

FACTORS RESTRICT TREATMENT EFFICIENCY IN ASTHMA PATIENTS

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Abstract

Background: A number of modifiable factors that contribute to poor asthma control have been identified. We wanted to know how many patients had insufficient therapy, adherence, or major inhaler technique errors, and how they affected asthma control.

Methodology: We conducted a cross-sectional multicenter observational research with asthma patients who were referred for the first time from primary to specialized treatment. Adequate prescription according to guidelines, treatment adherence, and illness control were among the data collected. 35.9% of the 1682 patients (age 45-17 years, 64.6 percent men) had insufficient prescriptions, 76.8% had low adherence, and 17 percent had critical inhaler technique errors, with Easyhaler users making significantly fewer critical errors than other dry powder inhaler users (10.3 versus 18.4%; $p < 0.05$). Inadequate prescription (OR: 3.65), non-adherence to therapy (OR: 1.8), and inhaler abuse were all linked to poor asthma control (OR: 3.03). A greater number of risk variables were linked to a greater likelihood of having poorly managed asthma.

Keywords: Asthma, interdental cleaning, elderly, prevention, periodontal disease, caries.

Introduction

Asthma is a frequent disease that costs a lot of money in terms of healthcare and lost productivity [1]. Asthma is becoming more common around the world, with about 1000 people dying from it every day, according to a study published in 2015 [2]. According to the most recent data on asthma prevalence worldwide, 334 million people are affected [3]. However, its frequency varies widely between countries, with wealthy countries having the highest prevalence¹. Exacerbations are associated with high direct (medications, hospitalization, Emergency Department treatment, etc.) and indirect (school absenteeism, loss of work productivity, etc.) costs. Asthma exacerbations are currently one of the most common reasons of Emergency Department⁴ visits, highlighting asthmatic patients' poor management. Exacerbations can be caused by a variety of circumstances, including exposure to external stimuli, poor adherence to medication, inadequate therapy, and poor inhaler technique in the case of uncontrollable asthma [4-6]. Several studies have found that asthmatic patients had poor

medication adherence: 50 percent in children and 30-70 percent in adults, depending on the nation, age, sex, and ethnicity [7,8]. Limited understanding or recognition (among patients and/or physicians), beliefs or side effect worries, inhaler features, and directions for use were all factors that contributed to this difference. As a result, asthma control as a therapeutic goal is still a long way off [9]. Better control would improve not only cost effectiveness but also quality of life, lower school absenteeism, and boost workplace productivity. The same problem can be seen in asthma management in primary care. Several research on asthma in primary care appear to imply that, despite accessible medications, asthma control in practical practice is inadequate. European publications [10,11]. have revealed little apparent improvement in symptom control in recent years. The study's primary goals are to (1) determine the appropriateness of prescribed treatment, as well as the presence of poor adherence and critical errors in inhalation technique in patients referred from primary care to a specialist for the first time, and (2) investigate the

relationship between these factors and poor asthma control. This real-life study could help us figure out whether asthma management in primary care has improved in terms of prescription quality, inhaler technique, and patient adherence to treatment in the 30 years since asthma guidelines were implemented in Spain [13-17].

Material and Methods

Participants and Study Design

Patients aged 18 years who used any type of inhaler device and were referred from general care to a pneumologist or allergologist for the first time for any reason were included in a cross-sectional multicenter observational study. From September through December 2016, data was gathered. The lack of a signed informed permission and incapacitating illness or mental disease were also exclusion criteria, making participation in the study impossible according to the research requirements. Spirometry and a bronchodilator test were performed on all patients to confirm or rule out asthma [19-24].

