

COPD: understanding patients' adherence to inhaled medications

António Duarte-de-Araújo¹⁻³

Pedro Teixeira^{1,2}

Venceslau Hespanhol^{4,5}

Jaime Correia-de-Sousa^{1,2,6}

¹Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal;

²ICVS/3B's, PT Government Associate Laboratory, Braga, Portugal;

³Respiratory Department, H. S^a Oliveira, Guimarães, Portugal;

⁴Department of Pneumology, Centro Hospitalar de S. João, Porto, Portugal;

⁵Faculty of Medicine (FMUP), University of Porto, Porto, Portugal;

⁶Horizonte Family Health Unit, Matosinhos, Portugal

Background and objective: Adherence to inhaled medications by COPD patients is a challenging issue, but relatively understudied. The aim of this study is the characterization of adherence to inhaled medications by COPD patients, with a focus on patient-related determinants.

Methods: Stable COPD outpatients ≥ 40 years of age from a respiratory unit and diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease criteria were included in a cross-sectional study. The Measure of Treatment Adherence (MTA), the Beliefs about Medications Questionnaire (BMQ) and demographic, clinical, and COPD questionnaires were used. After completing these questionnaires, semi-structured interviews were carried out and participants were encouraged to justify their opinions and behaviors. Field notes were made during the interviews and each interview was analyzed before the next one. Quantitative and qualitative analyses of the variables were then performed.

Results: A total of 300 out of 319 participants (mean age = 67.7 years, 78.1% males) completed the MTA questionnaire. Of these, 31.3% were considered poorly adherent and 16.7% as non-adherent to the inhaled therapy. A statistically significant negative association was found between adherence and current smoking status ($P=0.044$), and between adherence and FEV₁ % ($P=0.000$). The mean BMQ Necessity score was higher in adherent patients ($P=0.000$), but the mean Concern score was similar for both ($P=0.877$). We found nine patterns of poor-adherence, six reasons given for poor-adherence behaviors, five reasons for good-adherence behaviors and three patient-related domains on adherence to medications.

Conclusion: Adherence is related to need perception and to the functional severity of the disease. A non-adherent patient is usually a current smoker with lower degree of airflow limitation and lower perception of medication necessity. New information obtained was related to the patterns and reasons for different adherence behaviors, which are based on three major groups of patient related-determinants: health-related experiences, health-related behaviors and health-related beliefs.

Keywords: COPD, adherence, inhaled medications, adherence behaviors, beliefs

Background

Adherence to medications and its improvement is a challenging issue in the treatment of patients with COPD. In 2003 the WHO, although it focused on chronic conditions other than COPD and on provider and health system-related determinants, declared non-adherence a major public health problem.¹ In a country where access to health-care services is good and patients have access to a wide range of effective treatments, any planned improvement of treatment outcomes must address patients' adherence to medications. Adherence can be defined as the process by which patients take their medication as prescribed.² It means that adherence is a behavioral process and the decision about taking the treatment or not ultimately lies with the patient. As a behavior, adherence can be measured and self-reported questionnaires are currently the most commonly used

Correspondence: António Duarte-de-Araújo

Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal
Tel +351 96 554 2786

Email duartearaújo@sapo.pt

tools,³ and also the most cost-effective ones.⁴ The accuracy of self-reporting varies substantially with questionnaire design, but all questionnaires are subjective and potentially prone to bias because patients may report higher adherence rates than they actually have. In-depth patient interviews can complement self-reported questionnaires and provide insight in most types on non-adherent behavior, mainly intelligent non-adherence.⁵ There is growing evidence supporting individual beliefs and social representations of health and disease as major determinants of adherence to medications and these are potentially modifiable factors, subject to professional intervention.⁶ However, published literature identifies many determinants of non-adherent behaviors. In COPD patients, long-term adherence to inhaled medications is required for success of the treatment, but adherence remains particularly difficult to measure, and patient-related determinants are poorly understood. Some psychometric tools have been developed to explore the relationship between patient beliefs and adherence to medications,⁷ but to understand adherence as a complex and subjective phenomenon, qualitative methods have also been used in the development of knowledge,^{8–11} complementing quantitative studies. Despite the clinical burden of non-adherence,¹² it remains a neglected aspect of treatment of patients with COPD. Until recently, little attention was paid in medical literature to patient-related perspectives of adherence and to the best of our knowledge, this is the first study carried out in a Portuguese population of COPD patients concerning adherence to inhaled medications and patient-related determinants.

