

Influences of earlier adherence and symptoms on current symptoms: A marginal structural models analysis

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Background: The morbidity and mortality associated with asthma are suspected to be a result, in part, of poor adherence to inhaled corticosteroid regimens. One influence on adherence may be the perception of symptoms. Because symptoms and adherence affect each other over time, a conventional statistical approach for studying these relationships may provide biased results.

Objective: To understand the influence of previous asthma symptoms and previous adherence on current symptoms.

Methods: A total of 76 adults, mean age 48 years $\pm$ 15 years, with moderate or severe persistent asthma underwent 6 weeks of electronic monitoring of their use of inhaled corticosteroids and completed a daily symptom diary. We estimated the effect of earlier adherence on final symptoms by using marginal structural models, estimated by using a weighted estimation technique.

Results: Morning was better than evening adherence, which declined over the observation period. The variability of adherence appeared to increase over the observation period. In addition, earlier adherence predicted current adherence more strongly than earlier symptoms predicted current adherence. There was no overall significant relationship between cumulative adherence and final symptoms.

Conclusion: These data indicate that accurately determining past adherence will help identify patients to target to improve their future adherence. These analyses are important for understanding time-varying measures in the clinical setting. (*J Allergy Clin Immunol* 2005;115:810-4.)

Key words: Asthma, adherence, marginal structural models, biostatistics, time-varying analysis, symptoms, inhaled corticosteroids

Abbreviations used

ICS: Inhaled corticosteroid
MSM: Marginal structural model
OR: Odds ratio

Poor adherence to inhaled corticosteroid (ICS) regimens contributes to asthma morbidity.¹⁻⁴ Because some patients do not perceive the severity of their symptoms,⁵⁻⁷ they may not appreciate the need for medications, especially chronic medications like ICS, thus increasing the likelihood of missing doses. Moreover, Diette et al⁴ found that patients with lower current symptom severity tended to have poorer adherence to ICS.

Symptoms and adherence likely affect each other over time (Fig 1). For example, patients often take more medicine as symptoms increase, ie, symptoms influence adherence. As adherence to efficacious asthma regimens increases, symptoms are controlled (adherence influencing symptoms). A conventional statistical approach that does not account for these interrelationships may provide biased estimates of the effect of adherence to ICS on symptoms.⁸ Marginal structural models (MSMs) and their associated weighted estimation methods are an appropriate means of avoiding these biases, assuming the absence of unmeasured confounders. Understanding the time-varying nature of these variables can allow clinicians to make better recommendation on dosing regimens for their patients.

METHODS

Study protocol

The study was part of a larger observational cohort study whose methods are described elsewhere.² Men and women age 18 years and older with moderate or severe persistent asthma as defined by the National Heart, Lung, and Blood Institute Expert Report II⁹ were recruited from asthma specialty and primary care clinics of the University of Pennsylvania Health System. In the 3 years before entry, these subjects had a FEV₁ less than 80% of predicted with a 15% improvement in the FEV₁ after treatment. Their primary treating physician had prescribed ICSs for them. All subjects were scheduled to take inhaled corticosteroids twice daily.

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With the subjects' permission, adherence was measured by using an electronic monitor, the MDILog (Westmed Inc, Englewood, Colo). This device, which records the time and date of the inhaler actuation, enabled us to study individual patterns of actuation over time. Adherence was defined as the number of recorded actuations taken in a 12-hour interval divided by the prescribed number of actuations for that interval.

Seventy-six patients were monitored for 41 full days; monitors were collected on the 42nd day. Each patient kept a daily diary of asthma symptoms. The diary, adopted from Colice et al,¹⁰ was completed twice a day, once in the morning and once at bedtime. The morning diary was used to record the symptoms of the previous night, and the evening diary recorded the symptoms of the day. The extent to which asthma symptoms such as wheeze, cough, chest tightness, and dyspnea interfered with sleep was recorded by using a 0 to 4 scale in the morning diary. Limitation of daytime activities was recorded in the evening diary by using a 0 to 5 scale. Zero represented no symptoms. In addition, the use of short-acting β -agonists was recorded in the diary by the patient.

Sociodemographics (age, sex, educational attainment, race-ethnicity) and several other possible determinants of adherence that do not vary with time were taken into account. Questionnaires validated by the investigator^{2,3} measured attitude, belief that the benefits of a medication outweighs its risk; self-efficacy, belief in patients' ability to overcome barriers to medicine taking; knowledge, knowledge of medicine's actions and side effects; and communication, patient satisfaction with physician communication. Social support was measured by using the Medical Outcome Study Social Support Survey.¹¹ Baseline adherence (ie, adherence before the study period) was assessed by using a questionnaire from Morisky et al¹² and Dolce et al.¹³

Analysis

The primary analysis examines whether earlier adherence, defined as cumulative adherence across all time points until the final day, predicts symptoms on the final monitoring day (day 41) and previous night, controlling for time-varying confounders of the effect of adherence on symptoms. To accomplish this, 3 sets of analyses were performed: (1) descriptive statistics of symptoms and adherence; (2) an analysis of the association between cumulative earlier adherence and symptoms separately for the final day and previous night; and (3) a sequential analysis of this association across the study follow-up period with separate analyses at each follow-up time point, using each day's and previous night's symptoms as the dependent variable and cumulative earlier adherence as the independent variable. For the first analysis, the time-varying variables, symptoms and adherence are presented graphically, illustrating their central tendencies and variability over time.

