Original Article

Compliance with maintenance treatment of asthma (ADERE study)*

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ABSTRACT

Objective: To determine the rate of compliance with preventive treatment of moderate and severe persistent asthma. **Methods:** Physicians at various medical centers across the country were invited to nominate patients for participation in the study. Inclusion criteria were being over the age of 12 and presenting moderate or severe persistent asthma. Participating patients received salmeterol/fluticasone 50/250 µg by dry powder inhaler for 90 days and were instructed to return the empty packages at the end of the study as a means of determining the total quantity used. In order to evaluate compliance, a member of the research team contacted each patient via telephone at the study outset and again at the end of the 90-day study period. Asthma patients were considered compliant with the treatment if they used at least 85% of the prescribed dose. The following variables were studied: gender, age, race, marital status, years of schooling, smoking habits, other atopic conditions, comorbidities, asthma severity, use of other medication and number of hospital admissions for asthma. **Results:** A total of 131 patients from fifteen states were included. The overall rate of compliance was found to be 51.9%. There was a significant difference in compliance in relation to asthma severity: compliance was greater among patients with severe persistent asthma than among those with moderate persistent asthma (p = 0.02). There were no statistically significant differences among any of the other variables. **Conclusion:** The overall rate of compliance with maintenance treatment of asthma was low.

Keywords: Asthma/drug therapy; Asthma/prevention & control; Patient compliance; Patient education; Physician-patient relations

INTRODUCTION

Asthma is a chronic condition that can be controlled through a series of measures that typically include the use of medications to reduce airway inflammation and alleviate the symptoms resulting from the airway obstruction.[1] In this context of a need for prolonged treatment, asthma can serve as a paradigm and as the object of studies comparing it with other chronic conditions such as diabetes, epilepsy, hypertension, and smoking.[2] The use of controller and relief medications, as well as the observance of certain items (medical advice, treatment strategy, etc.), can significantly increase patient quality of life.[3]

Compliance with treatment is fundamental to achieving the above-mentioned improvement in quality of life. In patients with chronic diseases, low rates of compliance with therapeutic regimens have been well documented. Only approximately 50% of the patients act strictly according to the instructions given by the team of health professionals, whether related to prevention or to treatment.[4] In asthma, studies show that, each year, approximately half of the medical prescriptions worldwide are not followed.[5-6] This percentage can range from 20% to 72% according to gender, age, socioeconomic conditions, disease severity, and other factors.[7-8] These findings regarding low compliance with the asthma treatment are replicated in many countries, such as the USA, Australia, Canada, and the United Kingdom.[9] Low compliance with treatment is probably one of the causes of the high asthma-related morbidity rates.[2,10] In the USA, approximately 40% of the patients with moderate or severe asthma experience nighttime awakenings, whereas, 28% of the asthma patients in Europe experience at least one night per week of poor quality sleep caused by uncontrolled asthma, possibly due to inadequate compliance with preventive regimens.[11] Some authors[6] have demonstrated that compliance with inhaled corticosteroid regimens is significantly and inversely associated with the number of visits to the emergency room and the use of oral corticosteroids.

In Brazil, there have been few comprehensive studies on this subject, although there is unequivocal evidence that asthma is a significant contributor to the rates of morbidity and mortality in the Brazilian population.[12-16]

The present study aimed to evaluate, through the inclusion of patients from various medical centers across the country, the rate of compliance with maintenance preventive treatment dispensed by professionals among patients with moderate or severe persistent asthma.

METHODS

A prospective study design was used to evaluate patients classified as having moderate or severe persistent asthma according to the criteria established by the III Brazilian Consensus on Asthma Management.[3] Attending physicians from fifteen Brazilian states were invited to participate in the study. A description of the protocol, highlighting the inclusion and exclusion criteria, was sent to each physician, together with written informed consent forms and three dry powder inhalers (containing salmeterol/fluticasone 50/250 µg) to be distributed to the patients, free of charge, for three months, as well as general guidelines to be provided to the patients regarding asthma and the use of the devices.

