

Study protocol

Determinants of Treatment Success in Chronic Obstructive Pulmonary Disease

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ABSTRACT

COPD is a common, complex and heterogeneous disease. General objective is to identify factors which correction can be translated into improved health care for COPD patients.

The study will take place in Guimarães hospital's outpatient pulmonology care. COPD outpatients over 40 years of age, will be enrolled sequentially in order of appearance in the consultation during a one-year period. The most relevant demographic and clinical patients' characteristics will be studied using appropriate tools, and will be transformed into variables, which will be used for descriptive and inferential analysis. The variables degree of severity, medication adherence, beliefs about the disease and about the inhaled medications, and the inhalation technique are intended to be related to each other, in order to understand the relative weight of each of these variables under study as factors of therapeutic success in COPD.

Keywords: COPD, study protocol, treatment success.

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BACKGROUND

COPD is the most common chronic respiratory disease worldwide with an estimated prevalence of 7.6 to 8.9% of the adult population¹. In Portugal, the prevalence may be as high as 14.2% in adults over 40 years². The goals of treatment are the improvement of symptoms, quality of life, exercise tolerance, and prevention of disease progression and exacerbations. The therapeutic success depends on a plurality of factors³, such as appropriate treatment, good adherence to medication and correct inhalation technique⁴. Adherence to the recommended treatment for COPD and standards of care are still unknown in many countries. Many studies have shown a general lack of knowledge of therapeutic guidelines by physicians, and an excessive use of some medications, as inhaled corticosteroids, in dissonance with the guidelines⁵.

In COPD, as in many chronic diseases, poor adherence to medication are a well-known factor of therapeutic failure⁶, but patient's adherence is not still regularly monitored in clinical practice⁷, and it is studied only for research purposes. The evidence regarding adherence to therapy in COPD is not very robust, and seemed to be more influenced by patients' beliefs on medicines than by the disease severity or other demographic factors⁸. Adherence to treatment and its improvement is a critical point in patient's treatment⁹, but most of the investigations referring poor adherence patterns in COPD were carried out before the use of once or twice daily inhaled medication became the rule, and many original papers did not describe the profiles of patients with regard

to the degree of dyspnea or airflow limitation¹⁰. Recently published studies reported variability in the prevalence of poor adherence, when using different methods or instruments, and different populations¹¹. Adherence to medication remains an open issue, and merits further investigation¹².

However important the knowledge of adherence to medication, the psychometric tools are omitted about the reasons for the non-adherence¹³. Sociodemographic variables seems to be poor related to adherence behaviors¹⁴ and some authors proposed a study protocol in order to better understand the factors related to adherence, and to intervene positively in patients with COPD, exploring motivational and cognitive aspects¹⁵. The Beliefs about Medicines Questionnaire can be useful to explore the relationship between beliefs and adherence to inhaled medication, in COPD patients^{16,17}.

In the compliant patient, the effectiveness of inhaled medication depends on a good inhalation technique, a subject not well studied in actual pulmonary practice¹⁸. A large proportion of COPD patients use their inhalers incorrectly^{19,20}, and in a recent published study assessing the use of 3393 inhalation devices, errors were observed in over 50% of handlings, regardless of the device used²¹. In fact, the inhaler technique has been a problem since the launch of the first inhaler device, and it is not yet solved²². In real-life clinical practice, outcomes are linked to the inhalation technique, to adherence to medication and to the ability to found treatable characteristics in each patient, based on the best medical evidence. Pragmatic studies

that reflect real-life clinical practice are important in doctors' clinical judgment, and "real-world" research has been the focus of an increasing number of scientific publications. Its goal is to complement classical randomized controlled trials (RCTs), representing less than 5% of the "real" target patient population²³. In respiratory medicine, RCTs can exclude up to 90% of COPD routine care patients.

OBJECTIVES

The general objective is to understand the factors of therapeutic success in COPD. The specific objectives are 1) to evaluate the degree of severity of COPD outpatients, focused on the symptomatology, number of exacerbations and respiratory function; 2) to characterize prescribed treatments, determining how international guidelines are being followed, and identification of major deviations; 3) to characterize patient adherence to the prescribed inhalation therapy, linking it to beliefs about inhaled medication, degrees of severity and demographic variables, and 4) to assess inhalation technique for each of the prescribed inhalation devices, in order to evaluate their correct use, and its relationship with adherence to therapy, severity of COPD and demographic variables.