Study Measurements

The following important characteristics were evaluated: adequate asthma therapy based on GINA recommendations⁴⁴ (GINA treatment steps 1–5 were used to determine the appropriateness of current patients' treatment based on asthma control at the time of the visit). Treatment adherence according to the MG questionnaire (patients were classified into reliable or not reliable according to a punctuation from 0 to 4, with 0 = reliable and 1 = not reliable)^{45,46}, adherence to inhalers (TAI 50 reliable; 50 not reliable)^{45,46}, adherence to inhalers (TAI 50 reliable; 50 not reliable)^{45,46}, adherence to inhalers. item 12 of the TAI questionnaire revealed severe issues with patient inhaler technique. Only the primary inhaler was tested for maintenance therapy. This item includes a realistic demonstration of patients' inhaler technique as well as the physician identifying crucial faults. This item depicts two types of patients: those with one critical mistake and those without. A questionnaire from the GEMA teaching material

was used to assess additional patient knowledge about asthma (Supplementary Table 3) [25-27].

Asthma severity according to the 2015 GINA criteria⁴⁴, comorbidities (allergy, occupational exposure to allergens or irritants, smoking, etc.), and asthma control according to both GINA and ACT criteria^{44,48} were all gathered. These factors, according to GINA, were considered: Symptoms of the patients throughout the day and at night (two times per week for daytime symptoms and no nocturnal symptoms). As a result, patients were divided into two groups: well-controlled (all previous items) and partially/not-controlled (one to four previous things). Patients were divided into the same two categories by the ACT, but this time through five items from the validated Spanish version of the ACT (21: well controlled, 21: partially/not controlled). All data was gathered in a single visit using an online patient notebook that was suited to the study's needs. The study was approved by the Ethics Committee (Hospital Clinic de Barcelona, Registration number HCB/2016/0647), and it was carried out in accordance with the Helsinki Declaration (1964). All participants gave their informed consent [29-35].

Statistical Analysis

For categorical data, the Pearson's chi-squared test (2) was used, and for continuous data, the analysis of variance test was used. To establish the independence of discovered components, a binary logistic regression was performed (OR). Cohen's k coefficient, Spearman's correlation coefficient, and R square were used to express the relationship and concordance between ACT/GINA regarding asthma control (R2). SPSS 20.0 was used to analyze all of the data [35-40].

Results

Demographics and Clinical Characterization

The trial involved 1682 patients, with men accounting for 64.6 percent of the total. The average age was 45 years and 17 months. Table 1 summarizes the cohort's characteristics [41-45].

Table 1: Baseline demographic and clinical characteristics.

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients: EFIMERA observational study

Variable	Results	Number of patients evaluated
Age (years), mean ± SD (range)	45.2 ± 17.9 (18–90)	1681
Females, n (%)	592 (35.4)	1670
Males, n (%)	1078 (64.6)	1670
Age at diagnosis (years), mean ± SD	33.8 ± 15.7	1682
Disease duration (years), mean ± SD	14.9 ± 14.1	1682
Time between treatment initiation and diagnosis (years), mean ± SD	1.1 ± 6.6	1677
Current smokers, n (%)	263 (15.7)	1678
Ex-smoker, n (%)	294 (20.8)	1414
Any allergy, n (%)	665 (39.8)	1671
Any comorbidity, n (%)	841 (50.4)	1668
Obesity, n (%)	242 (14.5%)	1668
Rhinosinusitis, n (%)	190 (11.4%)	1668
Rhinitis/conjunctivitis, n (%)	313 (18.8%)	1668
Gastroesophageal reflux disease, n (%)	149 (8.9%)	1668
Other comorbidities, n (%)	268 (16.1)	1668

