Original Article

Predictors of adherence to treatment in patients with severe asthma treated at a referral center in Bahia, Brazil*

Preditores da adesão ao tratamento em pacientes com asma grave atendidos em um centro de referência na Bahia

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Abstract

Objective: To determine the rate of adherence to treatment with inhaled corticosteroids in patients with severe asthma, to identify predictive factors for adherence and to evaluate the relationship between adherence to treatment and parameters of clinical and functional response. **Methods:** Prospective cohort study of patients enrolled in the Program for the Control of Asthma and Allergic Rhinitis in the state of Bahia, Brazil. The study comprised 160 patients with severe asthma, monitored for 180 days in order to evaluate adherence (dependent variable) to the prescribed inhaled corticosteroid. Independent variables were assessed at baseline and for a six-month follow-up period by means of interviews and the completion of a standardized questionnaire. Patients recorded the missed doses in a diary. **Results:** Of the 160 patients, 158 completed the study. Adherence rate was 83.8%. Of the 158 patients, 112 (70.9%) were considered adherent (cut-off point: 80% of prescribed doses administered). There was a significant association between asthma control and adherence to treatment. Predictors of poor adherence were adverse effects, living far from the referral center, limited resources to pay for transportation and dose schedule. Other factors, such as depressive symptoms, religion and economic status, were not associated with poor adherence. **Conclusions:** Adherence to asthma treatment was high and was associated with the clinical response to treatment, in a sample of patients with severe asthma enrolled in a public program that provides free medication and the assistance of a multiprofessional specialized team in a referral center.

Keywords: Asthma; Directly observed therapy; Treatment outcome; Patient compliance; Pharmacy.

Resumo

Objetivo: Determinar a taxa de adesão ao tratamento padrão com corticóide inalatório em pacientes com asma grave, identificar seus fatores preditores e avaliar a relação entre adesão ao tratamento e os parâmetros de resposta clínica e funcional. **Métodos:** Coorte prospectiva de pacientes atendidos no Programa de Controle da Asma e da Rinite Alérgica na Bahia, Brasil. O estudo incluiu 160 pacientes com asma grave, acompanhados por um período de 180 dias para medida da adesão (variável dependente) ao corticóide inalatório prescrito. As variáveis independentes foram determinadas na avaliação inicial e durante seis meses através de entrevistas e aplicação de questionário estruturado. Os pacientes registraram em um diário as doses não utilizadas. **Resultados:** Do total de 160 pacientes, 158 completaram o estudo. A taxa de adesão ao tratamento foi de 83,8%. Dos 158 pacientes, 112 (70,9%) foram considerados aderentes ao tratamento (ponto de corte: 80% de todas as doses administradas). Houve associação significante entre o controle da asma e adesão ao tratamento. Os fatores relacionados a uma baixa adesão foram efeitos adversos, local de residência distante do centro de referência, dificuldade de pagar pelo transporte e regime posológico. Outros fatores, como sintomas depressivos, religião e classe econômica, não tiveram relação com a adesão. **Conclusões:** A adesão ao tratamento foi considerada elevada, havendo relação com a resposta clínica ao tratamento em uma amostra de pacientes com asma grave atendidos em um programa público com fornecimento gratuito de medicamentos e atendimento multidisciplinar em unidade de referência.

Descritores: Asma; Terapia diretamente observada; Resultado de tratamento; Cooperação do paciente; Farmácia.

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Introduction

Asthma is a chronic inflammatory syndrome that is highly prevalent worldwide, affecting approximately 300 million individuals of all ages.[1] In Brazil, it is calculated that there are over 16 million asthma sufferers of all ages. In the major Brazilian cities, approximately 24% of all children and 19% of all adolescents present symptoms of asthma. It has also been reported that 46.6% of the children living in the city of Salvador have a history of wheezing. In Brazil as a whole, there is a tendency toward an increase in the rate at which children and adolescents are diagnosed with asthma.[2,3]

In addition to the loss in patient quality of life, asthma results in high direct and indirect costs related to visits to the emergency room, hospitalizations and medical appointments, as well as to school and work absenteeism.[4] The annual number of asthma-related hospitalizations through the Brazilian Unified Health Care System is estimated at 350,000. In addition, there are approximately 2,000 asthma-related deaths, as well as thousands of asthma-related outpatient clinic and emergency room visits, every year.

