Universidade do Minho
Escola de Medicina

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Determinants of Treatment Success in Chronic Obstructive Pulmonary Disease

novembro de 2019

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Determinantes de Êxito Terapêutico na Doença Pulmonar Obstrutiva Crónica

Tese de Doutoramento em Medicina

Trabalho Efetuado sob a orientação do
Professor Doutor António Jaime Botelho Correia de Sousa
e do
Professor Doutor Venceslau José Coelho Pinto Hespanhol

novembro de 2019

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To my father Dr. Francisco Araújo, already deceased, and to my former department director, Dr. Orlando Yeep, also deceased, for their teachings and for the trust that they always placed in me.

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

Determinantes de Êxito Terapêutico na Doença Pulmonar Obstrutiva Crónica

RESUMO

A Doença Pulmonar Obstrutiva Crónica (DPOC) é atualmente um dos principais problemas de saúde a nível global. Muitos fatores influenciam os resultados terapêuticos, sendo alguns comuns e modificáveis. O objetivo desta tese foi entender a adesão à medicação inalatória, apreciar a técnica inalatória e caracterizar a adesão à estratégia terapêutica do GOLD. No primeiro trabalho avaliou-se a gravidade dos doentes e estudou-se a associação entre diferentes variáveis. No segundo trabalho testou-se uma possível associação entre irregularidade dos sintomas e história de agudizações frequentes. No terceiro e no quarto trabalho a adesão à medicação inalatória foi caracterizada e relacionada com as representações sociais da doença e medicação. O quinto e o sexto trabalho caracterizaram a técnica inalatória, relacionando-a com as caraterísticas dos doentes e dos dispositivos inalatórios bem como a eficácia do seu ensino. No sétimo trabalho foi testada uma possível associação entre técnica inalatória, adesão à medicação e à estratégia terapêutica do GOLD, e algumas caraterísticas clínicas e funcionais. A DPOC apresentou-se como uma doença heterogênea, e algumas caraterísticas dos doentes associaram-se a maior sintomatologia ou a agudizações mais frequentes. A adesão mostrou-se sobretudo associada à gravidade funcional da doença e à perceção da necessidade da medicação, tendo sido encontrados padrões e razões para os diversos comportamentos relacionados com a adesão. As mulheres, os doentes mais idosos e aqueles com menor escolaridade ou nível socioeconómico mostraram pior técnica inalatória, que também variou com o dispositivo inalatório prescrito. Após ensino da técnica inalatória verificou-se a sua melhoria a longo prazo, sobretudo no grupo de inaladores em que os doentes mais facilmente confirmavam um uso adequado. Não se verificou uma associação positiva entre má técnica inalatória, má-adesão à medicação ou à estratégia terapêutica do GOLD e piores resultados terapêuticos. Para além da correta avaliação do doente e de um robusto conhecimento científico, o sucesso do tratamento é arbitrado por determinadas caraterísticas, comportamentos e crenças relacionadas com a medicação. Estas dimensões, relacionadas com os doentes, devem também ser levadas em consideração como determinantes de êxito terapêutico.

Palavras-chave: DPOC; GOLD; Adesão à medicação; Técnica inalatória; Adesão às diretrizes clínicas.

Determinants of Treatment Success in Chronic Obstructive Pulmonary Disease

ABSTRACT

Chronic Obstructive Lung Disease (COPD) currently represents one of the most significant health problems at international level. Many issues can be related to clinical outcomes, and some of them are common and modifiable. The objective of this thesis was to understand adherence to inhaled medication, to evaluate the inhalation technique and to characterise prescribers' non-adherence to GOLD strategy. The first study characterised the morbidity of a COPD hospital cohort of stable outpatients and the association between different patients' characteristics. In the second study, an association between symptoms irregularities and a history of frequent exacerbations was tested. In the third and fourth studies the adherence to inhaled medications was characterised, focused on patients' related determinants. In the fifth study, the inhalation technique was characterised and related to patients and inhaler characteristics. In the sixth study the effect of an educational intervention on a long-term improvement of inhalation technique was evaluated. In the seventh study an association between adherence to inhaled medication, inhaler technique or prescribers' adherence to GOLD strategy and some clinical outcomes was tested. COPD was recognised as a heterogeneous disorder. Some groups of patients possess specific characteristics, and some are related to more symptoms or frequent exacerbations. Adherence were associated to the functional severity of the disease and to needs perception, and different reasons and patterns of adherence behaviours have emerged. Elderly patients, women, and those with lower education level or socioeconomic status demonstrated a worse inhalation technique. The inhaler technique was also related to the type of prescribed inhaler device. After teaching, improvement in critical errors was found mainly in the group of inhalers with an easy feedback to the patient, denoting that a significant amount of medication was inhaled. Non-adherence to medications or to GOLD strategy, and inhalers mishandling were not positively related to poor clinical outcomes. A correct medical decision depends on an accurate patient evaluation and on a robust scientific information, but a successful treatment is also arbitrated by some patients' characteristics and by their behaviours and beliefs related to the disease and medication. These dimensions, related to the patients, must also be taken in account.

Keywords: COPD; GOLD; Adherence; Inhalation technique; Outcomes; Adherence to guidelines.

TABLE OF CONTENTS:

LIST OF ABBREVIATIONS AND ACRONYMS USED:

ANOVA	Analysis of Variance
ATS	American Thoracic Society
BMQ	Beliefs about Medicines Questionnaire
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
ECOPD	COPD Acute Exacerbations
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in One Second
GLI 2012	Global Lung Function Initiative 2012 predict equations
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ID	Inhaler Device
mDPI	multiple-dose Dry Powder Inhaler
mMRC	modified Medical Research Council Dyspnoea Questionnaire
MTA	Measure of Treatment Adherence
pMDI	pressurized Metered-Dose Inhaler
sDPI	single-dose Dry Powder Inhaler
SMI	Soft Mist Inhaler
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organization

«Non scholae sed vitae discimus.»

(We do not learn for school, but for life.)

Lucius Annaeus Seneca, 4 BC- 65 AD

«E Medicina era isso mesmo: penetrar na natureza humana, num quotidiano de luta sempre renovada»

Fernando Namora

(in Deuses e Demónios da Medicina)

PREFACE

The current classification of human disease derives from the association between symptoms and signs and organs/histopathology findings. A better understanding of human biology, and the finding of different molecular signatures related to different biological responses to injury, will lead to a new disease nosology and to a new definition of disease expression. This is currently known as P_4 medicine.[1]

The way how the scientific community understands and treats airway diseases have not stopped evolving, leading to the discovery of new molecules, new inhaler devices and new treatment paradigms, largely based on patients' phenotypic characteristics. The present revolution in the understanding of human biology promises a new era of a personalised medicine. Medical decision will certainly continue to be based on the best patient's evaluation and on the best available medical evidence, but medical diagnosis will be more precise and done earlier. The therapeutic possibilities will be also more diversified, making medical decision an increasing challenge.

Nevertheless, and despite the significant contribution that biology can take to medicine in the forthcoming decades, medical science will certainly continue to incorporate the experiential and social perspectives defining what a disease is. The relationship between the patient and the physician, the trust placed on the healthcare structures, health-care professionals and prescribed therapy, will certainly continue to be important in the medicine of the XXI century. Patient's beliefs related to disease and treatment, their health literacy, and the social and cultural representations of the disease, will certainly continue to influence adherence to medication and clinical outcomes. Inhalation therapy has been the mainstay of COPD treatment, at least from the last half of twenty century to nowadays, and the correct knowledge of inhalation technique will certainly continue to make sense, at least in the nearest future. The application of statistics to the study of adherence and inhalational technique will contribute to a better understanding of the patient suffering from COPD.

The present thesis is designed in the perspective of a better knowledge of the patient with COPD, and two different concepts have driven this study: the assumption that the greatest opportunity to improve outcomes for patients over the next quarter century will probably come mainly from the learning of how to deliver existing effective therapies,[2] and the recognition of the need for an acknowledgment and study of human behaviour, in the transition from health to illness, despite the promise of new biological markers and new technology.[3]

Study rational

Chronic Obstructive Pulmonary Disease (COPD) currently represents one of the most significant health problems at international level. It is the 4th leading cause of death and the most common chronic respiratory disease worldwide. From a "completely over-looked" disorder, as written by Laennec in the nineteen century, COPD has recently gained importance and visibility. COPD has a global estimated prevalence of 11.7% in people over 30 years old, and 14.2% in the Lisbon adult population. Despite the significant burden of COPD, published literature concerning the characterisation of the disease in Portuguese patients is scarce. All of this brings visibility and utility to any investigation related to this common and incurable disease.

COPD is a very complex disorder, whose paradigms of orientation and treatment are constantly changing. A persistent obstruction of the airways is essential for the diagnosis, but this is the easiest feature to document in clinical practice. COPD is well recognised as a heterogeneous disorder with many systemic manifestations and medical comorbidities that occur across the spectrum of disease severity. Moreover, different patients may have different perspectives of the disease, and different treatment objectives. Some COPD patients mainly want to continue living full and satisfying lives, by preventing and managing limitations in daily activities. The prevention of exacerbations, by limiting social life and daily activities can be the objective of others. Therefore, any investigation on COPD is always an interesting task.

The role of Medicine is mainly to help patients. Treatment can be described as successful if an appropriate change is measured in an appropriate outcome.[4] However, outcomes have different relevancies, strengths and limitations. The choice of the correct outcomes and the correct tools in order to be able to measure them is a controversial and challenging issue in medicine.

Some factors relying in patients, in health-care providers or in the physician-patient relationship can be significantly related to poor clinical outcomes. Some of them are common and modifiable, and their knowledge can be relevant for a successful treatment. Prescribers' non-adherence to

therapeutic standards, patients' non-adherence to inhaled medications, and inhalers' mishandling are common and modifiable factors whose understanding can be useful in clinical practice. An official American Thoracic Society/European Respiratory Society statement, published in 2015, stressed these two last issues as needed research questions in COPD. In a country where access to health-care services is good and patients have access to a wide range of effective treatments to COPD, any planned improvement of treatment outcomes must address this question. Therefore, their discussion seems to be useful and unavoidable.

Prescribers' non-adherence to therapeutic standards in COPD seems to be very common, even though variable from country to country. It is possible to be measured, but difficult to be understood. The science of medicine is characterised by its evidence-based approach and its constant revision. As a human activity, it is necessarily subject to dogmas and beliefs that can influence physicians' understanding of disease and treatment. This can be a window of opportunity to rethink our clinical practice.

Adherence to medications and its improvement is a challenging issue. There is growing evidence supporting individual beliefs and social representations of the diseases as major determinants of adherence to medications. These individual or social beliefs can be subject to intervention. Inhalers mishandling is an old problem, even if unsolved, despite the progressive technical improvement of inhaler devices. However, the knowledge of difficulties and barriers that hinder a correct inhalation technique is of paramount importance to develop any educational intervention regarding the correct use of inhaler devices in COPD patients. Demographic factors, and the patients' beliefs about the need of their inhaled medication, may influence patients' inhaler technique. The study of adherence and inhaler technique can help physicians to understand COPD from the patients' perspective, giving another dimension to research on COPD.

Motivations

Over the past 26 years, already as a specialist in respiratory medicine, I have spent most of my time helping persons with different respiratory diseases. I have observed and treated many patients and I have faced many difficulties. Some were related to poor scientific explanations, some to the translation of scientific knowledge to the particular patient. Medical decisions, in many moments of my professional activity, have been difficult to take. However, medical decision is the cornerstone of medical activity, and must be based on the best scientific information currently available, though adjusted to the individual patient. Obstructive airways diseases, such as chronic obstructive

pulmonary disease (COPD), have always been a privileged source of interest. COPD is a very relevant disorder in pulmonary medicine due to its morbidity and mortality. My motivation lies in the expectation of being able to contribute with evidence-based information, hoping that these contributions can translate into benefits for patients. The main ideas that guided the research developed and presented in this thesis can be summarised in the understanding of factors whose correction can be translated into improved care for patients with chronic obstructive pulmonary disease.

