negatively with higher education level ($p=0.02$).

Conclusions—Nonadherence to prescribed asthma therapy seems to be influenced by socioeconomic factors and by perceived and actual severity of disease; these factors are important to assess when trying to estimate the degree of medication adherence and its relationship to clinical presentation.

INTRODUCTION

The most effective treatments for persistent asthma are ICS medication for long-term management and IBA for quick relief of bronchospasm¹. Though clinicians prescribe these medications for their patients to achieve and maintain asthma control, many do not take them as directed, with adherence among adults estimated at approximately 50%^{2,3}. The causes of nonadherence are thought to include misunderstanding of directions, health beliefs, and a lack of understanding about the roles of control and rescue medications. The objectives of this study were to describe medication adherence behavior among adults with asthma and to identify predictors of nonadherence.

METHODS AND MATERIALS

Overview

We analyzed data for 158 subjects from a larger investigation of physical and socio-environmental factors in adults with asthma. This analysis was limited to subjects participating in a home visit component of that study, who were prescribed IBA ($n=154$) or ICS medication ($n=113$). Data were derived from structured telephone interviews and the subsequent home visit. Information was collected about medications prescribed and actual use, weight, height, serum IgE measurement, and spirometric lung function. The study was approved by the institutional review board and all subjects gave informed consent.

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Study Cohort and Telephone-Administered Interviews

The study subjects are part of a multi-wave, longitudinal cohort study of adults with asthma and/or rhinitis. Subjects were originally recruited using a random sample of pulmonary and allergy specialists and family practitioners in Northern California (USA) ^{4,5}. Additional subjects were later identified through random digit dialing and added if a physician's diagnosis of asthma or rhinitis was reported ⁴. Beginning in 2000–2001, these subjects were integrated into a single ongoing cohort (n=548) completing the same structured telephone interview and followed regularly thereafter. The combined cohort (n=548) was interviewed together for the first time in 2000–2001. In a follow-up step, carried out in 2002–2003, we re-interviewed 416 (76%) subjects from the combined cohort. Analyses of data derived from these interviews have been reported previously ^{4–15}. Of those not re-interviewed, 6 subjects (1%) had died, 114 (21%) declined participation, and 12 (2%) could not be contacted. Among the original physician-recruited group, 281 (81%) were re-interviewed while among the random digit dial sample, 135 (68%) were re-interviewed. The re-interviewed group of 416 subjects included 340 individuals reporting a physician's diagnosis of asthma with or without concomitant rhinitis and 76 others with rhinitis alone. Data collection was performed using a structured interview averaging 45 minutes in duration. We used computer-assisted telephone interview software (Entry point 90 Plus, Phoenix Software International, Inc. Los Angeles, Ca) to facilitate data entry and appropriate completion of skip patterns. There was no evidence of fatigue or drop-out due to interview duration. The survey instrument included questions covering asthma severity (medical history, symptoms, and medications), an asthma-specific quality of life (AQOL) instrument, and survey items addressing demographics and socioeconomic status. Subjects with asthma still living in the region at the time of request were asked to participate in a home visit; of those, 158 subjects agreed to the visit. Eligibility for this current analysis was limited to the subjects with asthma who participated in home visits.

Determination of Medication Use and Adherence

During the home visits, subjects were asked to provide all current asthma medications for inspection, which the study nurse identified and documented. For each medication, the study nurse asked each subject “How many puffs and how many times per day did your doctor tell you to use this?” and “Over the past 14 days, how many puffs and how many times per day have you used this?” The recall period of 14 days (previous two weeks) was chosen because it is the recommended recall limit in the NHLBI asthma guidelines¹.

We defined medication nonadherence by categorical variables. Subjects were classified as nonadherent to ICS if they reported less than seven days of use over the previous 14-day period. Subjects were classified as overusing IBA if they used an average of more than eight puffs of short-acting beta-agonist (SABA) or more than two puffs of long-acting beta-agonist (LABA) per day. LABA use was based on use of a single product or a combination inhaler containing a LABA. Other relevant medications (specifically theophylline, leukotriene modifiers, or oral steroids) currently being used by subjects for their asthma were also documented^{14–15}.

Lung Function and Specific IgE

During the home visit, lung function was assessed using an EasyOne™ spirometer (ndd Medical Technologies, Chelmsford, MA) that met American Thoracic Society (ATS) 1994 spirometry standards¹⁶, and a protocol that met ATS performance guidelines¹⁷. Blood samples drawn during the home visit were assayed for specific IgE antibodies including cat dander, dog dander, and two types of dust mites (Der p 1 and Der f 1) by a commercial clinical laboratory.