The *Programa de Controle da Asma e da Rinite Alérgica na Bahia* (ProAR, Bahia State Program for the Control of Asthma and Allergic Rhinitis) is an educational project of research and treatment project that integrates the Brazilian Unified Health Care System and the public university, based on the Brazilian National Asthma Plan. One of the proposals of the program is to guarantee the integrated control of asthma and allergic rhinitis by regularly providing free medication to patients with severe persistent asthma through the Exceptional Medication Program of the Brazilian National Ministry of Health.[5]

The use of these medications contributes effectively to the control of severe asthma. Studies show that complete discontinuation of the treatment will probably result in clinical deterioration, having been shown to be associated with the degree of hyperresponsiveness.[6] Adherence to treatment is one of the most important factors that guarantee the success of the treatment. More conservative estimates indicate that almost half of the medication annually prescribed and dispensed is not used as prescribed. Primary noncompliance (failing to follow the first prescription) varies from 6% to 44%.[7,8] Some of the first researchers to use electronic devices to measure adherence to treatment found an adherence rate of approximately 47% for a four daily-dose regimen of treatment with inhaled corticosteroids (ICs).[9] Research on the theme has evidenced the factors that can influence adherence to treatment.

The aim of the present study was to determine the rate of adherence to standard treatment with ICs in patients with severe asthma treated via the ProAR, to identify predictive factors and to evaluate the relationship that adherence to treatment has with clinical and functional (spirometry) response parameters.

Methods

A prospective cohort study was conducted between August of 2006 and July of 2007. The sample consisted of 160 consecutive patients who were monitored for a 180-day period by the research team for the quantification of adherence (outcome measure) to the prescribed IC. The independent variables of association with adherence were measured at the time of inclusion of the patient in the study, and for six months thereafter, through interviews and application of a structured questionnaire. During the interview, data related to the following aspects were collected: socioeconomic and demographic characteristics; history of asthma; severity of the symptoms based on the Asthma Control Questionnaire[10]; medication used; whether the patient understood the purpose of the IC; depressive symptoms (assessed through application of the Beck Depression Inventory)[11]; beliefs; acceptance of the disease; knowledge of the benefits and risks of the treatment; and degree of communication with the health professionals who monitored the patient. Patients were submitted to pulmonary function tests (spirometry) for evaluation of the functional response to the treatment.

After inclusion in the study, the patients completed a questionnaire containing the independent variables, applied by a research assistant previously trained for such. At the end of each visit, the patients received sufficient medication to use until the next visit, as well as a log to record the missed doses during their participation in the study. At each visit, this log was reviewed by the research assistants. Patients were instructed to return the empty packages of the medication dispensed in all visits, in addition to the patient log for evaluation of adherence.

Patients of presenting the following characteristics were selected: aged 18 years or older;

presenting severe persistent asthma defined by the criteria established by the III Brazilian Consensus on Asthma[12]; and admitted to the outpatient clinic of the ProAR, at the Carlos Gomes Health Care Center in Salvador, Brazil.

The use of ICs was monitored for 180 days by counting the used capsules or by weighing the inhalers in order to determine the quantity of dry powder consumed over the period. The rate of adherence to the IC treatment was calculated as follows:

- For the ICs in capsule presentation, the following formula was used: (NU ÷ NT) × 100; where NU is the number of capsules actually used during the period, and NT is the number of capsules that should have been used.
- For the ICs in dry powder presentation for oral inhalation, the inhalers where weighed at the time of dispensing, as well as after 30 days of use, at which point the following formula was used: (U ÷ T) × 100; where U is quantity (in g) actually used during the period, and T is the quantity (in g) that should have been used.

At the end of the follow-up period, the pharmacy database was analyzed in order to compare it with the information collected by the research assistants, as well as to determine the dates of patient visits and the quantity of medication dispensed at each visit.

The study design was approved by the Ethics in Research Committee of the Federal University of Bahia Climério de Oliveira Maternity Hospital. All patients gave written informed consent, and their identification data were maintained confidential.

Data were analyzed using the Statistical Package for the Social Sciences, version 9.0 (SPSS Inc., Chicago, IL, USA). The mean and standard deviation were calculated for the quantitative variables that presented normal distribution. Categorical variables were presented as frequency and percentage. The chi-square test was used for the evaluation of

Table 1 - Sociodemographic characteristics of the patients with asthma and the observed adherence to treatment.