INTRODUCTION

Definition of COPD: an ongoing task

According to GOLD original 2001 document,[5] "COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases". In the first major revision GOLD 2006,[6] Chronic Obstructive Pulmonary Disease (COPD) was defined as a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. In this document, COPD was understood as a systemic disease, even though focused on the pulmonary component and on function defects. In Europe, primary care physicians treat the majority of COPD patients. The International Primary Care Respiratory Group (IPCRG) understand COPD as a common and under-diagnosed disease with increasing prevalence, causing persistent and progressive symptoms that impairs patients' quality of life.[7] In the NICE 2010 working definition "COPD is characterised by airflow limitation that is not fully reversible. The airflow obstruction does not change markedly over several months and is usually progressive in long term. COPD is predominantly caused by smoking. Other factors, particularly occupational exposures, may also contribute to the development of COPD. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations".[8] In this document, the focus remains on a pulmonary and functional level, however with a particularly concern on acute exacerbations. The 'working definition of COPD' has been deleted in the NICE guideline published in the December 2018 revision, because the authors recognised that it was not based on currently evidence and it was unclear whether the thresholds it used were correct and up to date.[9] In the GOLD 2011 major revision[10, 11] "Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients". In this revision, as in the succeeding updates, focus is now more back to the lungs and airways than it was in the previous GOLD document, but once again related to a chronic inflammatory response. The 2017 Spanish COPD Guideline (GesEPOC) defines COPD

as a respiratory disease characterised by persistent symptoms (dyspnoea, cough and phlegm) and airflow limitation usually due to cigarette smoking.[12] This guideline focuses in lungs and airflow limitation, but also on symptoms. In the GOLD 2017 and 2019 major revisions, COPD is defined as a "common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases".[13, 14] It focuses on both symptoms and airflow limitation, but also on pathological abnormalities: "the chronic airflow limitation that is characteristic of COPD is caused by a mixture of a small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person". Chronic inflammation, however causing "structural changes", does not appear in the working definition, like other key features such as comorbidities, exacerbations, and predisposing host factors.

Currently, COPD defining characteristics can be summarised as follows:

- Common, preventable and treatable disease.
- Frequently under-diagnosed.
- It is always a respiratory disease, but often systemic.
- It is related to a pulmonary injury by noxious particles or gases and predisposing host factors; smoking is the major cause of the disease.
- It is clinically characterised by persistent respiratory symptoms. Dyspnoea and limitation of physical activity are the commonest ones, impairing patients' quality of life.
- Exacerbations and comorbidities contribute to the overall severity.
- Its pathophysiological hallmark is the chronic airflow limitation, usually progressive.
- It is characterised by structural changes in the small airways and parenchymal destruction due to chronic inflammation.

Classically, many different sorts of characteristics can be used to define a disease: a clinical description, structural abnormities, imaging representations, disorders of function and aetiology. The consensus definition of COPD contains all of these elements. However,

- the imprecision of the disease definition, failing in differentiating unequivocally COPD from asthma,
- the possible necessity to identify and treat preclinical disease manifestations,
- the presence of different phenotypes within the same COPD definition, needing a tailored approach,

- the emerging of new genetic and molecular information and capabilities,

Lead some authors to emphasise the need for a new definition of the disease expression and its nosology, based on its molecular and environment elements.[15] A new definition must be more sensitive and specific, based on a molecular signature. It should be based on objectively identifying single defining characteristics, reflecting endotypes and clinical phenotypes, and the diagnosis must be based on validated biomarkers.[1]

The Oslerian' concept of a disease; a paradigm changing

Disease (dis-ease, a lack of ease) can be defined as a set of abnormal phenomena, exhibited by a group of individuals in such a way as to place them at a biological disadvantage.[16] The dividing line between disease and health is particularly vague, due to the wide range of variations between subjects and to whether some disease concepts are socially constructed.[17] The current classification of human disease dates to the late 19th century, and was established by William Osler, commonly referred to as the founder of modern medicine. It derives from the association between symptoms/signs and anatomic/histopathologic findings.[1] The patient seeks medical attention because of a collection of symptoms that have to be characterized and analysed algorithmically in order to define a diagnosis. The diagnosis is the name given to the conclusion of this objective evaluation,[16] and its main function is to facilitate the communication within the medical and scientific community. So far, this diagnostic strategy - relationship between syndromes and pathologic findings - continues to dominate medical philosophy, medical practice, and disease nosology, even if it demonstrates a lack of sensitivity in identifying preclinical disease and a lack of specificity in defining disease unequivocally.

COPD is defined by the presence of persistent respiratory symptoms and airflow limitation, airways and/or alveolar abnormalities, and exposure to noxious particles or gases. Despite the presence of all the elements defining a disease, there is a significant lack of specificity on this definition. Aetiology has limited usefulness to COPD definition, partly because even if the aetiology is removed (e.g. smoking), the disease persists, even though with a different progression grade. Moreover, asthma and COPD share some common risk factors, as genetic background and environment exposures. Symptoms usually presented by COPD patients are also shared by asthma and other airway diseases. Structural abnormities have also limited usefulness in the disease definition because they can be difficult to prove, the relative contributions of them vary from person to person, and both asthma and COPD are airway inflammatory diseases. Finally, either the disorder of

function defining COPD – the chronic airflow limitation - or the accelerated decline in lung function can also be present in some asthmatic patients. Moreover, COPD is a very heterogeneous disorder, comprising different clinical phenotypes that describe significant differences between subjects, related to different outcomes, response to therapy, rate of disease progression and mortality.

A philosophical conception of medicine, usually known as naturalistic or objectivist, was born in the 1970s, in opposition to a previous notion that incorporates experiential and social perspectives defining what a disease is. Christopher Boorse, the leading naturalist philosopher of medicine, believes that it was possible to derive a purely descriptive definition of heath based upon biological function.[18] This was called the Christopher Boorse's biostatistical theory of health and disease.[19] This reductionist biologically-based approach to the disease looks for fundamental mechanisms or underlying biologic criteria that defines the various diseases. Biomedical research has traditionally followed this strategy, moving from anatomy to molecular biology. However, a better understanding of the complexity of human biology, in health or disease, have recently been catalysed by a novel discipline of biology,[20] the systems biology, and the new concepts of scale-free networks and systems emerging properties.

Three different scientific fields can be perceived in biology: diversity related, simplicity related (the identifications of general laws) and complexity related.[21] The complexity of life and living systems justify the recent importance given to systems biology.[21] These biology systems approach aimed to understand fundamental biology by integrating data between the different levels of biology complexity, or scale-free networks, which are linked to each other (genes, molecules, cells, tissues, organs, entire body, and environment). Life organisms are complex systems because the interaction of a large variety of different components leads to the emergence of properties which do not correspond to any individual component of the network, but to the network itself.[22] The application of this network science to human biology, both in health and disease, will lead to a different nosology but also to a new definition of disease expression, in which molecular signature will replace histopathology in the diagnosis and in the prediction of outcomes.[15]

Different networks have been described to understand airway diseases: genetic, biological, clinical and environment ones.[1] The clinical expression of COPD (pathophenotypes) results from the interaction between gene and environment disturbances. Because not all phenotypes have clinical relevance, the term "clinical phenotype" has recently been proposed.[22] Many different phenotypes have been described in COPD. The Spanish GesEPOC guidelines propose four different phenotypes: no exacerbator, ACO, exacerbator with emphysema and exacerbator with chronic

bronchitis.[12] However, other phenotypes have also been proposed by different authors, as COPD with bacterial colonisation,[23] α1- antitrypsin deficiency, COPD-bronchiectasis overlap, COPD with rapid FEV_1 decline, COPD with persistent systemic inflammation and COPD with upper lobe emphysema combined with low exercise capacity after rehabilitation.[1] The biological armamentarium of human biology response to injury are inflammation, thrombosis/haemorrhage, fibrosis, immune response, cell proliferation, and apoptosis/necrosis.[15] Different biological responses to injury, alone or in combination, determine the so called intermediate phenotypes (endotypes). Different endotypes will lead to different clinical characteristics or phenotypes. Currently proposed endotypes in COPD are elastase-antielastase imbalance, oxidative stress, innate or acquired immunity abnormalities, defective catabasis, enhanced apoptosis, accelerated aging and abnormal repair.[24] The understanding of endotypes and their identification with specific biomarkers, may facilitate future development of new molecular treatments, targeting different biological pathways. This approach will lead to a personalised treatment, a pre-clinical diagnosis and a more precise prognosis. This is currently known as P_4 medicine: predictive, preventive, personalised and participatory.

Burden of COPD

COPD has a global estimated prevalence of 11.7% among people aged 30 years or more,[25] and currently represents one of the most significant health problems at international level. It is the most common chronic respiratory disease and a growing cause of morbidity and mortality worldwide, with the economic and social impact constantly increasing.[14] COPD represents today the 4th cause of death, but is projected to become the 3rd most common cause by the year 2030. It is the only leading cause of death with rising morbidity and mortality.[26] The increase in COPD-related mortality is mainly driven by aging, the expanding in epidemic of smoking, and the reduction of mortality from other common causes of death. Despite de high prevalence of COPD in some high income countries, 90% of COPD related deaths still occur in low and middle income countries. The high mortality is mainly due to exacerbations requiring hospitalisation, and in patients with hypercapnia and respiratory acidosis, the mortality reaches 10%, increasing to 40% in the first year after hospital discharge.

COPD is also associated to high costs, directly or indirectly related to the disease, and acute exacerbations are responsible for the greater proportion of the economic burden of the disease. In the European Union, COPD accounts for 56% of the cost of respiratory diseases, and in the United

States, the estimated direct and indirect costs are respectively $32 billion and $20.4 billion.[14] COPD is also an increasing contributor to disability worldwide: in 2005 and 2013 was respectively the eight and the fifth leading cause of Disability-Adjusted Life Years (DALYs) lost in the world, and in the United States is the second leading cause.

COPD prevalence, morbidity and mortality vary across countries and regions, and usually rise with age and increasing tobacco use. Urbanisation is another important risk factor for COPD, and rapid urbanisation of some regions may contribute to a regional and global increase of the disease. The highest estimated prevalence is in the WHO American region, and it is underestimated in low-income countries, where spirometry is not widely available. The Europe region shows the lowest increase in total number of COPD cases between 1990 and 2010, probably reflecting the reduction in smoking prevalence due to legal regulations and public health measures and the relatively low use of biomass fuel for heating and cooking.

The estimated COPD prevalence depends on epidemiological case definition and on the choice of the epidemiological model (e.g. subjects' ≥ 40 years, or more recently ≥30 years). Case definition can be based on doctors' diagnosis, self-reported (releasing indirectly on a previous diagnosis) and based on spirometry. Almost all of the recent studies on prevalence of COPD defined COPD by spirometry criteria alone, and not by the combination of symptoms and spirometry. This is because it is more consistent with the diagnosis of COPD worldwide. Usually, the criterion defining airflow limitation is a post-bronchodilator $FEV_1/FVC < 0.70$, as recommended by GOLD. Other criteria also have been used: pre-bronchodilator $FEV_1/FVC < 0.70$, $FEV_1/FVC <0.70$ + $FEV_1<80\%$, $FEV_1/FVC <$ LLN, $FEV_1/FVC < 0.75$, $FEV_1/FVC \leq 0.65$ and $FEV_1/FVC <88\%$ of predict in males and <89% in females. The impact of a post-bronchodilator testing on COPD prevalence estimates can be significant, as technical issues related to quality criteria of spirometry - choice of spirometer, level of training of the operators, processing of collection and storage of measurements. The population impact of different definitions of airflow limitation was described by Celli et al, in 2003, producing prevalence estimates that can vary by 200%.[27] The Burden of Obstructive Lung Disease (BOLD) program adopted for the first time a standardised methodology, comprising questionnaires and pre- and post-bronchodilator spirometry to assess the prevalence and risk factors for COPD in people ≥ 40 years. The criteria proposed by GOLD to define airflow limitation in describing an epidemiological case was adopted by BOLD, although using 200 μg of salbutamol for bronchodilation. The PLATINO study also adopted the same criterion defining airflow obstruction.

The 2001 World Health Report estimated a world-wide prevalence of COPD of 10.1 per 1000, based on doctor's diagnosis and including all ages, and accounting to 2% of total DALYs and 4.7% of all-cause mortality.[28] Celli et al, using a sample of 13,322 patients from 81 different sites in United States that could be extrapolated to the entire civilian non-institutional population, reported a prevalence of 16.8% in people aged 30-80 years, using the fixed criteria to define obstruction ($FEV_1/FVC<0.70$, without reversibility testing + FEV1 <80% of predicted).[27] As usual, COPD prevalence was higher in men (19.9%) than in women (13.8%), and in current smokers (23.2%, 9.0% in never-smokers). Using the lower limit of normal (LLN) to define obstruction, COPD prevalence was estimated in 14.2%.