To accomplish the second and third analyses, the effect of adherence over an extended period on symptoms, we must deal with the feedback relationship between adherence and symptoms fluctuating over time (Fig 1). This feedback is not accounted for in standard analyses (eg, random effects or multilevel models).¹⁴ We modeled the effect of cumulative adherence on symptoms at the end of follow-up by using a logistic marginal structural model. The logistic model provides an odds ratio (OR) as the measure of the effect of adherence on symptoms, which here is expressed as a binary variable. The MSM uses a method of weighting to estimate these ORs appropriately by adjusting for feedback and time-varying relationship between symptoms and adherence.¹⁴ The weighting procedure works by removing analytically the association between symptoms and subsequent adherence present in the data—that is, by attempting to mimic, by using our data, a situation in which adherence is not influenced by previous symptoms and adherence. In its simplest form, it is a 2-stage procedure in which symptoms are modeled as a weighted

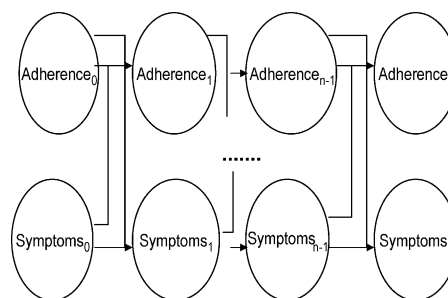


FIG 1. The time-dependent relationship of adherence and symptoms. This figure shows how, in a dynamic sense, discrete transitions from state to state of adherence and symptoms are influenced by one another and by their own previous states.

function of adherence. The weights consist of the inverse of the conditional probability, estimated in the first stage, in a logistic regression of adherence on past symptoms and other relevant covariates. The conditional probability is calculated at each follow-up time point. The weight is the product of the inverse conditional probabilities.

Because of the bimodality of the adherence distribution, ie, patients generally either took most of their ICS or did not take it, cumulative earlier adherence was coded as a dichotomous variable: greater than or equal to 0.7 ($A = 1$) and less than 0.7 ($A = 0$). We and others have used 70% as the dividing point, between good and bad adherence because this level of adherence appears to be clinically relevant.^{3,15} In addition, we varied this threshold between 60% and 80% and did not observe substantial differences in our results. The symptom outcome at each time point was represented by dichotomous variables. We first computed the average of the 4 items reflecting the previous night's symptoms. We separately obtained the average of the 5 items representing symptoms of the just-completed day. If the average was greater than or equal to 1, we considered that there were asthma symptoms and assigned 1 to the symptom variable ($Y = 1$); if the average was less than 1, the symptom variable was 0 ($Y = 0$). This criterion was chosen because of very few symptom codes greater than 1. For the third sequential analysis, we repeated the MSM procedures, analyzing the effect of cumulative earlier adherence on symptom outcomes at different points in time: days 1, 2, and 3 separately; and weeks 1, 2, 3, 4, 5, and 6 separately, with total cumulative adherence as the covariate in the model replaced with earlier aggregate adherence at a given time point such as week 1. Such an analysis provides an investigation of whether the association between cumulative adherence and symptoms varied across time and is presented in the Results section.

To assess the robustness of the MSM-based results, we varied the weight structure (data available on request) in several different ways to investigate whether such changes led to changes in inference. In addition, we compared our marginal structural model results with standard logistic models, which were defined the same way as the corresponding marginal structural models. However, the standard logistic models were implemented without the weights used to estimate the marginal structural models. Finally, we adjusted the results from the different analyses for multiple comparisons by using the Bonferroni approach.

RESULTS

A total of 76 patients were monitored, age 48 years $\pm$ 15 years, 56 women, 49 African Americans, with baseline FEV₁ 65% $\pm$ 21%. Because patients returned on day 42, data to day 41 were used.

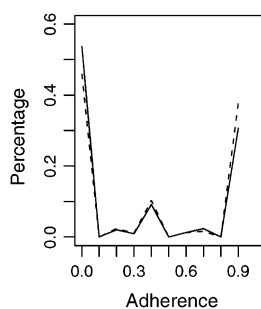


FIG 2. Percentage of adherence. Adherence, represented by the x-axis, is the percentage of doses taken divided by the number prescribed in a 12-hour period. The y-axis depicts the percent of total daytime or nighttime monitoring periods. The dotted line (---) represents AM adherence and the solid line (—) PM adherence.