Variables Potentially Associated with Adherence Derived from Interviews

Demographic and socioeconomic variables were derived from the telephone interviews. Three separate categories for higher education were created: education less than or equal to high school graduate, some college or associate degree, and education greater than or equal to college graduate. Annual household income was elicited as a categorical variable, with a maximum category of $\geq \$80,000$ per annum. For subjects who were single, household income was equal to personal income. Subjects who did not provide income data ($n=4$) and/or who were single (single, widowed, separated, divorced; $n=43$) were assigned household income based on the USA median earnings for their current reported occupation.

We also assessed perceived asthma severity, AQOL, perceived asthma control, general health status, and depressive symptoms using validated instruments administered during the telephone interview. Self-perceived asthma severity is a one-item instrument with ordinal responses of mild, moderate or severe¹⁸. We assessed AQOL score using the Marks AQOL questionnaire, an asthma-specific instrument using a 20-item Likert-type scale adapted for telephone administration^{19, 20}. To assess perceived control, we used the Perceived Control of Asthma questionnaire, an 11-item instrument²¹. General health status was assessed using the Short Form (SF-12), yielding the Physical Component Scale (PCS; normative score of 53 ± 7 among USA adults aged 18–44 years without chronic morbidity)^{22, 23}. Depressive symptoms were assessed by the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item scale developed for the general population^{24, 25}; a score of ≥ 16 suggests depression. The frequency of daytime and nighttime symptoms was rated on an ordinal scale as none, hardly any days/nights, occasionally but not most, most, but not all, or everyday/night. For this analysis we treated symptoms dichotomously as follows: none and hardly any were collapsed to a single category compared to occasionally or more.

Statistical Analysis

Participants were categorized as adherent or nonadherent to prescribed ICS and adherent or overusers of IBA, and compared on demographic and clinical parameters. Tests for normality were done on all variables. All variables were found to be normally distributed using descriptive statistics including skewness and kurtosis. To test significance we used the t-test for continuous variables that were normally distributed, the Continuity Adjusted Chi-Square for categorical variables, the Mantel-Haenszel Chi-Square for ordinal categorical variables, and the Fisher Exact test when applicable for dichotomous variables. Potential predictors of nonadherence were selected for multiple logistic regression analysis if the groups differed in the bivariate analysis at a significance level of $p < 0.10$, except oral corticosteroid, which was selected as a potential predictor of ICS under use for conceptual reasons. When predictors were highly correlated we selected only one for entry into the multiple logistic regression (for example, daytime and nighttime symptom frequency). Interaction effects were addressed in overall analysis and development of regression.

RESULTS

Medication Adherence

Of the 113 subjects prescribed an ICS, 75% ($n=85$) were adherent by our definition of use (Table 1). Of those adherent, the mean ($\pm$ SD) use of prescribed puffs was 91 ± 28 percent. Of the 154 participants with prescribed IBA, 32 (21%) overused them according to our definition. Of these 32 subjects, 18 overused LABA, 13 overused SABA, and one subject overused both. Of the 109 participants using both an ICS and an IBA, 56 (51%) were adherent to both; 26 (24%) adhered to ICS but overused IBA; and another 26 (24%) under used ICS but did not overuse an IBA. One subject was nonadherent to both medications. There were four participants prescribed an ICS without an IBA. There were 35 (31%) subjects using

theophylline or leukotriene modifiers among the 113 subjects on ICS, comprising 30 (35%) of the adherent group compared to 5 (18%) of the under users ($p=0.13$). Among the 154 subjects using IBA, 41 (27%) of subjects were also using theophylline or leukotriene modifiers, comprising 28 (23%) of the adherent group and 13 (41%) of the over users of IBA ($p=0.07$).

Subject Demographics and Adherence

The demographic data for our subjects are summarized in Table 1. Over half (68%) of the subjects were female. The sample was largely White, non-Hispanic (68%), well-educated, and middle-to-upper income. Nonetheless, ethnic and racial minorities and those with lower levels of education and/or income were well represented. Of the total sample, 27% of the participants had annual household incomes $\leq$ US\$40,000, and six percent were $\leq$ 125% of the national poverty level.