Sobradillo Penna et al, in the IBERCOP, a multicentre epidemiological study in Spain, reported a prevalence of 14.3% for men and 3.9% for women. The studied sample included 4,035 participants, and general prevalence was 9.1%, higher in smokers (15%) than in ex-smokers (12.8%) or never-smokers (4.1%).[29]

In the 1st study using the GLI-2012 reference equations, and studying 984 subjects aged 65-100 years, the authors found an incidence of airflow limitation of 28.2 per 1000 persons-year using the fixed ratio and 11.7 with LLN (1.41 –fold higher incidence rate using the fixed ratio).[30] The presence of airflow limitation defined by the fixed-ratio in subjects with FEV_1/FVC >LLN was not associated with increased mortality during a 6-year follow-up.

The Burden of Obstructive Lung diseases (BOLD) program, studying 9425 participants from 12 sites, estimated a prevalence of COPD grade ≥ 2 of 10.1% (11.8% for men, 8.5% for women, and 3-11% among never-smokers).[31] The analysis of data of 11,985 subjects from 17 countries participating in BOLD study, COPD was related to worse health status, the effect on the physical aspects of health being stronger than in the mental ones; severe COPD presented a degree of impairment in health status greater than diabetes or cardiovascular diseases.[32]

In Latin America, according to the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study, the prevalence of COPD ranged from 7.8% in Mexico City to 19.7% in Montevideo, in persons aged 40 years or older. The prevalence was higher in men, in older people, in those with low education level and greater exposure to smoking.[33]

In a systematic review and meta-analysis, searching for population-based prevalence studies published from 1990-2004, the prevalence of physiologically defined COPD in adults' ≥ 40 years was 9-10%. Prevalence was higher in smokers, in males and in urban residents.[34]

A more recent systematic review and meta-analysis estimated a global prevalence in 1990 of 10.7% (95% confidence interval, 7.3%-14%) in people ≥ 30 years, and 11.7% (8.4% - 15%) in 2010, also in people ≥ 30 years (14.3% in men and 7.6% in women).[25]

The Lisbon BOLD survey, published in 2013, is the first Portuguese study describing COPD prevalence with a standardised methodology, allowing comparison across different countries.[35] The estimated prevalence was 14.2% in the Lisbon population over 40 years, higher in men than in women. COPD prevalence increased with smoking habits and with age, presenting the highest estimated prevalence in men ≥70 years. The study also shows a high level of under diagnosis and a high prevalence of COPD in never smokers (9.2%). In Portugal, the previously reported prevalence was 5.34%, based on a study from 2002, with some methodological limitations related to the age range of the individuals studied (35-69 years) and to the criterion used for definition of airway obstruction (pre-bronchodilator fixed ratio).[35]

COPD as a complex and heterogeneous disorder

COPD is currently recognised as a complex and heterogeneous disease, both the respiratory complaints and comorbidities having a significant impact on morbidity and mortality.[36] Complex and heterogeneous are adjectives that define the opposite understanding of a disease previously believed to be centred in FEV_1: complex because the relationship between pulmonary and extra pulmonary components is not linear; heterogeneous because not all components are present in all patients at any given time.[37] There is a significant heterogeneity between different populations and also between different patients of the same population. To capture the complexity and heterogeneity of the disease, three main approaches have been described: the use of different independent and relevant variables, the use of multidimensional indices and the definition of clinical phenotypes. All of these approaches include three dimensions of the disease: airflow limitation, symptoms, and risk of future exacerbations. However, these approaches only assess complexity at a clinical and functional level, but COPD is a complex disease also at cellular and molecular levels. Recently, a multilevel network approach to COPD complexity, including genetic, biological, clinical and an environment levels, was proposed to better understand the complexity of the disease.[22]

In the last decade some important concepts have changed the understanding of the disease:

- FEV_1 does not capture the entire complexity of the disease, and not fully correlates with COPD outcomes.

- The deterioration rate of FEV_1 varies from patient to patient.
- Symptoms' perception may not be stable over short periods of time.
- Comorbidities strongly influence outcomes.[38]
- Systemic inflammation is not present in all patients.
- Airway colonisation and changes in lung microbiome may correlate with important clinical outcomes

Agusti et al,[39] analysing data collected at recruitment of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) fulfil relevant observations reflecting the heterogeneity of the disease:

- Age and the amount of smoking were not related to severity of airflow limitation.
- Co-morbidities were independent from the degree of airflow limitation.
- Females had less smoking exposure for the same degree of airflow limitation and were more prone to exacerbate. Osteoporosis and depression were more common in women, but diabetes and cardiovascular disorders were more common in men.
- Patients with chronic bronchitis (CB) were more frequently current-smokers and had a poorer health status than patients without CB.
- Within each GOLD stage of severity, symptoms, exercise tolerance, co-morbidities and reported exacerbations vary widely between subjects.
- Patients with severe airflow limitation were frequently less symptomatic, and reported no exacerbations or impaired exercise tolerance.

Many of these observations are consistent with many other different studies, allowing to conclude that the entire picture of COPD is not driven by airflow limitation, symptoms, acute exacerbations, or any other clinical, demographic or functional characteristics. The heterogeneity of COPD is related to different clinical presentation, pathophysiology, imaging, decline of lung function, response to therapy and survival. Miravitlles et al, studying 833 COPD patients from four different countries, in the Enfermedad Pulmonar Obstructiva Crónica en Acción (EPOCA) study, found statistical significant geographic differences in demographic, socioeconomic, clinical and functional characteristics of COPD patients.[40] However, some trends were common:

- Major prevalence in males and the elderly.
- Major prevalence in low and intermediate socioeconomic status.
- Low education level predominance.
- A high mean of tobacco consumption.

- A larger prevalence of chronic cough and sputum, beyond dyspnoea.
- Lung function significantly compromised.
- Higher prevalence of co-morbidities.
- A high trend to exacerbate.

Relevant differences in demographic and clinical characteristics and relevant exposures for COPD have been described in different countries. Significant differences in demographic, clinical and functional characteristics between subjects are also present in any sample of patients suffering from COPD. Some findings have been increasingly identified:

- The growing prevalence of COPD in females.
- Relevant gender differences, suggesting that women are more susceptive to tobacco smoke.
- A significant proportion of never-smoking patients, referring indoor exposure to household air pollution or occupational exposure.
- The heterogeneous nature of acute exacerbations and the impact of the un-reported exacerbations in the quality of life and in the natural history of the disease.
- The impact of previous diagnosis of asthma on symptoms, exacerbations and lung function decline.

As previous referred in this thesis, COPD is a complex disease also at cellular and molecular levels, and the basis of this complexity and heterogeneity can be summarised as:

- Complex genetic network (genetic mutations, polymorphisms, disease-modifying genes)
- Different (interrelated) environment perturbations (injury)
- Different human biology response to injury, leading to
- Different endophenotypes (endotypes), leading to
- Different clinical characteristics of the disease.

COPD as an exercise intolerance disease

COPD is defined based on irreversible airflow limitation, but patients seek health-care mostly due to exercise related dyspnoea and limitation of physical activity. Dyspnoea is the most common symptom reported by COPD patients and leading to the initial diagnosis of the disease. It is also the most troublesome symptom, regardless of COPD severity,[41] and an important patient reported outcome.[42] Breathlessness, a physiological warning of potentially catastrophic system failure,[43] can be understood as a complex and multidimensional experience, with many sensory and emotional

qualities. Dyspnoea is a major cause of disability and anxiety associated with COPD, and is linked to patients' physical activity. The widely used mMRC dyspnoea scale in COPD patients reflects this association with the grade of physical activity, and can also be understood as a measure of patient disability.

COPD is more prevalent in older persons. The process of aging is associated with a loss of physical function. Two important factors limit physical activity in the elderly: the decline of muscle function and the decline of pulmonary function. Because pulmonary function does not respond to exercise training, age-related decline in pulmonary function can be the more important limiting factor for physical activity in the elderly.[44] This is particularly true among COPD patients, because they present a more increased decline in respiratory function, due to the nature of the disease itself. COPD can be understood as an exercise intolerance disease that can affect daily life and patients' activities, the degree of physical activity being a good predictor of acute exacerbations and mortality, independently of the degree of airflow limitation.

Physical inactivity due to exercise intolerance is a central problem on COPD patients, and is always present, even if not reported in the early stages of the disease. Sedentary occupations, low socioeconomic status and living with the family are associated with physical inactivity.[45] With disease evolution, patients progressively decrease their physical activity, leading to the development of different comorbidities that also contribute to impair exercise capacity.[46] Most COPD patients not only walk less time per day, but also walk slower and spend more time in the lying position, as compared with healthy subjects.[47] Leisure activities are often the first to be eliminated, [48] as they are not critical to daily life: and as much as 30% of patients with moderate or severe COPD are effectively housebound, presenting depression, social isolation and a worse quality of life.

Physical activity is a complex behaviour, related to many different factors, but frequently limited by exercise tolerance.[49] In COPD patients, the limitation of exercise capacity is generally multifactorial: increased exercise dyspnoea due to pulmonary function abnormalities, as dynamic lung hyperinflation or impaired gas exchange, insufficient energy supply to peripheral and respiratory muscles, morphologic alterations of diaphragm muscle fibres and reduced functional metabolic capacities of limbs muscle fibres.[50]

Assessment of patients' daily life physical activity should be routinely performed in clinical practice. Patients' self-reported physical activity demonstrated to have predictive value related to death and risk of exacerbations. Moy et al, on a retrospective cohort study with 3440 COPD patients,

concluded that patients self-reporting higher levels of physical activity presented a lower risk of dying from COPD.[51] However, patients usually overestimate their level of physical activity. Simple questions or questionnaires (e.g. the Short Questionnaire to Assess Health Enhancing Physical Activity – SQUASH) are only informative about the patient perception of their physical activity. For objective measurement, accelerometers or pedometers can be useful in clinical practice. Waschki et al, in a prospective study with 170 COPD outpatients, found that objectively measured physical activity was the strongest predictor of all-cause mortality.[52] Donaire-Gonzalez et al, objectively quantifying physical activity in 177 COPD patients, observed that a greater quantity of low-intensity physical activity reduces the risk of COPD-related hospitalisation.[53] The same group, found that COPD patients were able to accomplish bouts of moderate-to-vigorous physical activity, making the improvement of physical activity feasible in clinical practice.[53]

To assess exercise tolerance, the 6-minute walking distance test (6MWD) is probably the most popular and easier test in clinical practice. It evaluates the global and integrated responses of all systems involved during exercise - pulmonary and cardiovascular system, neuromuscular units and muscle metabolism - reflecting the functional exercise level for daily activities.

Prescribers' non-adherence to therapeutic standards in COPD

The role of medicine is mainly to help patients. Medical decision and pharmacologic treatment must be based in the best currently available scientific information. The objective of clinical guidelines is to produce useful recommendations, by searching for the more relevant scientific information. In the production of medical evidence it is essential the use of standardised methods, and data on respiratory symptoms should be collected using standardised questionnaires. They are crucial for academic purposes. In clinical practice standardized tools and recommendations should be adapted to individual patients. A standard of care is now well established at international level regarding COPD, as in many other disorders. National guidelines, however, can present significant differences, justified by different healthcare systems, cost-effectiveness of drugs, reimbursement issues or availability of medications.[54] In patients suffering from COPD, as in other chronic conditions, overall non-adherence to guidelines seems to be very common, but there is currently no standard threshold of good or even satisfactory adherence. Adherence is variable from country to country,[40] and barriers to guidelines' adherence remain poorly understood.