Descriptive statistics

Adherence. The distribution of adherence for the sample is bimodal (Fig 2) with the modes at 0% and 100% adherence. That is, patients tended to either take all or none of their prescribed ICS. Morning and evening adherence changes over the 41-day period as depicted in the profile plots of the mean of the 76 patients are presented in Fig 3. These plots show that morning adherence was higher than evening adherence. In addition, both morning and evening adherence decreased over the observation period. The decrease of adherence over time was more obvious in the evening adherence. Also, the variation in adherence increased for both evening and morning adherence over time.

Symptom diaries. The fluctuation of symptoms over time is shown in the profile plots of diary symptoms in Fig 4. Because the symptoms diary used different scales for morning and evening, we standardized the symptoms to allow comparison. There was little difference between night and day symptoms. Daytime symptom scores were slightly higher than nighttime symptoms, but the difference was not clinically significant. As in the profile plots of adherence, these symptoms profile plots show a decrease of asthma symptoms over time.

Models for symptoms

The adjustment for potential confounding of the cumulative nonadherence and final day or evening symptom relationship indicates no such relationship. That is, earlier adherence was unrelated to subsequent symptoms. Table I presents the ORs for the weighted MSM and standard unweighted logistic analyses with weights including time-varying average earlier adherence. There was little difference between the 2 sets of ORs for these models, indicating that there was no confounding. Moreover, none of the symptom on adherence effects in the first stage analysis were significant (ie, the minimum *P* value and associated OR are .07 and 0.79, respectively).

Table II presents the ORs and associated *P* values from MSM and standard logistic analyses paralleling the primary analysis for the final time point, but repeated for

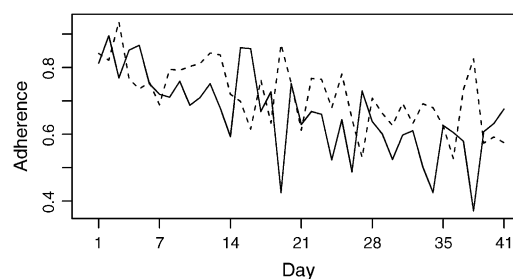


FIG 3. Profile plots of morning and evening adherence. Adherence (y-axis) is defined as the number of recorded actuations in a 12-hour period divided by the prescribed number for that interval. Thus, adherence < 1 represents at least 1 missed puff, and adherence = 0 represents no puffs taken in the time interval, but adherence = 1 implies that all puffs were taken during the interval. The dotted line (---) represents AM adherence and the solid line (—) PM adherence.

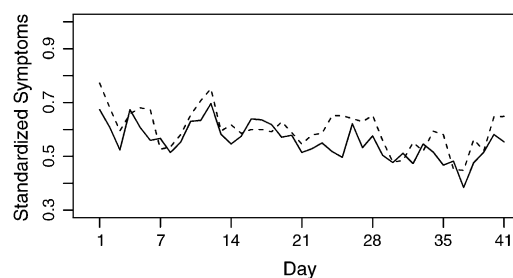


FIG 4. Profile plots of symptoms over the daytime and nighttime. Because the symptoms diary used different scales for morning and evening, we standardized the symptoms over a range of 0 to 1 for both scales to allow comparison. The dotted line (---) represents AM adherence and the solid line (—) PM adherence.

a range of follow-up time points. This sequential analysis indicates how the cumulative earlier adherence and symptom relationship varies across time.

Time-varying adherence-symptom association: the sequential analysis

The results for the sequential analysis of time-varying associations between earlier average adherence and symptoms at separate day and night time points are shown in Table II. The patterns for intermediate day and night are quite different from the final day and night patterns in Table I. The association between symptoms and adherence was stronger immediately after the start of treatment, when adherence was highest. In Table II, the MSM sequential analysis for earlier average adherence versus day symptoms suggests a strong but nonsignificant OR for the first week beyond the first day and weakening association over time. We consider the association between symptoms and adherence significant when the *P* value is less than or equal to $\alpha = 0.05/9 = .006$. We adjusted the significance level because of multiple comparisons. Similarly strong associations for the first week after day 1 and decreasing associations afterward are observed in the standard logistic analysis in Table II. In both analyses,

TABLE I. Association of symptoms with earlier adherence using MSMs*

	Analysis	P value	OR	95% CI
Day symptoms	MSM	.96	1.00	0.96–1.04
	Logistic regression	.32	0.99	0.97–1.01
Night symptoms	MSM	.31	0.98	0.94–1.02
	Logistic regression	.25	0.99	0.96–1.01

*This MSM analysis with weights including time-varying average earlier adherence and using logistic MSMs is compared with standard logistic analysis.

none of the associations are statistically significant at the adjusted α level.