≥80%	1042 (62.3)	1673
<80%	507 (30.3)	1673
<60%	124 (7.4)	1673
Categories of asthma severity (2015 GINA), <i>n</i> (%)		
Mild	719 (42.9)	1674
Moderate	780 (46.6)	1674
Severe	175 (10.5)	1674
Level of asthma symptom control (2015 GINA)		
Well controlled	474 (28.2)	1679
*Partly controlled	635 (37.8)	1679
*Uncontrolled	570 (33.9)	1679
Current treatments, <i>n</i> (%)		
Only maintenance inhaler	492 (29.6)	1662
Only rescue inhaler	357 (21.5)	1662
Maintenance inhaler + rescue inhaler	468 (28.2)	1662
Maintenance inhaler + oral treatment	78 (4.7)	1662
Rescue inhaler + oral treatment	40 (2.4)	1662
Maintenance inhaler + rescue inhaler + oral treatment	206 (12.4)	1662
Monoclonal antibodies	23 (1.4)	1662
Type of maintenance inhaler device, <i>n</i> (%)		
Rescue inhaler + oral treatment	40 (2.4)	1662
Maintenance inhaler + rescue inhaler + oral treatment	206 (12.4)	1662
Monoclonal antibodies	23 (1.4)	1662
Type of maintenance inhaler device, <i>n</i> (%)		
Multiple-dose DPI	935 (75.2)	1244
pMDI	240 (19.3)	1244
Single-dose DPI	26 (2.1)	1244
pMDI + multiple-dose DPI	39 (3.1)	
pMDI + single-dose DPI	4 (0.3)	1244

DPI dry powder inhaler, FEV₁ forced expiratory volume in 1 s, GINA Global Initiative for Asthma, PEF peak expiratory flow, pMDI pressurized metered-dose inhaler.

*Poorly controlled.

According to the recommendations of the Global Initiative for Asthma (GINA), 35.9% of patients had a prescription that was insufficient or inadequate (Table 2). GINA 1–5 steps were considered in order to determine whether the prescription was adequate or not. The maintenance treatment of the patients was compared to their previous exacerbations and current symptoms. According to the Asthma Control Test (ACT), 82.5 percent of patients with inadequate prescriptions had poorly controlled (partly/uncontrolled) asthma, whereas 56.3 percent of patients with adequate treatment had poorly controlled asthma (odds ratio (OR) 3.65, 95 percent confidence interval (CI): 2.87–4.65, *p* 0.0001; Table 3) [46].

Factor	<i>n</i> (%)	Number of patients evaluated
Inadequate prescription (GINA)		
Yes	604 (35.9)	1681
No	1077 (64.1)	1681
Adherence according to Morisky–Green questionnaire		
Adherent	522 (31.5)	1658
Non-adherent	1136 (68.5)	1658
Adherence according to TAI		
Adherent	381 (23.2)	1639
Non-adherent	1258 (76.8)	1639
Critical inhaler mistakes		
No errors	1394 (83.0)	1680
≥1 error	286 (17.0)	1680

GINA Global Initiative for Asthma, TAI Test of Adherence to Inhalers.

In terms of treatment adherence, the Test of Adherence to Inhalers (TAI) questionnaire revealed that 76.8% of patients had poor adherence, while the Morisky–Green (MG) questionnaire revealed that 68.5 percent of patients had poor adherence (Table 2). Furthermore, according to the ACT, 68.8% of patients with poor adherence had poorly managed asthma, whereas 55.1 percent of patients with strong adherence had poorly controlled asthma (OR 1.8, 95 percent CI: 1.42–2.27, *p* 0.0001; Table 3). According to the extended TAI test, nearly 17% of patients exhibited at least one major error in inhaler technique (errors in the use of the device that jeopardize the effectiveness of inhaled medication) (Table 2). According to the ACT, 83.2 percent of patients with critical inhaler errors had poorly managed asthma, compared to 62.1 percent of patients with poorly controlled asthma and no critical inhaler errors (OR 3.03, 95 percent CI: 2.18–4.21, *p* 0.0001; Table 3). Misuse rates varied depending on whether the device was a pressurized metered-dose inhaler (pMDI) or a dry powder inhaler (DPI). As a result (Table 4), EH users had a much lower need for technique adjustment than other DPI users (*p* 0.0001; Table 4) [47-50].

Table 4: Number of critical mistakes and need of technique adjustment according to DPI device.