Aim

The aim of this study is the characterization of adherence to inhaled medications in COPD patients, focused on patient-related determinants. We intended assessing whether demographic variables, clinical and functional severity of COPD, and beliefs about inhaled medications are associated with patients' adherence to inhaled medications.

Materials and methods

A cross-sectional study was conducted in the outpatient respiratory care of Guimarães Hospital, between March 2016 and May 2017. Stable patients over 40 years old and diagnosed as suffering from COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were consecutively included.¹³ Exclusion criteria were refusal to participate and an inability to understand simple questionnaires. All participants gave their written informed consent, and the study was approved by the Hospital de Guimarães

Ethics Committee, the Research Ethics Committee of Minho University and the Portuguese Data Protection Agency. A survey of demographic and clinical data and the Graffar Social Classification,¹⁴ validated for use in Portuguese population, were carried out. An easy-to-answer questionnaire on COPD, relating to the patient's knowledge of their disease, was developed and applied. It included questions about the name and nature of the disease, on chronicity, on severity and its justification, and about their searching for any kind of information about the disease. Evaluation of symptoms was done using the Portuguese versions of the COPD assessment Test (CAT) and the mMRC Dyspnoea Questionnaire. The number of COPD exacerbation (ECOPD) referred in the last year was evaluated. We defined ECOPD according to GOLD, as an acute worsening of respiratory symptoms that resulted in additional therapy, but also requiring an unplanned medical visit, because patients have difficulty remembering un-reported exacerbations. Adherence was assessed using the Measure of Treatment Adherence (MTA), a psychometric tool derived from Morisky et al's.¹⁵ The MTA was validated for the Portuguese population in 2001, with a reported Cronbach's alpha of 0.74. It consists of seven items in the questionnaire, reflecting common patterns of intentional and unintentional non-adherent behaviors, answered on a 6-point Likert scale (with 1=always, 2=almost always, 3=often, 4=sometimes, 5=rarely, and 6=never). Points are summed, total scores range from 6 to 42, and higher scores indicate higher self-reported adherence. Recent published papers stressed on the need for a correct taxonomy for defining adherence to medications.² However, currently different terms, eg, "poor-adherence", "sub-optimal adherence", "lower-adherence" and "non-adherence", have been used to describe the opposite behavior, when patients do not take their medications as prescribed. Non-adherence was defined by a score ≤ 5 , after dividing the total score by the number of questions. This cutoff was validated by the MTA authors.¹⁵ Because the words adherence and non-adherence cannot fully describe the complexity of adherence-related behaviors, poor-adherence was also defined by a total score ≤ 6 , after transforming the Likert scale into dichotomous (with rarely and never=1, always to sometimes=0).

The cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese was validated as an interviewer-administered questionnaire and published in 2013.¹⁶ It was applied to explore the relationship between beliefs and adherence. The BMQ is an 11-item questionnaire with a 5-item Necessity scale and a 6-item Concern scale. Answered on a 5-point Likert scale (1=strongly disagree

to 5=strongly agree), the points are summed, and total scores range from 5 to 25 on the Necessity scale and 6–30 on the Concern scale. The Necessity and Concern scales assess, respectively, the beliefs about the necessity for prescribed medications and the beliefs about side-effects, dependence and long-term toxicity of medications. Both MTA and BMQ were used as interviewer-administered questionnaires, and were later related to each other. After the application of these questionnaires, semi-structured face-to-face interviews were carried out and participants were encouraged to justify their opinions and behaviors in a mixed qualitative design.¹⁷ Field-notes were made during and after the interview and each interview was analyzed before the next one. The objective was to obtain new information from patients themselves. Qualitative and quantitative analyses of the variables were then performed.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY, USA). The reliability of the MAT scale was assessed using Cronbach's alpha measure for internal consistency. Independence between variables was tested using the chi-squared test and the non-parametric Mann–Whitney test for nominal and categorical data. Binary logistic regression models were tested to explore adherence predictors. Results were considered statistically significant when *P*-values were below 0.05.