After having given written informed consent and having been registered by the attending physician, each patient was contacted via telephone by a specifically trained professional (co-author) of the central team headquartered in the Pulmonology Department of the Pontifical Catholic University of Rio Grande do Sul Hospital São Lucas in the city of Porto Alegre, located in the state of Rio Grande do Sul. The first telephone contact was made in order to collect demographic and clinical data, and the final contact (at the end of the three-month study period) was made in order to evaluate treatment compliance. On that occasion, patients were instructed to return the empty packages (three dry powder inhalers), at no cost to the participant, to the central team, who made the final calculation of the total quantity used.

The inclusion criteria were as follows: having been diagnosed with moderate or severe persistent asthma; being twelve years of age or older; having been diagnosed at least three months prior; having enough schooling to complete the forms; having a residential telephone; having no other disease that might interfere with the study; and not being addicted to alcohol or any other drugs.

Exclusion criteria were mild persistent asthma, pregnancy, puerperium/breastfeeding, comorbidities, the use of other medications that might interfere

with the study, and any chance that the attending physician would be changed in the near future. The exclusion of patients who declined to participate or who did not cooperate with the data collection, at any point of the study, was also anticipated.

The primary outcome measure, compliance, was determined by dividing the total quantity of medication used by the quantity prescribed for the period studied (three months). Subanalysis of the compliance per package of medication was not carried out. Asthma patients who used more than 85% of the prescribed dose of medication were considered compliant with the treatment.

The following variables were studied: age; gender; race; marital status (defined here as having a steady partner or not); years of schooling (elementary/junior high school, high school or higher education); smoking habits (being a smoker, being a former smoker or never having smoked); asthma severity (stage, frequency of use of relief medication and number of nighttime awakenings); number of visits to the emergency room and number of hospital admissions for asthma; other atopic conditions and comorbidities; and the chronic use of other medications (not for the treatment of asthma).

This study was designated the Adere Study in order to facilitate communication among the researchers. The present study was approved by the Ethics in Research Committee of the Pontifical Catholic University of Rio Grande do Sul, pursuant to the National Health Council Resolution 345/05. The collaborating physicians were selected because they were considered compliant with the Guidelines for Good Clinical Practice.[17-18] All patients gave written informed consent prior to enrolling in the study. The content of the consent form, as well as the process of obtaining consent, were in accordance with the applicable regulatory requirements.

The sample size was calculated based on a margin of error set at a maximum of 10% and an estimated rate of compliance of 50%. Therefore, we determined that at least 100 patients were necessary for the study to have a statistical power of 80% and to make $\alpha = 0.05$.

Data relating to quantitative variables are expressed as means and standard deviations, whereas those relating to categorical variables are expressed as frequencies and percentages. In cases of asymmetry of the quantitative variables, medians and interquartile ranges were used. The levels of

significance were determined using the Student's t-test (for quantitative data), the chi-square test (for categorical data), and the Mann-Whitney U test (for quantitative data that were asymmetric). The strength of the correlations among the variables studied was determined using odds ratios (ORs) and the respective 95% confidence intervals (95% CIs). The multiple logistic regression model was used to adjust for the effects of potential confounding factors. The level of significance was set at $\alpha = 0.05$. The Statistical Package for the Social Sciences (SPSS) program was used to process and analyze the data.

RESULTS

A total of 135 patients were initially included. In 4 of those cases, the initial telephone contact was not possible. Therefore, we analyzed data related to 131 patients, whose demographic characteristics are described in Table 1. The overall mean age was 44.4 $\pm$ 16.6 years. In the group of patients that were

TABLE 1

Demographic characteristics of the patients (n = 131)

Characteristics	Patients
Age ± SD, years	44.4 +16.6
Female, f (%)	93 (71.0)
Race, Caucasian, f (%)	78 (59.5)
Origin, Southeast, f (%)	95 (72.5)
Marital status, steady partner, f (%)	60 (45.8)
Years of schooling, f (%)	
Elementary/junior high school	57 (43.5)
High school	55 (42.0)
Higher education	19 (14.5)
Asthma stage, severe persistent, f (%)	61 (47.3)
Use of relief medication[1], median (25-75% interquartile range)	4 (0-14)
N of visits to the emergency room for asthma[2], media (SD)	0.6 (1.1)
N of hospitalizations for asthma[3], median (SD)	4.7 (11.7)
N of nighttime awakenings due to asthma[4], median (SD)	0.7 (1.5)
Use of other medications[5], f (%)	54 (41.2)
Other atopic conditions, f (%)	74 (56.5)
Other comorbidities, f (%)	46 (35.1)
Nonsmoker status, f (%)	7 (5.3)