From: Prevalence of modifiable factors limiting treatment efficacy of poorly controlled asthma patients : EFIMERA observational study

DPI device	Critical technique mistakes, <i>n</i> (%)	Need of technique adjustment, <i>n</i> (%)	Number of patients evaluated
Accuhaler	30 (19.5)	106 (68.8)	154
Easyhaler	13 (10.3)	43 (34.4)	126
Nexthaler	17 (16.0)	52 (51.5%)	106
Turbuhaler	36 (17.5)	120 (58.3%)	206

DPI dry powder inhaler.

Each of these risk variables (insufficient prescription, poor adherence, and inhaler abuse) had a statistically significant effect on asthma control ($p < 0.0001$; Table 3). Furthermore, having a higher number of risk factors was linked to having poorly controlled asthma, with a maximum of 93 percent for the ACT and 100 percent for the GINA if all three problems were present, and 46 percent for the ACT and 54 percent for the GINA if none were present. When the GINA score was compared to the ACT questionnaire score, there was a moderate agreement (Kappa = 0.458; Rho = 0.709; $r^2 = 0.503$). Supplementary Tables 1 and 2 and Supplementary Figs 1 and 2 show the relevant tables for the GINA asthma control, which are quite similar to the ACT control.

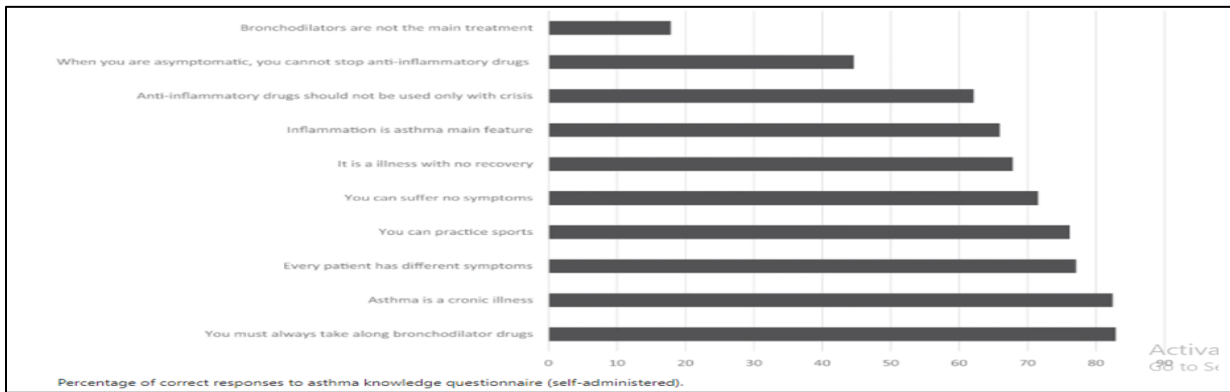


Figure 1: Asthma knowledge questionnaire
From: Prevalence of modifiable factors limiting efficacy of poorly controlled asthma patients : EFIMERA observational study

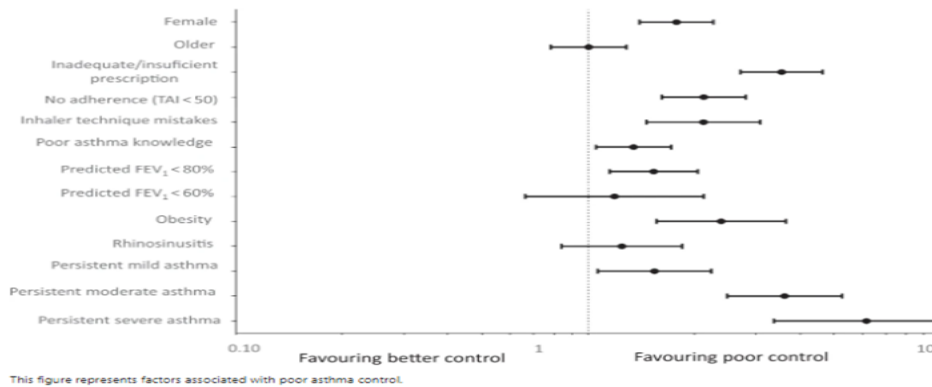


Figure 2: Binary logistic regression model with poor asthma control (ACT < 21) as dependent variable.
From: Prevalence of modifiable limiting treatment efficacy of poorly controlled asthma patients EFIMERA study