Miravitlles et al,[40] in the EPOCA study, comprising 77 investigators, 17 countries and 833 patients, concluded that implementation of international guidelines is not uniform around the world, and

observed significant differences in management of COPD according to the socioeconomic status of the patients. In a recently published study among COPD patients in Hong-Kong, a suboptimal adherence to GOLD 2011 guideline was observed, mainly due to overtreatment, usually related to inhaled corticosteroids (ICs) overuse in low risk patients.[55] In many other different studies overuse of ICs was also the most common related deviation to international standards of treatment.[56, 57] However, the role of ICs in COPD is mainly to reduce the risk of exacerbations, and they have been associated with local and systemic side effects, as oral candidiasis, osteoporosis, early onset of diabetes, cataracts or increased risk of pneumonia. In an US population study, once again, overuse of ICs was also common among both general practitioners and pulmonologists, and adherence to GOLD guidelines were associated with lower healthcare costs in patients with moderate to severe COPD. In a Spanish population, among patients with stage II COPD, adherence to GOLD recommendations was also associated with lower healthcare costs, related to drugs use reduction. However, when patients with stage III disease were treated according to guidelines, there was an increase in total costs due to a higher number of exacerbations.[58] One of the largest studies to evaluate real-life treatment patterns of COPD indicates that in the UK, in primary care, it was not treated according to GOLD and the National Institute for Health and Care Excellence (NICE) recommendations. The most frequent related deviations to current guidelines were the absence of any treatment in 17% of COPD patients and the overuse of ICs.[59] A poor clinical outcome related to non-adherence to guidelines would be predictable, but the relationship between adherence to guidelines and some clinical outcomes, such as the number of acute exacerbations, can be different than expected. A recent study found exacerbation-related hospitalisations improving adherence to GOLD guidelines.[60]

The difficulties in distinguishing between asthma and COPD may in part explain the generalised overuse of ICs in COPD patients. However, the medical representation of COPD as an inflammatory disorder may also have contributed to the generalisation of the use of ICs in patients with low risk of acute exacerbations. Barriers to guidelines' adherence, especially among primary care physicians, are usually related to poorer familiarity with the recommendations, discordance with guidelines, time constraints, lack of sufficient training in the interpretation of spirometries and difficulty assessing response to therapy.[61] This last issue can be better demonstrated in patients with infrequent exacerbations, as the decreased rate of exacerbations is an important outcome easily measurable in clinical practice. COPD ABCD group misclassification, depending on whether the mMRC scale or CAT score is used to access the symptomatic impact of the disease, can justify

the incorrect use of long-acting bronchodilators in some patients, leading to over or under treatment. Lower familiarity with clinical guidelines is always associated with non-adherence, and referred by physicians as lack of adequate training in COPD management. Nonetheless, the increased knowledge of guidelines by physicians treating COPD patients regularly may not necessarily translate into better clinical practice.

Guidelines are useful as long as they are updated. Paradoxically, the changing over time of treatment protocols is another reason to low adherence in clinical practice.[56] A recent published study on adherence to guidelines among primary care physicians, and using a self-reported methodology,[62] showed that self-efficacy, outcome expectancies and barriers related to spirometry use and interpretation, may be more determinant to guideline adherence than their knowledge and familiarity. This and other published studies draw attention to the importance of assessing and measuring therapeutic response, bringing important feed-back to the physician regarding the type and amount of medication needed in a given patient. Physicians' rating of different treatment outcomes is another limiting factor to guidelines' adherence in COPD.

Clinical guidelines reduce uncertainty and promote the standardisation of clinical practice.[63] Well-designed randomised controlled trials (RCTs), together with systematic reviews and meta-analysis, remain the cornerstone of clinical research and provide the basis for guideline recommendations.[64] RCTs present strong internal validity, with narrow inclusion criteria and demanding exclusion criteria, to reduce bias. Therefore, patients enrolled in RCTs significantly differ from those treated in routine clinical practice, reducing the possibility of extrapolation of their findings to unselect patient populations.[65] Moreover, there is no robust knowledge of how representative their patients are from a typical patients' population from whom they intend to develop their findings and conclusions.[66] This can also help to explain the widespread non-adherence to guidelines in clinical practice.

Some outcomes are usually studied in the evaluation of COPD management in the community: the early diagnosis of COPD, the decreased in disease severity over time, the prevention of disease progression and the reduction in the number of exacerbations.[67] The specific management of COPD, by simple measures such as improving rates of smoking cessation, immunisation against influenza or treating patients in accordance with international guidelines, is another studied outcome. The assessment of prescribers' adherence to guidelines can be more useful if studied as an outcome to evaluate the treatment and the trends of COPD management in the community, than as a factor of successful treatment of COPD among individual patients.

Adherence to inhaled medications in COPD patients

Adherence to inhaled medications is an issue of paramount importance in COPD, as in other chronic diseases. In the antiquity Hippocrates stated, "The physician should keep aware that patients often lie when they state that they have taken certain medicines",[68] and in 2003 the World Health Organization (WHO) declared non-adherence a major public health problem.[69] However, it remains a neglected aspect when studying COPD patients. Adherence can be defined as the process by which patients take their medication as prescribed. It is usually divided in a sequence of three temporal steps: initiation, implementation and persistence. Initiation begins when the patient takes the first dose. The implementation is the extent to which a patient's actual dose corresponds to the prescribed dosing regimen. Persistence is the length of time between initiation and the last dose, or discontinuation.[70] Different reasons for non-adherence behaviours such as economic ones, inability to use inhalers, feeling better, rate of side effects, confusion about prescribed regimens and running out of medication, can impair adherence in different temporal steps.

Adherence is a complex phenomenon that can vary in form and intentionality. The classical types of non-adherence are

- underuse,
- overuse,
- improper use,

either sporadic or systematic.[71] The World Health Organisation distinguished three types of non-adherence,[72]

- erratic non-adherence, or forgetfulness,
- intelligent or conscious non-adherence,
- unwitting non-adherence (lack of knowledge),

and some authors argued that inhalers misuse must be included in the assessment of adherence, because it results in no medication being effectively delivered.[73] Recent published literature stressed the need for a correct taxonomy for describing patients' adherence to medications, understood as doctor-patient partnership. Many terms, as "compliance", reflecting some patients' passivity, "concordance", frequently used as a synonymous for compliance, and "persistence" are currently unused, because they lead to confusion and misunderstanding. Nonetheless, different terms, as "poor-adherence", "sub-optimal adherence", "lower-adherence" or "non-adherence" continue to

be used in describing the process by which patients do not take their medication as prescribed, making the comparison of results between different studies and populations difficult.

Adherence is a patient' behaviour, and can be measured. Medical interview, by simply asking the patient about their adherence, is an ineffective way to assess adherence. Clinical indicators, physician reports, patients' diaries, prescription refills, objective medication measurements (pill counts) and electronic monitoring can be used to measure adherence.[74] Recent electronic monitors, as the Inhaler Compliance Assessment (INCA), are considered the gold standard for objectively quantifying adherence to inhaled treatment.[73] However, self-reported questionnaires are currently the most commonly used tools, and in-depth patient interviews can complement them, providing insight in most types of non-adherent behaviour.

Self-reported questionnaires should be brief and easy to administer, acceptable to patients, valid, reliable and cost-effective. They have the ability to distinguish between different types of non-adherence and to provide information about behaviours and beliefs.[75] However, they are subjective and potentially prone to bias. Patients may report higher adherence rates than they actually have, or simply have difficulty to remember. As patients frequently undervalue non-adherence, self-reported questionnaires tend to overestimate adherence.

There is no gold standard to measure self-reported adherence. The Morisky-Green 8-items Medication Adherent Scale (MMAS-8) is the most widely used questionnaire in chronic disorders, being able to identify barriers to non-adherence. It was designed to evaluate adherence with oral medication in the treatment of arterial hypertension. It is easy to score and very adaptable to different types of medication. The Self-efficacy for Appropriate Medication Use (SEAMS) is another useful instrument to be used in patients with low literacy skills, and presents a good internal consistency reliability (Cronbach´s alfa = 0.82). The 5-items Brief Medication Questionnaire (BMQ) and the 14-items Hill-Bone High Blood Pressure Compliance Scales are specific to hypertensive patients. The Medication Adherence Rating Scale (MARS) is a 10-items scale, easy to administer, but has only a moderate internal consistency (Cronbach's alfa = 0.60). The 12-items Adherence to Refills and Medications Scale (ARMS) present high internal consistency (Cronbach's alfa = 0.814) and good performance characteristics even among patients with a low-literacy.[75]

The Medication Adherent Report Scale (MARS-5) is a 5-items questionnaire evaluating unintentional and intentional non-adherence to inhaled medication. It is not validated to Portuguese language and a recent study found this questionnaire inaccurate in identifying non-adherence in COPD

patients.[76] The Medication Adherent Rating Scale for Asthma (MARS-A) was developed to determine adherence to inhaled corticosteroids in asthma and it is also not validated to Portuguese language. The test of the adherence to Inhalers (TAI) consists of two complementary questionnaires, the 10-items TAI, completed by the patient, and the 12-items questionnaire, completed by the patient and the health-care professional.[77] It was specifically designed to identify non-adherence to inhalers in asthma and COPD patients, and is available in Portuguese-Brazilian language. TAI holds good psychometric properties and seems to be able to recognise the predominant pattern of non-adherence.[72] TAI was developed in Spain, and published in 2016. The validation study, conducted in 1009 patients, 410 of them suffering from COPD, showed a good internal consistency (Cronbach's alfa of 0.860) and a good test-retest reliability (0.883).[72] The 10-item TAI was used to assess the adherence profiles to inhaled therapies in seven Latin American countries (Brazil included) in the LASSYC study, published in November 2017.[78]

The Measure of Treatment Adherence (MTA) is a psychometric tool also derived from the Morisky-Green Medication Adherent Questionnaire. It is an unspecific questionnaire, validated to Portuguese Population in 2001 with a reported Cronbach's alfa of 0.74. MTA is a seven items questionnaire, reflecting common patterns of intentional and unintentional non-adherent behaviours.[79] Unlike the TAI, MTA also measures non-adherence by overuse, and long acting bronchodilators are frequently overused or used as needed by COPD patients.

Available evidence of non-adherence to medications in COPD is not very strong, but seems to have a high prevalence. The significant variability in the reported prevalence of non-adherence is probably related to using different methods, different instruments or studying different populations. Despite a significant variability in prevalence of poor-adherence or non-adherence, related to the use of different methods, instruments or populations, most studies reported poor adherence to inhalation therapies in clinical practice. However, available evidence of non-adherence to medications in COPD is not very strong. The LASSYC study, published in 2017, and studying 795 patients, found a prevalence of good-adherence to inhaled medications in around 50% of participants.[78] The TAI test, in a cross-sectional multicentre study on of 910 Spanish asthma and COPD patients, found that 62.5% of patients were non-adherent, and the erratic pattern of non-adherence was more common than the deliberate (conscious) or the unwitting patterns.[77]

The World Health Organization defined five dimensions of non-adherence: socio-economic, healthcare related, condition-related, therapy-related and patient-related. The patients' beliefs about their disease and medication seems to be among the major determinants of adherence,[80]

and the role of health beliefs in adherence to treatment has been recognised as a priority for adherence research.[81] The key beliefs influencing patients' common sense evaluations of prescribed treatment can be grouped under two categories: perceptions of personal needs, and concerns about treatment potential adverse effects.[82] Both of them may trigger intentional non-adherence. Nonetheless, concerns about prescribed medication are not just related to side effects, but are also common even when the medication is well tolerated, because patients may be concerned by real or imagined risks of medications, and deliberately reduce dosing.[83]

Some psychometric tools were developed to understand the relationship between adherence to medications and patients' beliefs. The Horne et al' Beliefs about Medicines Questionnaire (BMQ) has proven to be useful in exploring patients' beliefs about the treatment benefits, and their relationship to adherence. In many chronic diseases other than COPD, non-adherence appears to be dependent on the balance between perceived necessity and specific medications concerns. The cross-cultural adaptation of BMQ into Portuguese was validated and published in 2013, and can be a useful instrument to assess patients beliefs about inhaled therapy.[84]

An association between adherence and some patients' demographic or clinical characteristics, as age and gender, socioeconomic and education level, smoking status and quality of life, are conflicting in the literature.[85] A recent study, using an objective method to assess adherence to inhalers, found cognitive impairment as the major determinant of poor adherence behaviour.[86] Non-adherence has been associated with mortality, poor disease control, poor quality of life, higher healthcare utilizations and higher costs usually related to frequent acute exacerbations. In the LASSYC study,[78] poor adherence was associated with lower smoking history, lower education level, worse health status, frequent exacerbations in the previous year and lower airflow limitation. Vestbo et al, using data from TORCH, a multicentre randomised double-blind study, found significant differences in survival and risk of severe exacerbations according to the degree of adherence.[87]

Inhalation therapy and inhalers' mishandling in COPD patients

Inhaled medication is the mainstay of COPD management. Therapeutic success depends on the maintenance of a correct inhalation technique, and the choice of inhaler devices (IDs) can be as significant as the drug itself. Clinical guidelines, as the *Global Initiative for Chronic Obstructive Lung Diseases (GOLD)*, the *National Institute for Health Care Excellence (NICE) guidelines,*[88] or the Spanish *Guía de Práctica Clínica para el Diagnóstico y Tratamiento de Pacientes con Enfermedad Pulmonar Obstructiva Crónica (GesEPOC*) advise about the importance of inhaler technique in clinical practice.[89] However, there is a growing evidence concerning inhalers misuse as a common problem worldwide, even though their impact on COPD outcomes remain currently unknown. The knowledge of difficulties and barriers that hinder a correct inhalation technique is of paramount importance to develop educational interventions regarding the correct use of inhaler devices.