As shown in Table 1, of the demographic variables, only income varied significantly by ICS adherence status ($p=0.04$), with a lower likelihood of ICS under use associated with higher income. A different pattern was manifest for IBA overuse. Educational level was statistically associated with IBA overuse ($p=0.02$), with a lower likelihood of overuse associated with higher education.

Clinical Status and Adherence

Table 2 shows the clinical variables of interest. The frequencies of daytime and nighttime symptoms were unrelated to ICS adherence ($p=0.30$ and $p=0.27$, respectively). Only FEV₁ % predicted was associated with ICS adherence. Subjects who under used ICS had better lung function (mean FEV₁ % difference 11.0%; CI 2.8, 19%). Among the 113 subjects using ICS, 13 (11.5%) were also taking oral corticosteroids at the time of the home visit. We did not collect information about reasons for using oral corticosteroids.

There were several clinical variables associated with IBA overuse. Those who perceived their asthma as more severe, as measured by the Self-Assessment of Severity instrument ($p=.001$) tended to overuse. IBA overuse was also associated with poorer AQOL (mean difference 7.1; CI 1.1, 13.1), and with poorer general health status reflected in lower SF-12 PCS values (mean difference -4.6; CI -0.2, -9.1). Lower FEV₁ % predicted values (mean difference -6.3%; CI -13.25, 0.7%) were seen in those who tended towards overuse although the confidence intervals did not exclude zero.

Risk of Inhaled Steroid Non-Adherence

Based on these findings, we tested a multivariate predictive model of ICS nonadherence (Table 3). In a logistic regression analysis combining income, oral steroid use, and FEV₁ % predicted as predictors, the overall model was significant (Chi-Square Likelihood ratio 14.0; $p=0.007$). Subjects in the highest income group were 70% less likely to be nonadherent when compared to the lowest income group (OR 0.30, CI 0.10 to 0.93, $p=0.04$). Being in the intermediate income group was also protective, with a 25% reduced risk, though not statistically significant. Subjects with better lung function were significantly less likely to be adherent (OR 1.41, CI 1.08 to 1.85, $p=0.01$) per 10% change in FEV₁ % predicted.

Risk of Beta-agonist Overuse

In a logistic regression analysis of IBA overuse combining educational level, self-perceived severity, FEV₁ % predicted, AQOL, and frequency of nighttime symptoms, the predictive model was statistically significant (Chi-Square Likelihood Ratio 20.4, $p=0.002$). Relative to high school graduate education or less, both some college (OR 0.32, CI 0.10 to 1.03, $p=0.06$) and college graduate (OR 0.27, CI 0.08 to 0.88, $p=0.03$) were protective factors against overuse.

Although the confidence interval of the former OR did not exclude 1.0, both point estimates of risk were similar, suggesting that greater education did provide risk reduction. Self-perceived severity was a significant predictor of overuse (OR 4.5, CI 1.6 to 12.9, $p=0.006$), though neither FEV₁% predicted nor symptom frequency were significant predictors of over use in this analysis. In those subjects using IBA, the decrement in FEV₁% predicted associated with perceived moderate to severe disease ($n=78$) was modest compared to those with perceived mild disease ($n=75$): mean decrement -5.5% ; CI -11.2 to 0.2% , $p=0.06$ (data not in Table).

DISCUSSION

Although adherence to treatment for a chronic condition may be in one's best interest, many people do not adhere to prescribed treatment²⁶. We were specifically interested in ICS under use, since ICS medications are considered the most effective treatment for asthma, and IBA overuse, which is considered dangerous. Conversely, neither ICS overuse nor IBA under use would be considered especially clinically important because neither is associated with adverse asthma outcomes.

Our results show significant levels of nonadherence to prescribed asthma medication, and further show that when two medications are prescribed, approximately 50% are adherent to only one. Several predictors of medication-taking behavior were identified including income, education, and patient perception. The predictors varied depending on the medication prescribed and whether the issue was overuse or under use. Apter, et al. found that adherence to ICS was negatively associated with African American race, lower education, and lower income and positively associated with greater frequency of asthma symptoms²⁷. Our findings are interesting for the ways in which they do and do not fit this pattern.