Discussion

Despite years of asthma guidelines implementation, poor asthma control was found to be highly linked to modifiable variables associated with medication failure in this investigation [60]. According to a recent study, although numerous factors may be implicated in poor asthma control, three factors appear to be the key causes of poor asthma control in primary care. Inadequate prescriptions, poor medication adherence, and poor inhaler technique^{6, 9,13,14,15} are all factors. Obesity has a negative impact on asthma control, and preliminary evidence suggests that losing weight can improve asthma control and quality of life¹⁶. However, whereas diet-induced weight loss is associated with a slew of general health benefits, there is currently little evidence on asthma control; as a

result, the authors did not include this factor among the modifiable ones. According to the GINA and the ACT, 71.7 and 65.7 percent of patients in our study had inadequate symptom control, respectively. Several studies in primary care have been undertaken in recent years, with various measured variables and designs¹⁶. Despite their differences, they all had a tendency to have poor asthma control. Calvo *et al.*¹⁹, in a recent Spanish article, revealed inadequate asthma control (ACT 20) in 638 asthmatic patients, ranging from 23.4 to 75.6 percent, depending on the patients' medical consultation. Almost half of the patients had poor control on average. According to the authors of another study²⁰, 45 percent of asthmatic patients in Spain who received any sort of treatment had uncontrolled asthma. Other European countries' asthma control isn't much better: a recent Swedish primary care research found that 53.6 percent of patients had

uncontrolled asthma (600 doses of short-acting beta agonists and/or 1 exacerbation each year). 21. The Asthma Control Questionnaire was used to assess asthma control in the European LIAISON study²², and the percentage of patients with partially or poorly managed asthma was 56.5 among the 12 nations that took part in the study. In the United States, a similar situation exists: 50 percent of patients who visited primary care for a non-respiratory consultation had uncontrolled asthma (ACT 19)²³. When compared to our study, most studies reveal a little lower percentage of poorly managed individuals, which could be due to selection bias, as patients sent to specialist care are not expected to be asymptomatic. More than a third of our patients received inadequate treatment at the time of referral from primary care, which was linked to poor asthma control. Both doctors and patients have a tendency to underestimate the severity of asthma, which may explain why many people are undertreated. Lack of time and financial resources are some of the reasons for inadequate asthma management in primary care²⁴, despite the fact that it is well known that poor diagnosis and treatment have a negative impact on patients' health²⁵, resulting in increased care demand and expense. In this regard, the ACT was developed as a tool for detecting poorly controlled asthma and, as a result, identifying those patients who needed the most effective treatment. When a clinician uses it on a regular basis, it has been found to allow for better treatment adjustments. Electronic devices, which could be the gold standard⁸, (they are an objective approach to assess patients' adherence), are the best strategy for evaluating adherence, but they are expensive and difficult to use for many patients. As a result, self-reports appear to be the most cost-effective way to assess it⁷, despite the fact that patients are sometimes unwilling to disclose poor adherence²⁹. Two adherence questionnaires were employed in this study, and the TAI questionnaire appears to be more sensitive than the MG one (76 and 68.5 percent, respectively, have a poor adherence). The TAI has also been demonstrated to have a greater association with patient actual adherence³⁰. Furthermore, when asthma control is assessed using the ACT punctuation and GINA criteria, a statistically significant relationship is found. Similarly, in the REcognize Asthma and LInk to Symptoms and Experience (REALISE) study¹¹, nearly half of the patients had poor adherence to treatment, and in the LIAISON study, patients with poorly controlled asthma had a higher rate of low adherence (according to the MG) than those with well-controlled asthma²². To emphasize the significance of strict adherence, It should be noted that its absence is connected to a higher risk of asthma exacerbations, increased use of oral corticosteroids, the necessity for ER visits and/or hospitalization, deterioration of forced expiratory volume in 1 s values^{29,31}, and lastly, higher expenses and poor quality of life⁷. Every visit, strategies to promote adherence have been investigated, such as reviewing the inhaler usage method as well as patient adherence. Electronic reminders should also be employed because they are highly effective. ^{29,30,32,33}. In primary care, it has been proven that an educational program can help with adherence, cost control, and cost reduction. After proper