In 1965, Saunders published the first paper describing the misuse of inhaled medication.[90] This is an old problem that has not improved over the past 40 years, despite the increasing technical improvement of inhaler devices.[91] In controlled trials, a correct handling of inhaler devices is usually required as inclusion criteria. However, in clinical practice, up to 94% of patients can present inhalers' mishandling, according to recent studies.[92]

Molimard et al, [93]in the largest study assessing inhalers handling in real life, referred that 49-55% of the 3811 patients studied presented at least one error when using a DPI, and 76% when using a pMDI. In a recent study on 2935 patients, handling errors were observed in over 50% of demonstrations.[94] As expected, different studies reported different rates of misuse, using different methods and studying different populations.

Nebulisers are the oldest devices used in respiratory medicine.[95] There are three different types of devices, the jet nebulizer, ultrasonic and electronic devices. They remain widely used in hospital settings or at home, mainly in children or elderly people, who are unable to use portable inhalers. They are not commonly used and not recommended for chronic disease management in COPD.

The first portable inhalers developed were the metered-dose inhalers (pMDIs), in 1956.[96] They release a liquid aerosol, either a suspension or a solution. The physical and chemical compatibility between the formulation and both the container system and the metering valve, the chemical stability of the drug and the size of the particles to be inhaled, are critical technical issues. This group of inhalers is usually considered the most difficult to use, despite requiring a minimum inspiratory flow for correct airway deposition. Poor coordination and failure to inhale slowly and

deeply are among the most common causes of misuse.[97] The use of simple spacers, valved holding chambers, or breath-actuated pMDIs can overcome these difficulties.

The soft-mist inhaler (SMI - Respimat) is a more recently category of a device releasing a liquid aerosol: it is a portable nebulizer device, releasing a slow-moving aerosol cloud that can lead to high lung deposition. In patients with low inspiratory flow it can be a good therapeutic option, even though limited by the reduced number of drugs available on a SMI.

Dry powder inhalers (DPIs) are currently the most frequent inhalers used in clinical practice. Their formulation has many particle engineering challenges, from the size, shape and surface morphology of drug particles, to their stability and dispersibility. Devices vary in size and shape, have different intrinsic resistance properties, and are broadly classified as single dose inhalers (sDPI) or multiple doses inhalers (mDPIs). They are all passive inhalers, relying on patients' breath the activation of drug delivery. Their performance can be affected by two main driving forces, the inspiratory flow generated by the patient, and the turbulence produced inside the device. However, a lower inspiratory flow, because of the lower speed of the particles, can sometimes result on a better distribution and deposition. Nonetheless, the patient inspiratory flow must always be sufficient to allow the disintegration and the micro-dispersion of the drug. The diameter of the particles and its relationship with the resistance of the DPI can also affect lung deposition.[98] In this complex triangle of particles' diameter, ID resistance and patient airflow, a high compromised airflow is usually the limiting factor to efficacy.[99] The functional progression of COPD and the aging process, reducing inspiratory muscle function, decreases the ability to generate sufficient inspiratory flow to allow significantly lung deposition, limiting the use of dry powder inhalers in these circumstances.

Despite all the physics involved in inhalation, some systematic reviews failed to show significant differences between devices, in terms of clinical efficacy.[100] The effectiveness of inhaled medication, assuming that the patient has the capacity to generate sufficient inspiratory flow, depends on a good inhaler technique. This knowledge, that a good adherence to therapy and a good inhaler technique may be as significant as a good inhaler performance, resulted in the importance currently given to the inhaler technique evaluation and to the development of devices intended to give an adequate feedback to the patient on a correct inhaler' use.[101]

Presently there is no 'best method' to measure the inhalation technique. It is usually assessed in clinical practice by using check-lists with different number of correct steps, critical errors or essential steps,[102] by grading the inhaler use or classifying the quality of the inhaler technique.[103]

The evaluation of inhalation technique remains somewhat subjective. However, a trained observer can achieve a 98% success rate in predicting a significant bronchodilator response from the subject's inhaler technique.[104] The lack of standardised checklists of manoeuvres affecting drug delivery to the lungs, to facilitate comparisons of results, and the lack of consensus on definition of critical errors, makes assessment of inhalation technique a complex task.[105] Inhaler technique must be re-check and re-trained in all medical visits, because it can deteriorate over time. Face-to-face demonstrations of inhaler devices with verbal instructions or multi-media tools are effective methods of teaching the correct use of inhalers. Improvement of patients' inhalation technique can be documented after educational interventions.[106] In a recent systematic review, the authors found 11 studies where previous education or instructions were significantly related to a better inhalation technique, and 26 reporting a significant improvement in inhaler technique following an education intervention.[105]

Some tools, such as the In-Check Dial®, are available for testing inhalation parameters, assessing whether patients are able to produce a required flow rate needed for some inhalers,[96] mainly the high resistance devices.[101] However, they do not assess the quality of the inhalation manoeuvre nor the entire inhalation technique. Metered-dose inhalers can be used with low flow rates, within the range of tidal breathing. For DPIs additional effort is necessary for powder de-agglomeration and delivery of a correct dose of drug. Every DPI has a minimum threshold in terms of flow efficacy; however, no clear upper flow limit can be defined. For a good inhalation manoeuvre, further than a good flow, inhalation time and volume is also needed. Breath holding after inhalation, to promote a better sedimentation of drug particles, even though questionable, may affect the quality of the inhalation manoeuvre, and is not evaluated with this tool. Other different instruments are currently available to study the inhalation manoeuvre, but they were designed for specific devices, and do not assess all steps of the inhalation technique. Recent electronic monitors, designed to quantifying objective adherence to inhaled therapy, can also be used to study the inhalation technique.[86]

A good inhalation technique depends on to the type of ID, on the patients' preference and on the number of different type of inhalers used at the same time.[107] Some patient's characteristics are significantly related to inhalers misuse, as being older, having lower education level or lower socio-economic status. Pothirat et al,[108] studying 103 COPD patients, found low education level as the single most important factor related to incorrect technique. Females, in some published studies, present greater odds of having incorrect inhaler technique.[109] Usmani et al,[105] in a recent systematic review on critical inhaler errors, found age, education status, previous inhaler instruction,

comorbidities and socioeconomic status associated with handling error frequency. However, patients' clinical or functional characteristics were usually not related to inhalers' misuse,[110] and the impact of inhalers misuse on some COPD outcomes, as the number of acute exacerbations, is currently unknown.

The definition of outcomes in COPD

Medical activity usually comprises three stages: assessment, intervention and evaluation of outcomes. Interventions to improve patients' health status are the added-value of medicine.

There are different models of clinical practice. Evidence-based medicine (EBM) appears in the medical literature in the early 1990s. EBM defines that medical practice and medical interventions, informed by science, are more effective towards achieving certain outcomes. Scientific evidence can be achieved by the application of clinical epidemiology to clinical problems. The concept of patient-centered medicine (PCM), born in Canadian Family Medicine, defines that the appropriate targets for therapeutic interventions (therapeutic outcomes) must be negotiated with the patient. Other models, as person-based medicine and values-based medicine (VBM), that recognise the necessity of incorporate the diversity of individual values in medical intervention, have also been described.[17]

A successful treatment can be described if an appropriate change is measured in an appropriate outcome.[4] Outcomes have different relevancies, strengths and limitations.[111] They can enable sufficient discrimination between degrees of disease' severity, but still not be useful to evaluate responsiveness to treatment.[112] Moreover, different perspectives – the physicians' perspective, the patients' perspective and the payers' perspective - value different outcomes. In patients' centred medicine, patients' values regarding health interventions can be an essential variable in the complex equation of any medical decision.

Different instruments were developed to measure important outcomes. Such tools also have different strengths and limitations, different measurements properties and feasibility in clinical practice. The choice of the relevant outcomes and the appropriate tools to measure them can be determinant also in clinical practice or for academic purposes. COPD is a chronic and incurable disease, moreover response to therapy is difficult to assess, and a successful treatment is difficult to define.

Mortality is always the most important outcome. However, it is rarely used as a primary outcome, because it requires a large number of patients and long observations times.[113]

Lung function, symptoms and acute exacerbations are important treatment outcomes in COPD, even in GOLD stage 1 COPD patients.[114] Other commonly studied outcomes are exercise capacity, physical activity and multidimensional scores.[115] Lung density, determined by computed tomographic scanning,[116] and markers of airways inflammation are outcomes receiving an increased attention, both in clinical practice and for academic purposes. In a systematic review of how patients value COPD outcomes,[117] exacerbations, symptoms relief, the level of breathlessness and adverse effects of medication, were highly valued by the patients.

Dyspnoea is the primary symptom of COPD and an important patient-centred outcome, but it is very subjective and does not correlate well with exercise capacity, because the level of breathlessness depends on the level of actual patient' activity. The mMRC scale is an instrument that stood the test of time.[118] It measures mainly dyspnoea-related disability and seem to be relatively insensitive to change due to therapeutic interventions. The Borg-Scale was specifically developed to measure exertional dyspnoea in COPD patients, but no minimal important differences have been defined. The dyspnoea management questionnaire (DM-56) analyse five different dimensions of dyspnoea, represented by 56 items.[119] It can be used to measure change in the level of dyspnoea following therapeutic interventions, but it is time-consuming and hard to use in clinical practice.

Health-status is an important patient-related outcome, and can be measured. Some questionnaires, as St. George's Respiratory Questionnaire (SGRQ) or the Study Short Form-36, are time-consuming, limiting their use in clinical practice. The clinical COPD questionnaire (CCQ), with three domains (symptoms, functional state and mental state) and the chronic respiratory questionnaire (CRQ), with four domains (fatigue, dyspnoea, mastery and emotional state) are disease specific health-related quality of life questionnaires.[120] However, they are also time-consuming, limiting their use in routine clinical practice. The COPD assessment test (CAT) is a multidimensional instrument assessing dyspnoea, cough, sputum production, fatigue and impact of symptoms on daily life activities.[121] It has strong measurements properties in the overall impact of the disease, it correlates well with SGRQ, and GOLD recommends its routine use in clinical practice.[118]

COPD acute exacerbations (ECOPD) are the single most important features of the disease. Frequent ECOPD indicate clinical instability and progression, and are related to increased mortality. It is an important outcome both from the physicians and patients' perspectives. ECOPD can be measured in many ways - absolute number of exacerbations, emergency department visits, hospitalisations or intensive care unit admissions - reflecting different severities. However, there is no standardised

definition of an exacerbation, and many of them are frequently unreported, but still having the same clinical relevance.