Results

A total of 319 COPD outpatients were included in the study, 5 patients refused to participate and 8 were unable to understand the questionnaires. Participants were predominantly male and elderly (62.1% ≥65 years), 83.7% were retired, 89.3% were living with their families and 79.3% were living in predominantly urban spaces. The majority of patients had low socioeconomic status according to the Graffar social classification. Tobacco smoking was the more common exposure identified in 71.7% of patients and 55 (17.2%) were current smokers. The most important demographic, clinical and functional characteristics of the patients are presented in Table 1. Some patients were unable to respond to CAT questionnaire but understood mMRC. A total of 300 participants completed the MTA questionnaire with a Cronbach's alpha of 0.70. However, only 252 (79%) were able to understand and respond to the BMQ. Due to the greater complexity of some questions, some questionnaires were more difficult to understand by participants with low educational level.

Table 1 Demographic, clinical and functional characteristics of COPD patients

Characteristics	n=319
Mean ± SD age (years)	67.7±10.26
Age ≥65 years	198 (62.1)
Male gender	249 (78.1)
Education level <4 school years	93 (29.2)
Education level ≤6 school years	281 (88.1)
Very low monthly income (<530 euros)	207 (65.5)
Low monthly income (<1,060 euros)	295 (93.3)
Graffar social classification 3 and 4	112 (35.5); 184 (58.4)
mMRC grade ≥2	196 (62.6)
CAT score ≥10	158 (72.4)
Frequent ECOPD (≥2/last year)	121 (37.9)
Mean FEV ₁ L (%)	1.38 (53.9)
GOLD 2017 stage and classification	
I – 34 (10.7); II – 136 (42.6); III – 109 (34.2); IV – 40 (12.5)	
A – 73 (22.9); B – 127 (39.8); C – 7 (2.2); D – 112 (35.1)	

Note: Data shown as mean ± SD or n (%).

Abbreviations: ECOPD, COPD exacerbation; CAT, COPD assessment test; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Poor-adherence was referred by 94 patients (31.3%) and 50 (16.7%) were considered non-adherent to inhaled medications. Age and gender were not statistically related to adherence (20.5% of patients <65 years and 14.4% ≥65 years were non-adherent, *P*=0.165; 21.7% of females and 15.2% of males were non-adherent, *P*=0.198). Education level, income and Graffar social classification were also not statistically related to adherence (17.8% of patients ≤3 years and 16.2% >4 years at school were non-adherent, *P*=0.735; 18% of patients with monthly income <530 euros and 14.3% having income ≥530 euros were non-adherent, *P*=0.420; 16.1% of patients scoring 2 and 3 and 16.9% scoring 4 and 5 of Graffar classification were non-adherent, *P*=0.865). An association between adherence and mMRC grade and CAT score was found. A total of 22.9% of patients with mMRC grade <2 and 13.8% with mMRC grade ≥2 were non-adherent, *P*=0.047; 26% of patients with CAT score <10 and 12.9% ≥10 were also non-adherent, *P*=0.028. There was no statistical association between adherence and the number of reported exacerbations (non-adherence was found in 20.6%, 15% and 12.6% of patients reporting 0, 1 and ≥2 ECOPD, *P*=0.219). An association with statistical significance was found between non-adherence and current smoking status (26.5% of current smokers and 14.8% of ex-smokers or never-smokers were non-adherents, *P*=0.044). Binary logistic regression indicates an odds ratio of 2.4, indicating 2.4 times more risk of non-adherence for current smokers, when controlling for age, gender, education level and FEV₁%. Regression also reveals a statistically significant negative association between FEV₁% and adherence to

Table 2 Relationship between BMQ and adherence to inhaled medication

	BMQ necessity (mean ± SD)	BMQ concern (mean ± SD)
Adherent patients	Score=20.58±4.104	Score=10.76±4.265
Non-adherent patients	Score=15.75±5.777	Score=10.65±4.383
P-value	P=0.000	P=0.877

Abbreviation: BMQ, Beliefs about Medications Questionnaire.

medications ($P=0.000$). When the mMRC grade and CAT score are added to the regression model, the only statistically significant relation is the negative association between FEV₁% and adherence to medications ($P=0.041$). The relationship between BMQ and adherence to inhaled medications is presented in Table 2, and the relationship between adherence and GOLD 2017 stage and classification in Table 3. Non-adherence is statistically related to GOLD stage but not to ABCD groups. The mean BMQ Necessity score was statistically higher in adherent patients. The mean BMQ Concern score was similar for adherent and non-adherent patients.