training, the program should include medical practitioners as well as nursing services³⁴. In terms of the third major cause of poorly managed asthma, insufficient inhaler technique, this study found that 17% of patients referred from primary care make crucial errors, which is linked to poor asthma control (GINA OR 4.76; ACT OR 3.03). Serious inhaler technique errors are those that have the potential to impede medication uptake and distribution to the lungs. Although the percentage of key errors in some studies (ranging from 50 to 90 percent)³⁵ is higher than in ours, this step is unquestionably important in achieving asthma control. Poor inhaler technique has been linked to an increase in symptoms³⁶, the need for hospitalization¹², and, most importantly, less effective asthma control. In a Dutch study, between 47.7% and 64.9 percent of patients referred to primary care had inhaler abuse; a pragmatic intervention improved this factor significantly³⁷. Between inhaler devices, the percentage of major mistakes varies greatly. Patients performed better with the DPI devices than the MDIs in our trial, as expected. When compared to other DPIs, EH was related with a lower number of critical errors (Turbuhaler, Nexthaler, Accuhaler). Previous investigations have shown that the EH device has a higher rate of acceptance and satisfaction^{38,39}, which supports this conclusion. Furthermore, some studies suggest that an explanation of how to use an inhaler, as well as a practical demonstration of patient abilities with the device, are beneficial. Some publications, for example, recommend that before a patient is discharged from the Emergency Department, an explanation of inhaler technique be given. Inadequate prescriptions, treatment adherence, and inhaler technique all contribute to the fact that 73.3 percent of patients have poorly managed asthma (according to GINA criteria) and 65.7 percent of patients have poorly controlled asthma (according to the ACT questionnaire). As already stated These three characteristics are critical for asthma control^{5,6,9,24}, and as additional risk factors are present, control worsens, ranging from 58.4 percent of poor control (ACT 20) when one condition is implicated to 93.5 percent when all conditions are implicated (or 54–100 percent using the GINA criteria). Although the GINA could detect a higher proportion of under controlled individuals than the ACT, our investigation appears to demonstrate such a concordance between the ACT and the GINA criteria for asthma control. Most patients assume that bronchodilators are the major medication for treating asthma and that anti-inflammatory treatment can be stopped during remission times, which is not encouraging. When asthma comprehension is looked at as a predictor of poor asthma control using a binary logistic regression, it appears to be an independent predictor. Patients' adherence is likely influenced by these concerns: in the REALISE study¹¹, half of the patients did not take their maintenance drugs correctly. Even when they experienced severe and persistent symptoms, nearly half of individuals in another study¹⁰ reported their asthma was well managed. Patients' understanding and, as a result, adherence to treatment could be improved by educational initiatives.

Our findings reveal that poor asthma management, adherence to therapy, inhaler technique, and asthma knowledge are key factors resulting in poorer asthma control at the primary care level. When referred to a Specialist, many patients do not obtain proper treatment and adherence to therapy is poor. Furthermore, individuals who make major errors in inhaler technique are a common occurrence [79].

Conclusion

This study shows that there is still room for improvement by focusing on these modifiable factors that appear to be key opportunities for improving asthma management at the primary care level, such as optimizing therapy, retraining on inhaler technique, and developing new tools to improve adherence to treatment.

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