Characteristic	Results	Adherence, %	p
Gender, n (%)			
Male	40 (25)	84.1	0.8
Female	120 (75)	83.7	
Age (years), mean ± SD	49 ± 13.9		
Number of children, mean	2.7		
Religion, n (%)			
Catholic	94 (58.8)	85.2	0.1
Protestant	34 (21.3)	81.1	
Other	30 (19.9)	80.5	
Permanent address, n (%)	153 (95.6)	83.8	0.4
Marital Status, n (%)			
Married	75 (46.9)	81.4	0.2
Single	46 (28.8)	85.2	
Divorced	23 (14.4)	86.4	
Widow/widower	16 (10)	87.6	
Employment status, n (%)			
Employed	49 (30.6)	78.4	0.7
Unemployed	31 (19.4)	89.1	
Retired	37 (23.1)	85.3	
Homemaker	39 (24.4)	84.3	
Level of education, n (%)			
Illiterate	15 (9.4)	84.8	0.7
Junior high	89 (55.6)	84.1	
High school	52 (32.5)	83.1	
University	4 (2.5)	83.9	

the statistical significance among categorical variables and the Student's t-test was used for the comparison among the means of the quantitative data. The Mann-Whitney U test and the Kruskal-Wallis test were used for the analysis of quantitative variables presenting asymmetric data. The logistic regression model was used for adjusting potential confounding factors.

The level of statistical significance was set at alpha < 0.05. The degree of association among the studied variables was evaluated using odds ratios with a confidence interval of 95%.

The calculation of the sample size was based on the following premises: total number of ProAR patients during the period (approximately 1,600 patients); relative margin of error of 5%; confidence interval of 95%; prevalence of adherence of approximately 50%, based on data found in the literature; power of 80%; significance level of 5%; and a possibility of 20% loss to follow-up—together revealing the ideal sample size to be 156 patients.

A cut-off point of 80% of the doses prescribed in the period was used to define patients as adherent. This value was adopted taking into consideration the severity of the disease and the availability of free medication to all of the patients treated via the ProAR.

Results

One hundred-sixty patients were included. Of those, 120 (75%) were female, with a mean age of 49 ± 14 years. Adherence to the use of IC was evaluated in 158 patients, and 112 (70.9%) were considered adherent according to the adopted cut-off point. The rate of adherence in the sample was 83.9% of the used doses. Adherence was not evaluated in two patients, since they withdrew the informed consent and decided to leave the study. Sociodemographic data and data on patient adhesion according to each variable are described in Table 1.

There was no difference in the mean age among the groups of adherent and nonadherent patients (49.7 and 46.8 years, respectively; p = 0.2). The mean duration of the asthma in the studied sample was 26.0 ± 15.8 years, with a median of 26 years. The adherent patients had a longer asthma history in relation to nonadherent patients (27.8 and 22.1 years, respectively; p = 0.043; 95% CI: 0.18-11.19).

The rate of adherence of the patients residing in the city of Salvador in comparison with the patients residing outside Salvador was, respectively, 85.0% and 78.1%. (p = 0.01; 95% CI: 1.3-12.4).

Eighteen patients (11.3%) referred to having difficulty in transportation. These patients presented lower adherence in relation to the other patients of this cohort (p = 0.013). The risk of nonadherence to treatment was 3.6 times higher among patients without conditions of transportation (95% CI: 1.3-9.8).

Observing side effect of the use of the medication was reported by 31 patients (19.6%). There was association between the presence of adverse events and adherence to pharmacological treatment (p = 0.017). The estimated risk of nonadherence was 33% higher among patients who presented adverse events in the present study (95% CI: 0.1-0.7) in relation to the patients who reported no adverse events. The adverse events most frequently reported by the patients were the following: epigastric pain in 3 patients; weight gain and heartburn in 2; and stomach acidity, agitation, conjunctivitis, loss of response, oral candidiasis, pharyngeal irritation, nausea, throat clearing, hoarseness, drowsiness, tachycardia, dizziness, tremors, blurred vision and xerostomia in 1.

Of the total, 51 patients (32%) reported having visited the emergency room in the period of the cohort, with a mean ± SD of 3.2 ± 2.6 visits. Of those, 18 (35%) were considered nonadherent to the treatment. One hundred and seven patients (68%) did not visit the emergency room in the period. Of those, 28 (26%) were considered nonadherent to the treatment. The patients who visited the emergency room had an adherence of 81.5%

Table 2 - Control characteristics of asthma among adherent and nonadherent patients.

Characteristic	Adherent	Nonadherent	p
Exacerbation, n (%)	51 (45.5)	23 (50)	0.7
Emergency room visits, mean ± SD	0.9 ± 1.9	1.4 ± 2.6	0.2
Asthma Control Questionnaire score, mean ± SD	1.6 ± 1.2	2.3 ± 1.5	0.008

Table 3 - Characteristics of the patients studied in relation to the depressive symptoms.