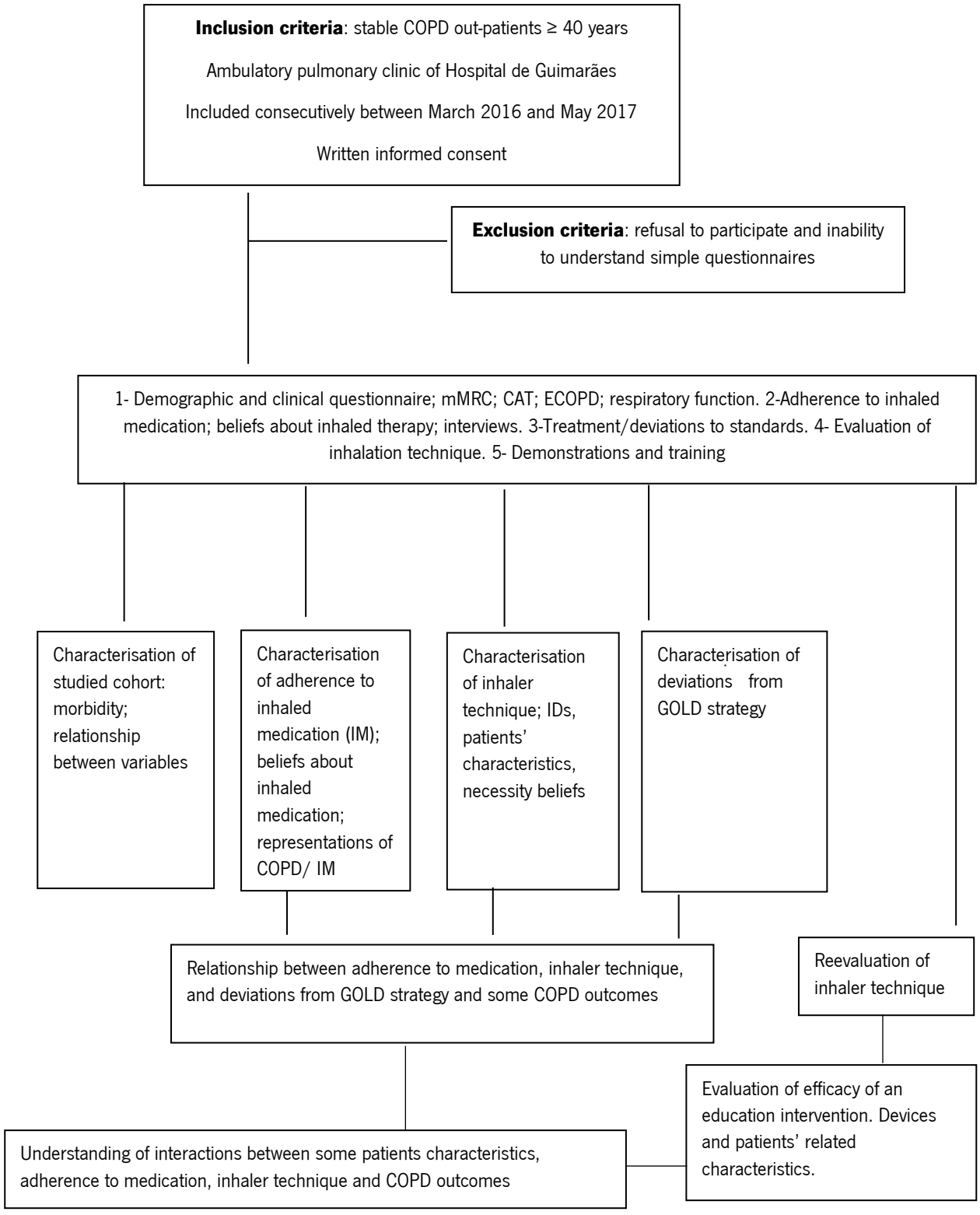
Lung function and FEV_1 decline are also relevant outcomes. FEV_1 strongly relate to health status and to all mortality causes, including cardiovascular. Its decline over time has been used to indicate disease progression. In the PLATINO study,[33] FEV_1 was the main predictor of both survival and lung-function decline. FEV_1 is a highly reproductive measurement, but it does not always correlate with symptoms and exacerbations. Patients with similar FEV_1 can present different phenotypes and be treated according to different algorithms. Moreover, no minimal clinically important difference (MID) has been defined yet, enabling to outline how much must FEV_1 improve to define a successful treatment. It is well known that lung volumes correlate better than FEV_1 with exertional dyspnoea that limits physical activity, but the reproducibility of these measurements and the severity grade of hyperinflation is not yet established.

Multidimensional indices are a significantly step forward to best describe the complexity of COPD. The requirements for a good multidimensional score are simplicity, easiness to be record and register, clinical significance of their components, and the ability to predict severity and mortality.[122] Multidimensional scoring systems, as BODE index, are multicomponent tools, comprising the nutritional state, airflow limitation, dyspnoea, and exercise capacity or exacerbations frequency. Composite outcomes have a better mortality predictive power than that of the individual components. Nevertheless, they were not developed to measure the effects of therapeutic interventions, and no MID is yet defined. Other multicomponent assessments, as ADO or DOSE, have predictive properties related to health status, healthcare consumption, exercise capacity, acute exacerbations, hospitalizations, and mortality.[123] Again, they were not developed to measure outcomes of therapeutic interventions. Probably, in the future,

- a best characterisation and distinction between disease severity and disease activity,
- the development of indicators capable of monitoring disease activity, and
- the identification of different biomarkers related to relevant COPD endotypes,

should significantly affect the understanding and management of the disease but also help in measuring treatment response, in a more personalised approach.

RESEARCH DESIGN:



AIMS AND OBJECTIVES

The aims of this thesis are:

1- To understand the factors whose correction can be translated into improved care for patients with COPD, focused on non-adherence to inhaled medication, prescribers' disagreement to therapeutic standards and inhalers mishandling.

2- To understand the relationship between non-adherence, inhalers mishandling or treatment deviations from guidelines and common clinical outcomes.

The specific objectives are:

1- To evaluate the degree of severity of COPD patients based on symptoms, number of acute exacerbations, respiratory function and comorbidities.

1.1- To find different patients' characteristics that can be related to each other.

2- The characterisation of prescribers' non-adherence to GOLD strategy.

2.1- To find if the prescribers' disagreements to therapeutic standards are associated with patients' symptoms, number of exacerbations or respiratory function.

3- The characterisation of patient' adherence to inhaled medications, focused on patient-related determinants.

3.1- To assess whether demographic variables, clinical and functional severity of COPD, and beliefs about inhaled medication are associated with patients' adherence to inhaled medications.

4- To characterise inhalation technique in COPD outpatients.

4.1- To assess if the type of inhaler device, patients' preferences, the number of inhalers used by each patient, patients' beliefs about inhaled medication, and demographic, clinical or functional characteristics are associated with a correct inhalation technique.

4.2- To evaluate if the learning of correct inhalers' use can improve inhalation technique in a sustained way.

4.3- To assess the inhalers and patients' related characteristics that are associated with improvements of inhalation technique.

METHODS

The methods used in the studies included in this thesis are described in the sections on materials and methods of the published articles. Nevertheless, some considerations have to be done. A total of 360 participants were recruited, but 41 were later excluded: five refuse to participate, eight were unable to understand simple clinical questionnaires, and in 28 subjects COPD was posteriorly ruled out. In the studies *"Characterisation of morbidity in a* COPD hospital cohort" and "*COPD: analysing factors associated with a successful treatment"* 303 participants were included. In the study "*Symptoms irregularity and increased risk of acute exacerbation*" 310 patients were included, and 319 in the study "*COPD: Understanding patients' adherence to inhaled medications"*. Of these 319, 300 were currently using inhaler devices, and their inhalation technique was described in the study "*COPD: Misuse of inhaler devices in clinical practice".* Due to limitations related with editorial criteria, the methods' section in the published studies were condensed. For the sake of clarity, a more comprehensive description of methods is described below. Two articles describing the study methodology were published, "*Study protocol: Determinants of Treatment success in Chronic Obstructive Pulmonary disease*" and "*Study protocol: Efficacy of an Educational Intervention in the Sustained Improvement of Inhalation Technique"*. They are included at the end of this section.

The initial data collection was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães, between March 2016 and May 2017. COPD patients 40 years or over, diagnosed according to GOLD criteria and without acute exacerbations for more than four weeks were consecutively included, after giving their written informed consent. Exclusion criteria were the refusal to participate and the inability to understand simple questionnaires. No participants were enrolled in another different study, at the same time. The study was approved by the Hospital de Guimarães Ethics Committee, the Research Ethics Committee of Minho' University and the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[124]

A questionnaire of demographic and clinical data and the Graffar Social Classification,[125] validated for use in Portuguese population (appendix, pg 224), were applied. An easy-to-answer questionnaire on COPD, concerning the patient's information about their disease was developed and applied (appendix, pg 226). It includes questions about the name and nature of the disease, on chronicity, on severity and its justification, and about searching for any kind of information concerning their disease. Evaluation of symptoms was done using the Portuguese versions of the

COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). Occupational exposure to dust, gas or fumes relevant to COPD were self-reported, and dichotomised as regularly exposed or not-regularly exposed. Indoor exposure to household air pollution from biomass fuel combustion was considered only for regular exposition for cooking, and also dichotomised as regularly exposed and not-regularly exposed. The number of COPD acute exacerbations (ECOPD) referred in the previous year and the patients' comorbidities were evaluated by using the hospital database, the health data platform, or patients' self-reported. We defined ECOPD, according to GOLD,[13] as an acute worsening of respiratory symptoms that result in an additional therapy, but also requiring an unplanned medical visit. Symptoms irregularity was evaluated. It was defined as a worsening of one or more respiratory symptoms in winter/or with changes in weather that led to the use of rescue medication, but did not require an unplanned medical visit. All participants performed spirometries according to the American Thoracic Society and the European Respiratory Society recommendations for standardised lung function testing,[126] and referenced according to Global Lung Function Initiative predict equations (GLI 2012).[127]

Adherence was assessed using the Measure of Treatment Adherence (MTA),[79] a psychometric tool derived from Morisky et al Measure of Medication Adherence. MTA was validated for the Portuguese population in 2001, with a reported Cronbach's alpha of 0.74. It consists of seven items questionnaire, reflecting common patterns of intentional and unintentional non-adherent behaviours. 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, and total scores range from 6 to 42, with higher scores indicating higher self-reported adherence (appendix, pg 225). Non-adherence was defined by a score ≤ 5, after dividing the total score by the number of questions. This cut-off was validated by the MTA authors. Because the words adherence and non-adherence cannot fully describe the complexity of adherence related behaviours, poor-adherence was also defined by a total score ≤ 6, after transform 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,[84] validated as interviewer-administered questionnaire, was published in 2013. It was applied to explore the relationship between beliefs and adherence. The BMQ is an eleven-item questionnaire with a five-item Necessity scale and a six-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 in the Necessity scale and 6 to 30 in the Concern scale (appendix, pg 199). The Necessity and the 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.

After the application of these questionnaires, semi-structured face-to-face interviews were carried out, and participants were encouraged to justify their opinions and behaviours about their disease and inhaled medication. Field-notes were made during and after the interviews, and each interview was analysed before the next one. The objective was to obtain new information from the patients themselves.

The provider's adherence to GOLD 2017 guidelines was assessed by comparing the patient's current medication with the therapeutic standards for the same ABCD groups. Evaluation of current medication was done by using the hospital database, the health data platform, or patients' self-reported. They were categorised as GOLD-concordant or GOLD-discordant based on criteria presented in the study "*COPD: analysing factors associated with a successful treatment".*

Inhalation technique was evaluated by using previous defined checklists, presented in the published paper *"COPD: Misuse of inhaler devices in clinical practice"*. They were developed according to the instructions provided by the manufactures and to published literature,[99] and included essential steps and critical errors. Errors were considered critical when they can substantially affect drug delivery to the lungs, and were related to priming/loading or inhalation manoeuvre. The number of IDs simultaneously in use by each patient was recorded. Patients using two or more inhalers were inquired for device preference, and invited to justify their answer, clearly stated that the question is related only to inhalers' aspects. This was an open question. Answers were then collected in five groups: more practical to use, easier to use, ID characteristics, accustomed to using, and others. Because of the difficulty to distinguish between "being more practical" and "easier", these two answers were later analysed together. Participants were then asked to demonstrate the use of their prescribed IDs just as they do it at home, and demonstrations were done with inhalers containing placebo medications. Assessment of patients' handling of inhaler devices, by recording the correct steps and critical errors, was done by a single trained senior pulmonologist, to avoid inter-observer variability. After this assessment, face-to-face demonstration and training with placebo inhalers were provided to all participants, until a correct use was achieved.

Ten to twelve months after the first medical visit, participants were invited by mail for a second medical visit, and re-evaluation of inhalers' technique was done by the same pulmonologist using the same check-list of steps and critical errors. Patients using different IDs were excluded.

STUDY DESIGN, SAMPLING PROCEDURE AND STATISTICAL ANALYSIS

A cross-sectional study was conducted in the outpatient respiratory care of a single middle sized hospital, and patients were recruited consecutively. Exclusion criteria in the present study were only the refusal to participate and the inability to understand simple questionnaires. This allowed the authors to include the wider range of diversity elements of the population from which the sample was taken. The present thesis also comprises an interventional prospective study on learning inhaler technique after a single education intervention, "*Teaching inhalation technique in COPD outpatients: can a sustained improvement be achieved?".* The number of patients included in the several studies that comprises the thesis were between 300 and 319. In the present work, statistics were used to describe the characteristics of the studied sample but also to draw inference, making generalisations about the population we intended to study.[128] Descriptive statistics were used to describe the studied sample. The measures of central tendency - median and mean - were used in the evaluation of quantitative variables when required.[129] To measure variation of quantitative variables, the standard deviation (SD) from the mean were used, and the confidence interval (CI) was obtained in accordance to Central Limit Theorem, and set at 95%.