The patterns and the reasons for poor-adherence behaviors and the reasons given for good-adherence behaviors were obtained during semi-structured interviews and are referred to in Boxes 1 and 2. Therefore, these boxes refer to only

Table 3 Relationship between non-adherence and GOLD 2017 stage and classification

	GOLD I-IV				Total
	I	II	III	IV	
Non-adherent					
N	9	28	12	1	50
%	18.0	56.0	24.0	2.0	100.0
Adherent					
N	19	97	96	38	250
%	7.6	38.8	38.4	15.2	100.0
Total					
N	28	125	108	39	300
%	9.3	41.7	36.0	13.0	100.0
$\chi^2=15.772$; P -value=0.001					
	A-D 17				Total
	A	B	C	D	
Non-adherent					
N	16	19	2	13	50
%	32.0	38.0	4.0	26.0	100.0
Adherent					
N	45	103	5	97	250
%	18.0	41.2	2.0	38.8	100.0
Total					
N	61	122	7	110	300
%	20.3	40.7	2.3	36.7	100.0
$\chi^2=6.697$; P -value=0.082					

Abbreviation: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Box 1 Reported patterns and reasons for poor-adherence behaviors**Reasons**

- Use as needed
- Shift in daily routine
- Fear of side effects
- Concerned about long-term toxicity or tolerance
- Confusion
- Dependence on others
- Economic

Patterns

- Forgetfulness
- Carelessness with schedules
- Ran out of medication
- Anticipation of inhalation
- Increased frequency/number of inhalations
- Stop all medication when less symptomatic
- Reduction in the number of inhalations/suppression of doses
- Suppression of one of the inhalers
- Complete withdrawal

qualitative data without any kind of hierarchy. Participants gave us patterns and reasons for poor-adherence behaviors and reasons for good-adherence behaviors in their own words, answering open questions. This new information obtained from patients themselves was then grouped and re-written, clearly and concisely, as it appears in the boxes. It should be noted here that inhaled medication is partially subsidized in Portugal for all patients, economic reasons being the justification. We found that different levels of adherence and poor-adherence behaviors were mainly intentional. Sometimes, conscious underuse and overuse were referred by the same patient. Participants justified their good-adherence behaviors in different ways and in different own words; however they could be grouped, as shown in Box 2, into

Box 2 Identified domains and reasons for good-adherence behaviors**Health-related behaviors**

- Having a caregiver (or some kind of help to remember, prepare and purchase the medication)
- Having a daily routine (that hinders oblivion)
- Use of quick-relief medication (avoiding excessive use of regular medications)
- Having spare medication/easy access to medications: discipline (on taking the medication)

Health-related experiences

- Previous negative experiences (previous dropout-related exacerbations)
- Satisfaction with prescribed medication (feeling better)

Health-related beliefs

- Trust in the doctor (and their knowledge)
- Trust in the medication (and its effectiveness)

three domains: past experiences, health-related behaviors and beliefs.

According to data collected through an easy-to-answer questionnaire referred to in the "Materials and methods" section, the majority of participants recognized COPD as a chronic disease (81.1%) and a serious illness (76.5%). Severity was mainly justified by symptoms (33.1%) or limitations (25.8%), fear of dying from the disease (5.6%) or by having no cure (5.1%). Other reasons given for severity were recreational limitations, frequent hospitalization, persistence of symptoms, progressive worsening, death of relatives from the same disease, inability to work and fear of becoming dependent on others. Only 10.8% of patients cited the disease by its correct name, 38.3% attributed other names to it, 23.2% did not refer to the disease but rather the affected organ or function, 18.6% referred to symptoms, 3.2% its etiology and 13.4% did not know what they were suffering from. Only a few patients (15.2%) reported having searched for any kind of information about their disease.

Discussion

In the present study, only 31.3% of the participants were considered poorly adherent and 16.7% were considered non-adherent. The patients' beliefs regarding the treatment of the disease were found to be the most powerful predictors of adherence to inhalation therapy, as also referred to by other authors.¹⁸ Adherence is also strongly related to the functional severity of the disease.