METHODS

The study will take place in the outpatient pulmonology care of Guimarães' hospital, a teaching institution in the North of Portugal. Patients will be enrolled consecutively after written informed consent. The study was approved by

local ethics committee, the Research Ethics Committee of Minho' University and by the Portuguese Data Protection Agency (record 5778/2016). Patients over 40 years old diagnosed as suffer from COPD according to GOLD criteria will be included, and the inability to understand and respond to simple questionnaires is the exclusion criterion. A survey of demographic and clinical data, and the Graffar questionnaire will be applied. The Medical Research Council Dyspnea Questionnaire (mMRC), the COPD Assessment Test (CAT) and the referred comorbidities and number of acute exacerbations in the last year will be used to assess the severity of the disease, and its impact on the well-being. The evaluation of respiratory function will be done according to GOLD criteria. We defined exacerbation as a worsening of one or more major respiratory symptoms, requiring unplanned medical visit that led to any treatment or modification of previous treatment.

The Measure of Adherence to Treatment Questionnaire (MTA) and the Beliefs about Medicines Questionnaire (BMQ) will be used respectively to evaluate adherence to prescribed therapy and the beliefs about the disease and the prescribed inhaled therapies²⁴. Finally, each patient will be asked to demonstrate the use of their prescribed inhalation devices, just as he or she does it at home. Assessment of errors will be done using a checklist for each ID, as defined by international recommendations for a correct inhalation technique. The most relevant demographic and clinical characteristics of patients will be studied and transformed into variables, which will be used for descriptive and

inferential analysis. A statistical analysis will be performed using the IBM SPSS Statistics for Windows software, version 22.0.

DESIGN

The first task is the study of demographic and clinical variables of COPD out-patients and evaluation of morbidity. The objective is to assess whether some clinical or functional characteristics can predict an increased risk of acute exacerbations of COPD, influencing therapeutic options. The second task is to evaluate whether symptoms, airflow limitation, number of exacerbations, Graft Social Classification and adherence to medication, can lead to deviations to GOLD 2017 standards of treatment. The third task is to measure compliance and identify patterns of poor adherence to inhaled treatment. We intend to assess whether beliefs about inhaled medication, the severity of COPD, the symptoms, the number of acute exacerbations, the type of ID or demographic variables, can predict patient's adherence to the prescribed inhalation therapy.

A fourth task is to assess if the degree of severity of COPD, the degree of adherence to treatment, the type of ID or demographic factors can predict an appropriate inhalation technique. Finally, we intend to discuss the relative weight and importance of the adherence to medication, the compliance with the GOLD guidelines and the inhalation technique, as factors of therapeutic success in COPD, being CAT score, mMRC grade and the number of exacerbations in the last year the clinical outcomes.

STRENGTHS AND LIMITATIONS OF THE STUDY

The study will be conducted in a single health care institution, with a limited number of patients (up to 350) recruited consecutively, so we cannot exclude selection bias. Deviations from the therapeutic standards must not be confused with inappropriate medication, and, because most patients are being treated by pulmonologists, fewer deviations from the therapeutic standards are expected. Adherence to medication is a difficult concept to define, but more difficult is to measure it, because there is no "best way". Some patients may report higher adherence rates than they actually have, but self-report questionnaires have high specificity for nonadherence. To study adherence, MTA was chosen because is validated to the Portuguese population. However, when compared to the test of Adherence to Inhalers, or the Morisky Medication Adherence Scale^{25,26}, it is not specific for inhaler devices nor to COPD. Assess inhalation technique by using checklists with some number of steps related to correct use of devices is always a subjective evaluation, especially the inhalation step. Nonetheless this is how, in real-life settings, clinical decisions are made in order to prescribe IDs. The mMRC and CAT questionnaires are validated tools to study dyspnea and the global impact of the disease on the patient's well-being, but at present there is neither a good definition nor an agreed classification of exacerbation, and unreported exacerbations also affect health status, and contribute to the overall severity of the disease. Referred COPD acute exacerbations, as defined in

this study, could not reflect the overall severity of the disease. As COPD is a chronic and incurable disease, the level of symptoms and acute exacerbations may reflect more the severity of the disease than the actual success in the treatment of the disease.

DISCUSSION

Discussion will be focused on the characteristics of patients that can lead to deviations to therapeutic standards, the features of patients that may relate to insufficient adherence and that related to incorrect inhalation technique. The demographic, clinical, and social characteristics related to beliefs about the disease and the inhaled medication, and its relationship with adherence will also be discussed. Finally, we intend to discuss the relative weight and importance of each of these variables under study as factors of therapeutic success in COPD.

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Author contributions:

Duarte de Araújo conceived the project, planned the work, wrote the first draft and collaborated in the final writing. Venceslau Hespanhol reviewed the various drafts and collaborated in final writing. Jaime Correia-de-Sousa reviewed all the drafts and collaborated in final writing. All the authors approved the manuscript.

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