We also observed a strong association between socioeconomic status (SES) and adherence, but not one that conforms to interchangeable assumptions about the measures used. SES may depend on a combination of variables including occupation, education, income, wealth, and place of residence²⁸, but typically, income and educational level are considered key measures. We found that ICS adherence was associated with higher income and that this relationship persisted even after accounting for lung function. However, ICS adherence was unrelated to educational level. Conversely, educational level was associated with IBA overuse, while income showed no association. Thus two measures of SES, education and income, demonstrated quite different associations with adherence, and may not completely reflect SES. Future exploratory work should use as many relevant SES variables to predict adherence behavior as possible to allow more complete analysis of the relationships among SES components and clinical or behavioral assessments.

We observed better lung function among ICS under users. It is possible that individuals with better lung function accurately perceive a decreased need for ICS medication. The mean FEV₁% predicted in ICS under users was 87%, well into the normal range. Although there is a range of ability to perceive airflow obstruction, it seems these subjects were aware of breathing comfortably and did not use their ICS medications as prescribed, perhaps because they felt well. Low asthma severity may not necessarily require treatment with ICS. The level of asthma severity can be inferred from spirometry except that both intermittent and mild persistent asthma specify FEV₁ criteria of $\geq 80\%$ predicted. These two categories are differentiated by frequency of symptoms. Our analysis showed no relationship between the frequency of daytime or nighttime symptoms and adherence to ICS. Conversely, IBA overuse was weakly associated with FEV₁% predicted and was significantly associated with perceived severity and with symptom frequency. When all three were tested in the same model, perceived severity, but neither lung function nor symptom frequency remained statistically associated

with overuse. Overall, the perceived severity was weakly associated with FEV₁% predicted in this group, suggesting that perceptions drive behavior. One might assume that perceptions would vary with asthma severity, but Teeter et al has shown that the correlations between perceived symptoms and lung function are poor to modest at best²⁹.

Others factors could explain variability in adherence. DiMatteo et al. conducted a meta-analysis on studies of adults with chronic illnesses and found that depression correlated with poor adherence to therapy³⁰. Feldman et al found that 5% of a sample of adult asthmatics had mood disorders and others had high levels of depressive symptoms³¹. We did not find depressive symptoms to predict nonadherence for either ICS or IBA. Others have found that IBA overuse was associated with poorer asthma control³². Our measure of perceived control did not demonstrate an association with IBA use. Other factors that have been associated with asthma medication nonadherence are beliefs about asthma,^{33, 34} doubts about the usefulness of ICS medications³², fear of side effects^{35–38}, and, among African-Americans, distrust of the healthcare system^{38, 39}. However, many of these studies were done in samples of children with asthma or their parents. Fewer studies of adult medication adherence have been done. One study found that adults who accepted that asthma is a chronic condition with acute flares were more likely to believe in the need for daily ICS medication, while those who perceived their asthma as symptom episodes took ICS sporadically⁴⁰. The type of provider (e.g. physician, nurse practitioner, or physician's assistant) may also affect adherence. This type of data were not available as part of this study.

Our study was limited in that our relatively small cohort may lack sufficient power to detect modest associations. For example, we could not carry out stratified analyses or analyze ethnic-racial subgroup effects. We had a relatively large proportion of subjects (n=41) prescribed IBA but not an ICS medication, reflecting either prescribing inconsistent with general guidelines, or varying disease severity. Because this is a well-educated, middle aged, regionally-selected study group, our findings may not be generalizable to other regional settings or age-education patient mixes. Finally, though all medications were directly inspected, we relied on self-report of actual medication use and did not quantify adherence through objective methods such as electronic monitors or pharmacy refill records.

We explored the medication-taking behavior of a cohort of adults with asthma in their own home settings rather than in a clinical trial or clinic-based setting. Thus, our study provides a unique perspective on the choices made by individuals living with chronic asthma. A novel outcome of our analyses is the finding that perceptions of people with asthma drive the decision to adhere to prescribed ICS medication or to overuse IBA medication. Clinicians need to be aware that many patients will make their own appraisal of the need to follow medical advice based on their own perceived need for medications. Asthma education is essential to provide patients with the self-management knowledge necessary to keep asthma under good control and use medications to that advantage.