[1]Use of relief medication for asthma per week. [2]Number of visits to the emergency room for asthma attacks per year. [3]Number of hospitalizations per patient. [4]Number of nighttime awakenings per week. [5]Frequency of concomitant use of any other medication except for asthma; SD: standard deviation; f: frequency observed

compliant with treatment, the mean age was 44.9 ± 16.2 years, compared with 43.6 ± 17.2 years in the group of patients that were noncompliant (p = 0.70).

The rate of compliance was found to be 51.9% (95% CI: 43.0 - 60.7). In Table 2, the treatment compliance rates are shown according to each of

TABLE 2

Rates of compliance according to selected variables and bivariate analysis (n = 131)

Variables	n	Rate of compliance (%)	OR	95% CI	p
Gender					
Male	38	65.8	2.2	1.0-4.9	0.05
Female	93	46.3			
Steady partner					
Yes	60	58.3	1.61	0.8-3.2	0.22
No	71	46.5			
Years of schooling					
Elementary/ junior high school	57	52.6	1		
High school	55	56.4	0.9	0.5-1.8	0.96
Higher education	19	36,8	1.4	0.5-4.2	0.63
Race					
Caucasian	78	52.6	1.07	0.5-2.1	0.90
Non-Caucasian	53	50.9			
Relief medication for asthma					
Yes	88	55.7	1.59	0.8-3.3	0.26
No	43	44.2			
Stage of persistent asthma					
Moderate	69	42.7	0.42	0.2-0.8	0.02
Severe	62	63.9			
Other atopic conditions					
Yes	74	48.7	0.74	0.4-1.5	0.48
No	57	56.1			
Visits to the emergency room					
Yes	51	58.8	1.58	0.8-3.2	0.22
No	80	47.5			
Hospitalizations for asthma					
Yes	70	54,3	1.23	0.6-2.4	0.61
No	61	49.2			
Nighttime awakenings					
Yes	33	63.6	1.90	0.8-4.3	0.16
No	98	48.1			
Use of other drugs					
Yes	54	55.6	1.28	0.6-2.6	0.59
No	77	49.4			
Comorbidities					
Yes	46	54.4	1.16	0.6-2.4	0.72
No	85	50.6			
Current smoking					
Yes	07	42.9	0.68	0.1-3.1	0.71
No	124	52.4			

n: number of cases; OR: odds ratio; 95%CI: 95% confidence interval; p: statistical significance

TABLE 3

Analysis of selected factors associated with treatment compliance among asthma patients, together with estimated odds ratios, 95% confidence intervals and statistical significance

Factors	Logistic regression		
	OR	95% CI	p
Male	1.9	0.8-4.4	0.15
With steady partner	1.1	0.5-2.5	0.80
Years of schooling			
Elementary/ junior high school	1.0		
High school	1.0	0.5-2.4	0.93
Higher education	0.4	0.1-1.3	0.13
Severe persistent asthma	2.4	1.1-5.1	0.003

OR: odds ratio; 95% CI: 95% confidence interval; p: statistical significance

the variables studied and are summarized in relation to the bivariate analysis.

Table 3 presents the variables studied according to the multivariate analysis using logistic regression.

In the bivariate analysis, being male was found to be protective against noncompliance (OR: 2.2; 95% CI: 1.0 - 4.9; p = 0.05). However, this was not confirmed in the multivariate analysis. There was a higher rate of compliance among patients with severe persistent asthma than among those with moderate persistent asthma (the more severe the asthma, the higher the rate of compliance found, both in the bivariate analysis and in the logistic regression), and this difference was statistically significant (OR: 0.4; 95% CI: 0.2 - 0.8; p = 0.02 vs. OR: 2.4; 95% CI: 1.1 - 5.1; p = 0.03).

The rate of treatment compliance was 43% among the patients with moderate persistent asthma and 64% among those with severe persistent asthma.

