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 ± 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 al[4] 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 II[9] 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 FEV_1 less than 80% of predicted with a 15% improvement in the FEV_1 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 al[12] 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

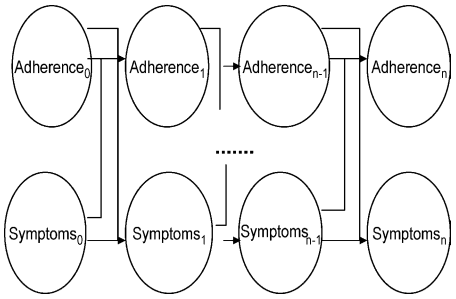

FIG 1. The time-dependent relationship of adherence and symptoms. This figure shows how, in a dynamic sense, discrete transitions from state to state of adherence and symptoms are influenced by one another and by their own previous states.

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 ± 15 years, 56 women, 49 African Americans, with baseline FEV_1 65% ± 21%. Because patients returned on day 42, data to day 41 were used.