A statistical significance association between variables were sought when clinical significance between them was recognised as useful.[130] The results were considered statistically significant when P-value <0.05. Statistical correlation between continuous variables can be visually assumed, and the correlation coefficient measure the strength of the linear relationship.[131] To compare the mean of two (quantitative) variables, the t-test was used. To test the independence (or relationship) between two qualitative variables the Pearson's CHI square test was used. To measure the uncertainty about the independence (or association) of variables, confidence interval was calculated and also set at 95%, allowing us that the results can be extrapolated into the population of COPD patients.[132] When it was important to adjust the evaluation of the association between different variables for potential confounders factors, multiple regression models were used.[133]

The present study can be defined as observational, cross-sectional study. Observational studies are important types of study design,[134] though they are considered to have less statistical power and causal inference cannot be established. They open an important window to daily medical practice.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. STROBE Statement is a checklist of 22 items that

should be addressed in writing articles, for a good reporting cross-sectional, case-control and cohort studies.[135] Though STROBE guidelines are only recommendations, they were followed in all the articles that comprises the thesis, to improve the quality of reports.

Adherence to inhaled medications was assessed using the Measure of Treatment Adherence (MTA). Any measurement instrument is subject to errors (variability in the process of measurement). The reliability of an instrument is the estimation of its ability to be consistent, i.e. to give the same result for the same quantities. Unsystematic errors are always present, and must be as small as possible. Systematic errors show that the measuring instrument is not a valid one. A measuring instrument must be valid and reliable, and one method of evaluating their reliability could be their use at different times, known as "re-test". However, the reliability of a measuring instrument is usually assessed statistically, by estimating its internal consistency. It is based on the principle that the greater the variability of results of the same instrument in a sample of subjects, the greater the information that the measurement carries, and the smaller the error associated with the measurement. The Cronbach's alpha is a statistical estimate of the internal consistency, and is a "lower-band" estimate of reliability.[136] A measuring instrument is believed acceptable if it has a Cronbach's alpha ≥ 0.70 and questionable between 0.60 and 0.69. In the present study, the reliability of the MTA scale was assessed with Cronbach's alfa measure for internal consistency.

The statistical analysis of all the articles that comprises the present thesis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Study Protocol: Determinants of Treatment Success in Chronic Obstructive Pulmonary Disease

(Acta Farmacêutica Portuguesa. 2017;6(1):38-44.)

Study protocol

Determinants of Treatment Success in Chronic Obstructive Pulmonary Disease

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ARTIGO ORIGINAL | ORIGINAL ARTICLE

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 population[1]. In Portugal, the prevalence may be as high as 14.2% in adults over 40 years[2]. 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 factors[3], such as appropriate treatment, good adherence to medication and correct inhalation technique[4]. 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 guidelines[5].

In COPD, as in many chronic diseases, poor adherence to medication are a well--known factor of therapeutic failure[6], but patient' adherence is not still regularly monitored in clinical' practice[7], 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 factors[8]. Adherence to treatment and its improvement is a critical point in patient's treatment[9], 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 limitation[10]. Recently published studies reported variability in the prevalence of poor adherence, when using different methods or instruments, and different populations[11]. Adherence to medication remains an open issue, and merits further investigation[12].

However important the knowledge of adherence to medication, the psychometric tools are omitted about the reasons for the non-adherence[13]. Sociodemographic variables seems to be poor related to adherence behaviors[14] 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 aspects[15]. 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 practice[18]. 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 used[21]. In fact, the inhaler technique has been a problem since the launch of the first inhaler device, and it is not yet solved[22]. 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 (RTCs), representing less than 5% of the "real" target patient population[23]. In respiratory medicine, RTCs 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 therapies[24]. 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 access 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, Graffar 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 forth 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' 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.

The authors have no conflicts of interest to declare.

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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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Study Protocol: Efficacy of an Educational Intervention in the Sustained Improvement of Inhalation Technique

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Study protocol

Efficacy of an Educational Action in the Sustained Improvement of Inhalation Technique

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ARTIGO ORIGINAL | ORIGINAL ARTICLE

ABSTRACT

Study methodology: This is an institutional, prospective and observational study on COPD out-patients. An inadequate inhaler technique remains a major cause of insufficient disease management. Face-to-face demonstration of inhalation devices are effective methods of teaching the correct inhalation technique. However, if some improvement is sustained over time, is not yet determined. This is the primary aim of this study. Secondary objective is to evaluate the factors that can predict a sustained improvement of inhalation technique. In a previous visit, COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. Participants were asked to demonstrate the use of their prescribed ID, just as they does it at home. For each inhaler device we defined a checklist of steps for a correct inhalation technique, and critical errors, which are likely to make therapy useless. After this evaluation, demonstrations and training with placebo inhalers were given to all participants, until a correct use is achieved. Patients will be invited for a second medical visit, 10 to 12 months after the first visit, and they will be asked again to demonstrate the use of their inhalers. It will be used the same check-list of the first visit, and the reevaluation will be done by the same healthcare professional.
Impact of the research: To the best of our knowledge this will be the first study carried out in Portuguese population of COPD patients, concerning the sustained improvement of the inhalation technique after a single educational intervention. The characteristics of both the patients and inhalation devices related to a sustained maintenance of a correct inhalation technique can be useful for planning education interventions on COPD patients. This can be the added value of this study.

Keywords: COPD, Inhalation Technique, Educational Action.

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BACKGROUND

Chronic Obstructive Pulmonary Disease is the 4th leading cause of death and the most common chronic respiratory disease worldwide. COPD currently represents the most significant health problem at international level, and its economic and social impact still is constantly increasing[1]. COPD is a chronic and incurable disease, but symptoms significantly improve with therapy. Inhalers are the vehicles used for effective administration of medication. A correct treatment, based on the best medical evidence, and a correct inhalation technique are well-known factors of therapeutic success[2]. However, inhaler misuse remains unacceptably high[3], and a major cause of insufficient disease management[4]. Many factors, related to the inhaler devices or to patients' characteristics, can influence the effectiveness of the medication. Choosing the right device for a given patient and education on inhaler technique are important factors of COPD management[5].

In clinical practice, inhalation technique can be measured using check-lists, counting the number of correct steps, defining critical errors or essential steps[6-7], grading the inhaler use, or classifying the quality of the inhaler technique[8]. However, the evaluation of inhalation technique remains difficult and somewhat subjective. In a country where the patients' access to health-care services and to efficacious therapies is good, any improvement in treatment outcomes must address the improvement of the inhalation technique.

Face-to-face demonstration of inhalation devices (IDs) with verbal instructions and multi-media tools are probably the most effective methods of teaching the correct inhalation technique for each ID. A successful maintenance of an effective use depends on correct instructions and demonstrations, but training the correct inhaler use is of paramount importance. Because inhaler technique can deteriorates over time, periodic re-training is also recommended[9]. However, beyond training and education, other domains, related to the patient and device, must be met in order for optimum inhaler technique maintenance[10].

In a previous study with 282 COPD out-patients performing 467 inhalation maneuvers, ten types of IDs were examined. We found that 48% of inhalations had at least one step incorrectly performed, and in 29.6% of demonstrations critical errors were observed[11]. A significant relationship between a correct inhalation technique and both the type of ID and some patients' characteristics like age, gender, education level and socioeconomic status was observed.

Study methodology

This is an institutional, prospective, observational study, enrolling COPD out-patients on the Respiratory Department of hospital de Guimarães. The primary objective is to evaluate if the application of an educational action in COPD patients, regarding the correct use of the IDs, can improve inhalation technique is a sustained way. Secondary objective is to evaluate if the type of ID or some demographic, clinical or functional characteristics of patients can predict a sustained improvement of inhalation technique. The study was

approved by the hospital de Guimarães Ethics Committee, the Research Ethics Committee of Minho' University and by the Portuguese Data Protection Agency (record 5778/2016).

In a previous visit[12], COPD out-patients over 40 years old, diagnosed according to GOLD criteria, were recruited consecutively, after giving their written informed consent. The inability to understand and respond to simple questionnaires was the exclusion criterion. A survey of demographic and clinical data was applied. Evaluation of symptoms was done using the Portuguese versions of the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). The number of COPD exacerbation in the last year was recorded. For each inhaler device, in accordance with the international recommendations, we defined a checklist with five steps for a correct inhalation technique, and two essential steps and critical errors, related to priming/loading and the inhalation manoeuver, which are likely to make therapy useless[13]. Participants were asked to demonstrate the use of their prescribed ID, and all inhalation maneuvers were evaluated. After this assessment, instructions, face-to--face demonstration and a training with placebo inhalers were given to all participants, until a correct use is achieved, or until the patient becomes tired.

Participants will be invited for a second medical visit, 10 to 12 months after the first visit. Exclusion criteria will be refuse to participate, quitting medication, and the use of different IDs from the first visit. Patients will be asked again to demonstrate the use of their inhalers. It will be used the same check-list of the first visit, and the reevaluation will be done by the same healthcare professional, to avoid inter-observer variability. A statistical analysis will be performed using the IBM SPSS Statistics for Windows software, version 22.0. Armonk, NY: IBM Corp.

Strengths and limitations of the study

To the best of our knowledge this will be the first study carried out in Portuguese population of COPD patients, concerning the sustained improvement of the inhalation technique after a single educational intervention. However this study has some strengths and limitations. It will be conducted in a single care institution, where patients are being treated by pulmonologists. This may limit the generalization of the results to other populations. As patients were enrolled consecutively in the first medical visit we cannot exclude selection bias. Inspiratory flow will be not objectively evaluated, and the assessment of inhalation technique is always difficult and somewhat subjective, especially the inhalation manoeuver[14]. However, this is how, in real-life setting, clinical data are judged and decisions are done. Although our choice of critical errors and number of steps was based on previous literature, it is subjective, deserving discussion. To minimise subjectivity, our check-lists were constructed full of steps and possible errors for each ID. All IDs in use by COPD patients will be evaluated. Inhalation technique was assessed in the first visit by a single trained pulmonologist, and the same pulmonologist will done the second evaluation, to avoid inter-observer variability.

Impact of the research

The misuse of IDs in COPD patients remains a topic of outstanding relevance. Verbal instructions and a face-to-face demonstration of the inhalation devices, patient' teach-back, and training the correct inhaler use are well-known factors for a correct inhalation technique. But inhaler technique can deteriorates over time. If some improvement, after a single education intervention, is sustained over time, is not yet determined[14]. This can be the added value of this study. Discussion will be focused on the comparison of the inhalation technique between the two medical visits, centered on critical errors and steps correctly performed. The role played by the education intervention, the maintenance of training by the daily use and the over-time deterioration of inhalation technique will be also discussed. Discussion will be also focused on the characteristics of patients and on the type of IDs that can predict a sustained improvement in the inhalation technique. This knowledge should be able to motivate physicians in teaching the correct inhalation technique for all IDs, and reinforce the need for a periodic re-training. It should also help the choice of the ID in which a better inhalation technique is expected to be maintained over-time. The knowledge of some demographic and clinical characteristics of patients related to the sustained maintenance of a correct inhalation technique can be useful for planning education interventions on COPD patients.

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RESULTS

Overview of the studies included in this thesis

This section is an overview of the results of the studies that comprises this thesis.

The study, "*Characterization of morbidity in a COPD hospital cohort"*, aimed to characterise the morbidity of the sample of COPD outpatients studied throughout the thesis, based on symptoms, acute exacerbations, FEV_1% and comorbidities. It also intended to explore associations between specific patients' characteristics and clinical features.

Another study, "*Symptoms irregularity and increased risk of COPD acute exacerbations"*, aimed to evaluate whether some patients' characteristics can predict an increased risk of acute exacerbations of COPD, and thus influence therapeutic options. Symptoms irregularity was one of the variables under study, because instability of symptoms can be understood as a minor form of a COPD exacerbation.

The study named "*Understanding patient adherence to inhaled medication: The social representations of COPD"*, was a preliminary study on the first 174 participants. It aimed to understand the patterns and reasons for non-adherence, and how the patients' representations of COPD influence adherence to inhaled medication.