The prevalence of poor-adherence and non-adherence in the present study is unexpectedly low and different from other published studies.^{19–22} However, some recently published studies refer to variability in the prevalence of poor-adherence, when using different methods, different instruments or in different populations.²³ Another recent study on COPD patients, using pharmacy data from a regional database, shows a high adherence to inhaled medications during a 4-year period.²⁴ Available evidence on non-adherence to medications in patients with COPD is not very strong.²⁵ MTA was chosen because it is validated for the Portuguese population, although it is not specific to inhaler devices or to COPD, and it may fail to capture some patterns of non-adherence when compared to other tests.^{26,27} The use of MTA as an interviewer-administered questionnaire may be questionable, but it was the best option, given the low education level of the participants. All of this may, to some degree, justify the high level of referred adherence in the studied population. Moreover, dyspnea is a limiting and disturbing symptom, and non-adherence to therapy can be surprising

from a clinical point of view, at least in very symptomatic patients with GOLD stage B or D, where 74.9% of patients of the present study are classified. In this aged population with a very low education level, "patient adherence" could be better described as "patient compliance", reflecting some patients' passivity to physicians' instructions.

Socioeconomic inequalities have recently been associated with risk of poor-adherence and poorer clinical prognosis.²³ However, the association between sociodemographic characteristics of patients and adherence to medications in COPD is conflicting in recent literature.³ In the present study, current smokers are more prone to be non-adherent to medications, but demographic and clinical variables were not significantly related to adherence.

In the present study, adherence to medications increases with the number of reported ECOPD, but without statistical significance. Previous papers described a positive association between poor-adherence behaviors and poor treatment outcomes,^{28,29} however, a link between necessity beliefs and a history of frequent exacerbations would lead to an assumption of acute exacerbations as a predictor of medication adherence. We hypothesized that we failed to demonstrate significant association between adherence to medications and ECOPD because many variables, other than adherence and related to ECOPD, were uncontrolled in the present study.

In the present work, there was also a lack of a significant association between adherence and ABCD groups of GOLD 2017 classification. Adherence is strongly related to the functional severity of the disease, probably because dyspnea, a bothersome symptom, is somewhat linked to FEV₁%. However, we found the association between adherence and FEV₁% even more powerful than that between adherence and mMRC grade or CAT score.

The cross-cultural adaptation of the BMQ into Portuguese was applied to explore patients' beliefs about the benefits of inhalation therapy and their relationship to adherence. Many studies have been conducted using BMQ.^{30–32} In many long-term diseases other than COPD, non-adherence appears to be dependent on the balance between perceived necessity and specific medications concern.⁷ In our study, only necessity beliefs are associated with adherence. Probably, because of the usually low rate of side effects perceived by patients, concerns about inhaled medications do not appear to significantly affect adherence in COPD.

In the present study, semi-structured interviews were carried out to obtain complementary information and better capture some health-care experiences. Mixed methods designs are known to maximize the strengths of both quantitative

and qualitative methodologies.^{33,34} With this methodology, different patterns and reasons for poor-adherence and different reasons for good-adherence behaviors have emerged. As expected, patient's beliefs about the disease were powerful predictors of adherent behaviors. Globally, predictors of adherence can be grouped into three domains: prior health-related experiences, health-related behaviors and health-related beliefs.

This is a study with a small sample size conducted in a single institution. This may limit the generalization of results to other populations.³⁵ As patients were recruited sequentially, we cannot exclude selection bias. However, some data can be used to design larger confirmatory studies. The study was done in a real-life setting, with simple tools that can be easily used in clinical practice. The power of this work lies less in the quantification of adherence to inhaled therapy than on understanding patient-related determinants of adherence. The strong association between adherence and the beliefs about the need for inhaled medications and the functional severity of the disease is new and important information. Complementary data obtained by semi-structured interviews gave strength to this information and a new understanding of the complexity of adherence-related behaviors. This could be useful in clinical practice, helping overcome barriers related to poor-adherence and plan strategies that could reinforce adherence to inhaled medications.

Conclusions

In this aged population, low socioeconomic status and low education level are contributing factors for a widespread lack of knowledge about COPD, the disease being represented by their symptoms and limitations. Adherence to inhalation therapy is strongly related to patients' beliefs regarding the need for prescribed medications and to the functional severity of the disease. The non-adherent patient is usually a current smoker with lower airflow limitation and lower perception of necessity of medications. New information obtained was related to the patterns and reasons for different adherent behaviors. Predictors of adherent behaviors can be grouped into three domains: past experiences, health-related behaviors and beliefs.

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Author contributions

Duarte-de-Araújo conceived and developed the study, carried out the collection of data and data interpretation, wrote the first draft and collaborated in the final writing. Pedro Teixeira carried out the statistical analysis and contributed to the section on methods and results. Venceslau Hespanhol reviewed the final draft. Jaime Correia-de-Sousa reviewed all the drafts and collaborated in the final writing. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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