Characteristic	Results	p	95% CI
Age (years), mean ± SD			
Patients with depressive symptoms	50.8 ± 13.5		
Patients without depressive symptoms	48.0 ± 14.1	0.2	(−1.7 to 7.3)
Number of children, mean ± SD			
Patients with depressive symptoms	3.3 ± 2.8		
Patients without depressive symptoms	2.3 ± 2.1	0.03	(0.12 to 1.69)
Adherence, %			
Patients with depressive symptoms	83.7		
Patients without depressive symptoms	83.9	0.9	(−5.3 to 4.8)

of the used doses. The others had an adherence of 85.7% (p = 0.08).

Of the total of the patients, 123 (77.8%) used medication twice a day, 34 (21.5%) three times a day and 1 (0.7%) only once a day. The mean daily dose of corticosteroids was 870 ± 200 µg (median, 800 µg), varying between 400 and 1,600 µg. The IC of choice was budesonide (87.5%). Adherence to treatment was significantly lower among patients who used the IC three times a day than among those who used it twice a day (78.9% and 85.2%, respectively; p = 0.02; OR = 0.34; 95% CI: 0.22-0.68).

According to the Asthma Control Questionnaire, 60 patients (38%) presented controlled asthma. The rate of adherence to treatment among patients with controlled asthma was 88.5% of the doses. In the group of patients with uncontrolled asthma, adherence was 80.9%. This result was significant (p < 0.001). The estimated risk of uncontrolled asthma was 2.9 times higher among nonadherent patients than among adherent patients (95% CI: 1.3-6.4). Table 2 presents the characteristics of asthma control in both groups of patients: those that were adherent to the treatment and those that were nonadherent.

The mean ± SD for the Beck Depression Inventory score was 13.4 ± 10.0 points (median, 11 points), and 54 individuals (33.8%) were classified as having depressive symptoms, scoring more than 20 points on the Beck Depression Inventory. Table 3 presents the principal characteristics of the studied patients in relation to depressive symptoms. There was no significant association between adherence to treatment and depressive symptoms (p = 0.23). The rate of adherence was similar in the two groups of patients (83%; p = 0.9).

Only 14 patients (8.8%) reported having difficulty in understanding the information given by the physician and pharmacist who monitored them. The rate of adherence to treatment among those patients was 82.6%, and there was no significant difference between them and the other patients (p = 0.7). As for the access to medical assistance, 7 patients (4.4%) reported having difficulty in scheduling extra appointments when necessary. Among those patients, adherence to treatment was 85% (p = 0.8).

Table 4 presents the results of the logistic regression analysis adjusted for the variables that were considered statistically significant in the bivariate analysis. All variables presenting a value of p < 0.2 in the bivariate analysis were included in the initial model. There were no statistically significant differences for the other variables studied.

We observed that a history of asthma was not considered a protective factor for adherence to treatment in the multiple logistic regression analysis.

Table 5 presents the other variables that had no relation to adherence to treatment.

Table 4 - Multivariate adjusted analysis, using logistic regression of the predictive variables of nonadherence evidenced in this cohort.

Variable	OR	95% CI	P
Residing outside Salvador	4.1	1.5-11.2	0.004
Longer duration of asthma	0.9	0.9-1.0	0.06
Occurrence of adverse event	3.9	1.3-11.5	0.01
Dose schedule: twice a day	5.8	2.2-14.8	0.0002
Transportation difficulties	4.0	1.3-12.8	0.017

Table 5 - Factors not associated with adherence to treatment in this cohort.

Variable	n	Adherence, %	P
Difficulty in communicating with the physician or pharmacist?			
Yes	120	86.5	
No	14	82.5	0.5
Do the dose schedules interfere much with your work or other activities in your life?			
Yes	26	81.3	
No	132	84.3	0.3
ls there someone who helps you use the medications (family member, friend, partner or other)?			
Yes	61	84.8	
No	97	83.1	0.4
Do you object to using medication due to philosophical, religious or spiritual beliefs?			
Yes	11	76.1	
No	147	84.4	0.07
Has the use of alcohol or drugs ever interfered with your use of the medication (e.g., causing you to forget to take the medication)?			
Yes	18	82.3	
No	140	84.0	0.6
Do you feel uncomfortable if other people watch you use the medications?			
Yes	50	84.1	
No	108	83.7	0.4