The sequential analysis of night symptoms yields patterns similar to the patterns observed for the standard logistic regression day analysis in Table II. Hence, Tables I and II provide evidence of strong but nonsignificant associations between adherence and symptoms in the first week, and little evidence of such associations in the subsequent weeks. The association in week 6, the final analysis, is in the opposite direction of the previous analyses. ORs less than 1 can be interpreted as follows: the odds of having asthma symptoms for patients who adhere are less than those of patients who do not. Although not statistically significant, the association of the final analysis is in the direction we expected.

DISCUSSION

This study investigates the influence of previous symptoms and previous adherence on current symptoms. Separate cross-sectional analyses were conducted across follow-up periods. The analysis uses a statistical modeling procedure, MSM, which takes into account time-varying confounders (symptoms and adherence).

We observed several findings important to the clinician. First, as noted previously, adherence declined over time.¹⁶ Second, adherence in general was better in the morning than in the evening. Third, patients' adherence tends to be bimodal: patients either take the prescribed dose or do not take it at all. Fourth, the association between adherence and symptoms, which was never strong, got progressively weaker as time went on and also as adherence decreased. Clinicians may want to take account of this information when scheduling ICS for patients and when counseling patients about adherence. In addition, we found that the variability of adherence increased over the observation period. Interestingly, daytime symptoms seem to be slightly more severe than nighttime symptoms. Patients with significant asthma usually have more symptoms at night—spirometry and peak flows are lower in the early morning hours compared with evening.^{9,17,18} Our finding could have been a result of the relative stability of the patients who did not report much variation in symptoms.

Our subjects knew that adherence was being electronically recorded. This knowledge could affect adherence and the report of symptoms, ie, the Hawthorne effect. The

TABLE II. Sequential analysis of the association of daytime and nighttime symptoms with earlier adherence*

	Daytime				Nighttime			
	MSM		Logistic regression		MSM		Logistic regression	
	OR	P value	OR	P value	OR	P value	OR	P value
Day 1	1.02	.98	1.15	.78	1.28	.59	0.88	.72
Day 2	1.38	.34	1.36	.22	1.27	.36	1.23	.30
Day 3	1.34	.15	1.24	.17	1.22	.33	1.17	.30
Week 1	1.18	.10	1.13	.06	1.08	.34	1.11	.11
Week 2	1.06	.21	1.08	.03	1.07	.13	1.09	.01
Week 3	1.09	.01	1.05	.04	1.05	.14	1.04	.11
Week 4	1.01	.84	1.03	.15	1.06	.06	1.03	.21
Week 5	1.06	.04	1.04	.01	1.02	.44	1.02	.14
Week 6	1.00	.96	0.99	.32	0.98	.31	0.99	.25

*ORs and P values from the MSM and standard logistic analyses are separately obtained for each time point. The OR estimates have been normalized to account for varying durations.

ethical conduct of research dictates that subjects must have this information. It is hard to predict what the results would have been if patients had not known they were being observed, but we would guess that adherence would not be better. Also, the reliability of the patient symptom diary is of concern. It is not uncommon for patients to fill out a month's worth of symptoms the night before a visit. For future research, the use of electronic symptom monitors that mark time and date with each response may be beneficial.

A potential limitation of any observational study is the likely presence of unmeasured confounders. In such cases, estimates of treatment effects will be biased. For example, more severe disease is an indication of the need for a higher dose or more fidelity to the prescribed treatment. Our analysis adjusted for underlying disease severity. Although symptom diaries are commonly used to measure symptoms, they may not be accurate; patients may fill them in just before turning in their diaries, forgetting remote events. As noted, patients differ greatly in their perception of symptoms.⁶ Those with airways obstruction do not always perceive the severity of symptoms. Finally, because there was little variability in symptoms, the observation of a relationship between adherence and symptoms may have been obscured.

Nevertheless, the weighted analysis based on MSMs provides a useful evaluation by adjusting for the temporal feedback relationship between adherence and reported symptoms across time. Given that earlier symptoms were not strong predictors of subsequent adherence, it is not surprising that the potential feedback relationship did not strongly confound the association of ICS and later/final symptoms.

We have used state-of-the-art analytic tools for controlling for time-varying potential confounding in estimating the effect of inhaled steroids. Our result, the lack of a significant overall relationship between adherence and symptoms, has been observed by others who did not control for time-varying confounding. Thus, this analysis

supports the previous findings. Complete resolution of the degree to which adherence influences symptoms awaits further study using stronger designs—ie, a randomized trial to encourage adherence. Analyses of such data can rely on other approaches to inference, which need not rely on assumptions about having measured accurately all determinants of adherence.

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