There were no statistically significant differences among any of the other variables studied (age; race; marital status; gender; years of schooling; smoking habits; concomitance with other atopic conditions; comorbidities; use of other medications; hospital admissions and visits to the emergency room for asthma; use of relief medication; and nighttime awakenings).

DISCUSSION

To the best of our knowledge, this was the first nationwide Brazilian study assessing treatment

compliance among asthma patients and evaluating some of the main intervening factors in asthma. The overall rate of compliance was approximately 52%, which is similar to the results found in other countries.[6,19]

In order to skirt the current discussion in the literature regarding the advisability of continuous or intermittent treatment in cases of mild persistent asthma,[20-21] individuals presenting such asthma were excluded from the study by design.

There are several factors that must be considered in order to understand compliance/noncompliance with continuous treatment. In the present study, some of these factors were analyzed. The stage of severe persistent asthma was the variable that was found to be associated with higher rates of treatment compliance. However, we found no association between noncompliance and other variables indicative of uncontrolled asthma, such as number of visits to the emergency room, use of relief medication, or number of hospitalizations for asthma. Other variables typically associated with higher treatment compliance, such as marital status (in this study defined as having a steady partner or not), higher educational level, presence of other chronic diseases, chronic use of other medications, hospitalizations for asthma, and visits to the emergency room for asthma,[22] were not found to be significant in the present study. In order to determine whether those are special characteristics of the population under study or a consequence of the sample size, it would be necessary to conduct further studies involving larger patient samples. The present study presented limitations regarding its external validity, especially due to the sample size, the varying proportions of patients included from each demographic region of Brazil, and possible selection biases. Therefore, all inferences and conclusions must be considered tentative, since they only apply to the specific population studied.

The generally held belief that female patients are more likely to comply with treatment, also could not be confirmed here. We observed a tendency toward a lower rate of compliance among female patients in the bivariate analysis, a finding that was not confirmed in the logistic regression.

Financial obstacles are a significant predisposing factor for inadequate treatment compliance, especially in cases of continued prescription of a certain medication.[23-25] Therefore, considering that free medication was made available to all patients included in the study, it is possible that the rates of compliance found here would be even lower if extrapolated to the general population.

Fear of adverse effects (especially those produced by corticosteroids),[26] doubts regarding the effectiveness of the treatment regimen proposed, and the misunderstanding of the instructions received[27] can result in a divergence between the expectations of the patient and those of the physician, despite the good intentions of both parties.[28]

Consequently, patients considered noncompliant with treatment cannot be simply classified as difficult, irresponsible or uncooperative, since they might have received little instruction, have misunderstood the information they were given, or not have yet been able to introduce their medication into their daily routine.[4,27] These aspects were not evaluated in the present study.

In addition, compliance with a treatment regimen is not a dichotomous condition, and there could be a wide spectrum in the percentage of patients who use the medications. In the asymptomatic phase of the disease,[20-21] there is a tendency toward limited use of the medications, whereas, during periods of exacerbation, the patient tends to become totally compliant with the prescription and the medical advice. This situation is particularly complex in asthma since it has been demonstrated that the rate of compliance is considered low even among asthma patients who have recently been discharged from the hospital.[29]

These considerations have contributed to broadening the concept of the term "compliance" to one that involves an active, voluntary, cooperative relationship between the patient and the health care professional in taking mutually acceptable measures to produce preventive and therapeutic health improvements. The previous, simplistic definition of compliance (the rate at which a patient follows medical advice),[30] although progressively falling into disuse, is still employed due to the objectivity of the data, which facilitates study design.

The concept of poor compliance with medical advice is linked to adverse health consequences: disease progression; exacerbations; prescription and unnecessary use of more potent (occasionally more toxic) medications; increased number of visits to the emergency room; and, finally, treatment failure. It is, therefore, a factor that significantly increases the cost of the disease to the health system.[7]

The data described herein offer, for the first time, a panorama of treatment compliance rates among asthmatic patients from various medical centers throughout the country. These data could serve as a basis for evaluating the efficacy of measures aimed at improving treatment compliance among asthma patients.

ACKNOWLEGMENTS

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