Discussion

The principal finding of the present study was that the patients monitored in the ProAR presented a high rate of adherence to treatment (83.9%) if compared with that reported for patients with asthma, which varies from 30% to 70%.[13] This result is similar to that obtained in a study conducted in Switzerland,[14] in which the rate of adherence to treatment was 93%, and is higher than the value found by other authors (51.9%) in a national multicenter study with a number of individuals (n = 131) similar to that of the sample analyzed in the present study.[15]

One of the aspects of the present study that should be taken into consideration is that we observed good communication between patients and the health professionals who work in the ProAR, together with easy and rapid patient access to medical care and to extra appointments. A good relationship between health care staff and patients and the facility of access to health care service is fundamental to guarantee adequate compliance with the pharmacological treatment and is reflected in the profile of the medication use. In a study using different parameters to evaluate adherence to treatment,[16] patient satisfaction was the only factor significantly associated with adherence.

Various factors can be considered predictors of adherence to treatment in patients with asthma. In the present study, we found an association between adherence to treatment and the following variables: adverse events; living far from the health facility; transportation difficulties; and dosage interval of multiple doses. Asthma was less controlled in patients presenting low adherence. In the present study, we were unable to evaluate the relationship between adherence to treatment and the different classifications of the severity of asthma, since all patients selected had severe persistent asthma according to the criteria of the Brazilian Thoracic Association.[12]

Depressive symptoms, as evaluated by the Beck Depression Inventory, presented no association with low adherence to treatment. It is of note that the frequency of such symptoms was elevated among the asthma patients in the present study. The adopted cut-off point (20 points) for the evaluation of the depressive symptoms was more conservative than the one adopted in other studies in which the prevalence of depressive symptoms is high. This result differs from the findings of other studies in which depression has been associated with low adherence to treatment.[17,18] However, this result is consistent with findings showing a relatively high prevalence of depressive symptoms in patients with more severe disease and presenting a low response to the treatment.[19,20]

There is little possibility that adherence was overestimated in the present study, since three different methods were used to evaluate adherence. All patients had their medication counted or weighed according to the presentation of the inhaler that the patient used. In parallel, the information registered in a log developed specifically for the present study was collected during the follow-up period. This information was used for the evaluation of adherence to treatment as well as to determine why the patient missed a given dose of the treatment. In addition, the pharmacy database was used in order to confirm the quantities of medication received by the patient in each visit.

This cohort study aimed to analyze adherence to treatment in a sample of patients with severe asthma who participated in a multiprofessional program of outpatient treatment, with free medication available. Therefore, the rates of adherence found in the present study cannot be extrapolated to the population in general, since some predictors of adherence, such as the costs of the medication acquisition and of medical appointments, which can influence the pattern of their use, are nor part of the scenario for the patients enrolled in this program.

Poor adherence to treatment increases the risk of visits to the emergency room, as well as the risk of hospitalization, as described in another study.[21] In the present study, the rate of nonadherence to treatment was higher among patients who had visited the emergency room. Although this difference did not rise to the level of statistical significance, there was a tendency toward an association between the number of visits to the emergency room and nonadherence, reflecting the inadequate asthma control among such patients.

The treatment regimen can influence the pattern of adherence. The results of the present study show that the patients who used a treatment regimen of two daily inhalations are more adherent to treatment than are those who used three daily inhalations. This result corroborates the findings of a systematic review of 76 clinical trials,[22] in which adherence was found to be inversely proportional to the frequency of daily doses.

In the present study, the adverse events reported by the patients constituted another factor associated with low adherence to treatment. We also observed that the effect of corticosteroid phobia, which has been described in other studies,[23] was not a determining factor for adherence to treatment. Although we found that a large number of patients feared the potential side effects of their medication, all patients stated that they considered the correct administration of the medication important. In addition, only half of these patients reported experiencing some adverse event which made it difficult to continue using the medication. Therefore, in our cohort, the patients failed to take their medication when they actually presented some side effect or adverse reaction to the medication.

The present study has some limitations in relation to its external validity. We cannot extrapolate our results to the general population.

Another limitation of the study is the possible selection bias. By including the patients consecutively, we risk selecting only patients who came to the visits habitually, and it was therefore impossible to identify and interview the patients who missed visits. However, in the present study, adherence was evaluated prospectively and objectively, as were the many possible predictors of adherence, in patients with severe asthma. In patients with asthma, adherence to treatment is important for reducing asthma-related morbidity and mortality. We know of no other study in which a comparable sample of patients with severe asthma was evaluated.

Among the patients evaluated in the present study, adherence to treatment was considered high. In a sample of patients with severe asthma treated via a public program that provides free medication and multidisciplinary treatment at a referral center, adherence to treatment was found to be associated with the clinical response to treatment.

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