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Table 1
Demographics of Study Participants by Medication Adherence Group

Predictors	Inhaled Corticosteroid Use N=113		Beta-Agonist Use N=154		P
	Adherent(n=85)	Nonadherent(n=28)	Adherent(n=122)	Overuse(n=32)	
	Mean ± SD or n (%)		Mean ± SD or n (%)		
Age (years)	48.7 ± 7.4	46.7 ± 8.5	46.5 ± 8.8	46.2 ± 7.3	0.9
Female Gender	58 (68)	19 (68)	86 (70)	20 (63)	0.5
Ethnicity: White, Non-Hispanic	61 (72)	16 (57)	87 (71)	24 (75)	0.8
Education					0.02
High School Graduate or Less	12 (14)	2 (7)	16 (13)	9 (28)	
Some College	32 (38)	15 (54)	46 (38)	13 (41)	
College Graduate or Greater	41 (48)	11 (39)	60 (49)	10 (31)	
Income					0.4
Less than \$40K	17 (20)	10 (36)	33 (27)	8 (25)	
\$40K to \$80K	23 (27)	9 (32)	28 (23)	13 (41)	
Greater than \$80K	45 (53)	9 (32)	61 (50)	11 (34)	
Ever Smoked*	27 (32)	7 (25)	41 (34)	12 (38)	0.8
BMI ≥30	37 (44)	10 (36)	48 (39)	16 (50)	0.4

* Only 7 ICS users and 9 Beta-Agonist users currently smoke.

Table 2
Clinical Variables and Differences by Medication Adherence Group

Predictors	Inhaled Corticosteroid Use N=113		Beta-Agonist Use N=154		p
	Adherent(n=85)	Nonadherent(n=28)	Adherent(n=122)	Overuse(n=32)	
	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	Mean ± SD or n (%)	
Current Oral Steroid Use	12 (14)	1 (4)	11 (9)	6 (19)	0.2
FEV ₁ % Predicted	76.2 ±20.2	87.1 ±13.8	81.8 ±17.5	75.5 ±18.9	0.08
Self-Perceived Severity: Severe/Moderate	53 (62)	15 (54)	53 (44)	25 (78)	0.001
Asthma Quality of Life Score ^{a,†}	19.8 ±15.3	18.6 ±17.6	16.5 ±14.7	23.7 ±16.9	0.02
Perceived Control of Asthma Score	40.4 ±6.1	41.0 ±6.1	41.1 ±5.5	39.8 ±7.6	0.4
SF-12 Physical Component Scale	43.5 ±11.4	44.7 ±11.7	44.8 ±10.8	40.1 ±13.4	0.04
CES-Depression Score	10.5 ±11.4	11.6 ±10.2	10.5 ±1.3	13.6 ±13.1	0.2
RAST + (Cat, Dog, or Mite)	29 (34)	10 (36)	39 (32)	6 (19)	0.3
Theophylline or Leukotriene Modifier Use	30 (35)	5 (18)	28 (23)	13 (41)	0.07
Frequent Daytime Symptoms	48 (56)	12 (43)	55 (45)	22 (69)	0.03
Frequent Nighttime Symptoms	33 (39)	7 (25)	34 (28)	16 (50)	0.03

* Data missing for one subject in beta-agonist group (n=153).

[†] Higher AQOL scores mean worse quality of life.

Table 3
Logistic Regression Model for Predictors of Inhaled Corticosteroid Nonadherence
(N=113)

Outcomes and Interactions	Odds Ratio	95% Confidence Limits		P Value
		Lower	Upper	
Income				
Less than \$40K(Referent)	1.0			
\$40K to \$80K	0.75	0.24	2.40	0.63
Greater than \$80K	0.30	0.10	0.93	0.04
Oral Steroid Use	0.32	0.04	2.78	0.30
FEV ₁ % Predicted *	1.41	1.08	1.85	0.01

Overall Model Chi-Square Likelihood Ratio 14.03, df =4, p=0.007

* OR for FEV₁% predicted expressed per 10% change.

Table 4
Logistic Regression Model for Predictors of Beta-Agonist Overuse (N=153)

Outcomes and Interactions	Odds Ratio	95% Confidence Limits		P Value
		Lower	Upper	
Education				
High School Graduate or Less (Referent)	1.00			
Some College	0.32	0.10	1.03	0.06
College Graduate or Greater	0.27	0.08	0.88	0.03
FEV ₁ % Predicted (10% change)*	0.89	0.70	1.13	0.33
Self-Perceived High Severity	4.47	1.56	12.89	0.006
Asthma Quality of Life Score [†]	1.00	0.97	1.03	0.91
Occasional or More Nighttime Symptoms	1.37	0.51	3.69	0.53

Overall Model Chi-Square Likelihood Ratio 20.4, df=6, p=.002

* OR for FEV₁ % predicted expressed per 10% change.

[†] Data missing for one subject in beta-agonist group (n=153) limiting the multivariate analysis to this number.