The study "*COPD: understanding patients' adherence to inhaled medication"* aimed to characterise the adherence to inhaled medications in the whole sample of the 319 COPD outpatients, focused on patient-related determinants. It intended to assess whether demographic variables, clinical and functional severity of COPD, and beliefs about inhaled medications are associated with patients' adherence to inhaled medications. The importance of this work lies on the understanding of patient-related determinants of adherence.

Another study was called "*COPD: Misuse of inhaler devices in clinical practice"*, and the objective was to evaluate the inhalation technique in COPD outpatients. We intended to assess whether the type of inhaler device, patients' preference or number of inhalers used at the same time, and the patients' beliefs about inhaled medication were associated with a correct inhalation technique. We also intended to understand if the demographic, clinical or functional characteristics of patients were associated with a correct inhalation technique.

The study "*Teaching inhalation technique in COPD outpatients: can a sustained improvement be achieved?"* is an interventional study published as a research letter. It aimed to evaluate if the application of an educational intervention in COPD outpatients can improve inhalation technique

in a sustained way, and to assess the inhalers and patient-related characteristics that are associated with some improvement in inhalation technique.

The objective of the study named "*COPD: analysing factors associated with a successful treatment*" - was to evaluate if non-adherence to inhaled medications, inhalers mishandling or the prescribers' non-adherence to GOLD strategy were associated with medical Research Council Dyspnoea Questionnaire (mMRC) grade, COPD Assessment Test (CAT) score, COPD acute exacerbations and FEV_1%.

Characterisation of morbidity in a COPD hospital cohort

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ORIGINAL ARTICLE

Characterisation of morbidity in a COPD hospital cohort

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KEYWORDS
COPD;
FEV_1;
Exacerbation;
Comorbidity

Abstract
Objectives: To characterise the morbidity of COPD out-patients based on symptoms, acute exacerbations, FEV_1 and comorbidities, and to explore the association between different patients' characteristics such as social, demographic, clinical history or exposure.
Methods: Stable COPD outpatients over 40 years old diagnosed according to GOLD criteria were included consecutively; the exclusion criteria were only refusal to participate and inability to understand clinical questionnaires. A survey of demographic and clinical data was conducted. Symptoms were evaluated using the CAT and mMRC questionnaires. The number of COPD acute exacerbations reported in the previous year was assessed, and spirometry performed on all participants according to ATS/ERS recommendations. Different variables were collected and then related to each other.
Results: We studied 303 COPD outpatients, all Caucasians, 79.5% males and mostly elderly. 65.7% of participants reported having low monthly income and 87.8% a low education level. Tobacco smoking was the most common exposure identified but a substantial proportion of COPD patients were non-smokers (26%). Frequent acute exacerbations were reported by 38.0% of patients. The mean post-bronchodilator FEV_1 was 53.2%. The distribution of patients according to GOLD 2017 stage and classification was respectively 9.9%, 41.9%, 35.0% and 13.2% from 1 to 4 and 23.1%, 39.6%, 2.3% and 35.0% from GOLD A to D. Only 29 patients (9.5%) presented no comorbid conditions, and the most common were hypertension, heart diseases and dyslipidaemia.
Conclusions: Our data confirms COPD as a complex and heterogeneous disorder, with a significant morbidity due to the nature of symptoms, frequent comorbidities and exacerbations. A substantial proportion of COPD patients were never-smokers, mainly women, calling attention to the need for COPD recognition in these cases. COPD in women, in never-smokers and

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in patients with a previous diagnosis of asthma presented some specific characteristics. Some patient characteristics are associated with frequent acute exacerbations. FEV_1 was strongly related both to symptoms and exacerbations.

Background and objectives

Chronic Obstructive Pulmonary Disease is the 4th leading cause of death and the most common chronic respiratory disease worldwide. In developed countries there is a growing recognition of COPD as a cause of mortality and disability, despite significant improvements in life expectancy and lower death rates in many diseases. COPD currently represents one of the most significant health problems globally,[1] and its economic and social impact is constantly increasing.[2] Despite the significant burden of COPD, there is little published literature concerning the characterisation of the disease in Portuguese patients.[3] However, population-based studies are the mainstay for health planning and economic investment for any chronic respiratory diseases.[4] The aim of this study was (1) to characterise the morbidity of COPD outpatients based on symptoms, acute exacerbations, FEV_1 and comorbidities, and (2), and to explore the association between different patient characteristics such as social, demographic, clinical history or exposure.

Materials and methods

A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães, Portugal, between March 2016 and May 2017. Stable COPD patients over 40 years of age, diagnosed according to GOLD criteria, were included consecutively after giving their written informed consent.[5] Exclusion criteria were the refusal to participate or inability to understand simple questionnaires. The study was approved by the Hospital de Guimarães Ethics Committee, the Research Ethics Committee of Minho University and the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[6]

A questionnaire of demographic and clinical data and the Graffar Social Classification,[7] validated for use in Portuguese population, was used. Symptoms were evaluated using the Portuguese versions of the COPD Assessment Test (CAT) and the Medical Research Council Dyspnoea Questionnaire (mMRC). Occupational exposure to dust, gas or fumes relevant to COPD were self-reported, and dichotomised as regularly exposed or not-regularly exposed. Indoor exposure to household air pollution from coal and biomass fuel combustion was considered only for regular exposure to cooking, and also dichotomised as regularly exposed and not-regularly exposed. The number of COPD acute exacerbations (ECOPD) reported in the previous year and the patients' comorbidities were evaluated by using the hospital data base, the health data platform, or patient self-report.

We defined ECOPD, according to GOLD, as an acute worsening of respiratory symptoms that result in additional therapy, but also require an unplanned medical visit. All participants performed spirometries according to the American Thoracic Society and the European Respiratory Society recommendations for standardised lung function testing,[8,9] and referenced according to Global Lung Function Initiative predict equations (GLI 2012).[10] It should be noted that, if we had used a post-bronchodilator FEV_1/FVC >lower limit of normal (LLN) instead of the fixed value suggested by the GOLD to define airflow limitation, COPD would have been ruled out in 46 patients (15.2%)

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp. Independence for categorical variables was analysed with Chi-square Test and a statistical significance was considered when $p < 0.05$. Binary logistic modelling was performed to analyse predictors' significance and effect size in dichotomous data.

Results

Patients' characteristics

A total of 344 participants were recruited. Five refused to participate, eight were unable to understand clinical questionnaires and COPD was later ruled-out for 28 subjects. We studied 303 COPD outpatients, all Caucasians, predominantly married (77.6%), retired (84.1%) and living with their families (89.8%). Many different exposures relevant for COPD overlapped in the same patients: 121 (39.9%) smoker or ex-smoker patients also reported occupational exposure. Tobacco smoking was the most common exposure identified in 74.0% of patients (86.7% of men and 24.2% of women), 18.2% being current smokers and 55.8% ex-smokers. Self-reported occupational exposure to gas, fumes and dust, either mineral or biological, relevant to COPD, were reported by 55.5% of patients, and sustained indoor-exposure to household air pollution from coal and biomass fuel combustion was reported by 63.8% of women. The most important demographic, clinical and functional characteristics are presented in Table 1.

Wheezing was reported by 82.5% of patients, but only in 3.3% was it a frequent symptom. Chronic bronchitis (CB) was reported by 24.7% of patients (23.5% men and 33.9% women, $p = 0.085$) and 32.3% of them were frequent exacerbators.

Table 1 Demographic, clinical and functional characteristics of COPD patients.

Characteristics	$n = 303$
Male gender	241 (79.5)
Mean age (years)	67.5 ± 10.2
Age ≥65 years	186 (61.4)
Education level ≤3 school years	89 (29.4)
Education level ≤6 school years	266 (87.8)
Graffar social classification	
Graffar 1	2 (0.7)
Graffar 2	13 (4.3)
Graffar 3	106 (35.5)
Graffar 4	174 (58.2)
Graffar 5	4 (1.3)
Very low monthly income (<530 Euros)	197 (65.7)
Low monthly income (530–1060 Euros)	83 (27.4)
Mean smoking amount (pack/years)	49.3 ± 32.4
mMRC grade ≥2	185 (61.1)
CAT score ≥10	152 (72.4)
Frequent ECOPD (≥2/previous year)	115 (38.0)
Post-bronchodilator mean FEV_1%	53.2 ± 19.7
GOLD stage	
I	30 (9.9)
II	127 (41.9)
III	106 (35.0)
IV	40 (13.2)
Gold 2017 classification	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)

Note: Data shown as mean ± SD or *n* (%).
Abbreviations: mMRC, Medical Research Council Dyspnea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

The most prevalent comorbid conditions are presented in Figs. 1 and 2. Only 9.5% of patients presented no comorbid conditions, and 14.2%, 17.5%, 17.8%, 20.5% and again 20.5% present respectively 1, 2, 3, 4 and ≥5 comorbid conditions.

Eighty-two patients (27.4%) reported a previous diagnosis of asthma under the age of 40, usually in childhood. It was not possible to confirm the data in the hospital data base or on health data platform. 173 patients had undergone a pulmonary computed tomography (CT) scanning in the previous 6 years and bronchiectasis was found in 45 of them, being of cylindrical type and clinically unexpected in 31 patients. Long-term oxygen therapy (LTOT) had been prescribed to 45 patients and home non-invasive ventilation (NIV) to 24 patients (16 under LTOT + NIV). The particular characteristics of these patients are beyond the scope of the present study.

Relationship between different variables

Table 2 presents the relationship between different variables. Current smokers have a significantly lower mean age than ex-smokers or never-smokers (respectively 61.2, 67.2 and 72.5 years, $p < 0.001$). We found no association between pack-years smoking history and GOLD stage (the average number of pack-year was 45.1, 44.6, 56.0 and 47.3 from GOLD 1 to 4, $p = 0.126$). There was no significant association between GOLD 2017 stage and classification and hypertension, heart diseases, diabetes and dyslipidaemia. Obesity was less prevalent in GOLD 4 (23.3% in GOLD 1, 35.4 in 2, 28.3 in 3 and 7.5% in 4, $p = 0.007$) and underweight in GOLD 1. When controlling for age, gender, monthly income, education level, smoking history, FEV_1, chronic bronchitis or previous history of asthma (Table 3), only FEV_1% and chronic bronchitis were associated with more symptomatic impact (CAT ≥10). When controlling the same variables (Table 3), only FEV_1, chronic bronchitis and education level were associated with breathlessness (mMRC ≥2).

Patients reporting a previous diagnosis of asthma were younger (mean age = 65.35/68.06 years, $p = 0.041$), reported lower mean tobacco amount (46.35/58.32 pack-years, $p = 0.020$) and were more symptomatic (CAT ≥10 in 82.3%/68.5%, $p = 0.029$). However, there were no differences between the two groups related to gender ($p = 0.114$), previous acute exacerbations ($p = 0.347$), mean FEV_1% ($p = 0.135$) and distribution according to GOLD stage ($p = 0.637$). CB was significantly related to GOLD classification (respectively 10.3, 27.8, 28.6 and 33.3% of GOLD A, B, C and D patients reported CB, $p = 0.011$) but not to age, airflow limitation or GOLD stage.

Age and smoking history were not associated to an increased risk of exacerbation. Table 4 describes the relationship between ECOPD and different variables. Binary logistic regression indicates an odds ratio of 1.7 times more risk of ECOPD for very-low educational level (≤3 years of school) and 1.9 times more risk of exacerbations for lower income, when controlling for age and gender. The mean FEV_1% of patients reporting 0, 1 or ≥2 acute exacerbations was respectively 59.2, 55.8 and 44.5, $p < 0.001$. Higher airflow limitation, according to GOLD stage, was also associated with risk of acute exacerbation (from GOLD 1 to 4, 10.0%, 29.1%, 45.3% and 67.5% of patients reported ≥2 ECOPD, $p < 0.001$). However, when controlling all the variables associated with frequent acute exacerbations, only CAT score and FEV_1% had a statistical significant association with ECOPD (Table 5).

Discussion

To the best of our knowledge this is the first study developed in a Portuguese population of COPD hospital outpatients fully describing their demographic, clinical and functional characteristics. Our data confirms COPD as a more prevalent condition in the elderly, in men, and people with low socioeconomic level. It also confirms previous evidence that a substantial proportion of patients were non-smokers, mainly women. There were four main findings in this study: (1) Women suffering from COPD smoked less, were more symptomatic and more frequent exacerbators. Obesity, osteoporosis and depression/anxiety were more common in the female gender. (2) Patients with a previous history of asthma were more symptomatic despite being younger and smoking less. (3) Predictors of ECOPD were gender, monthly

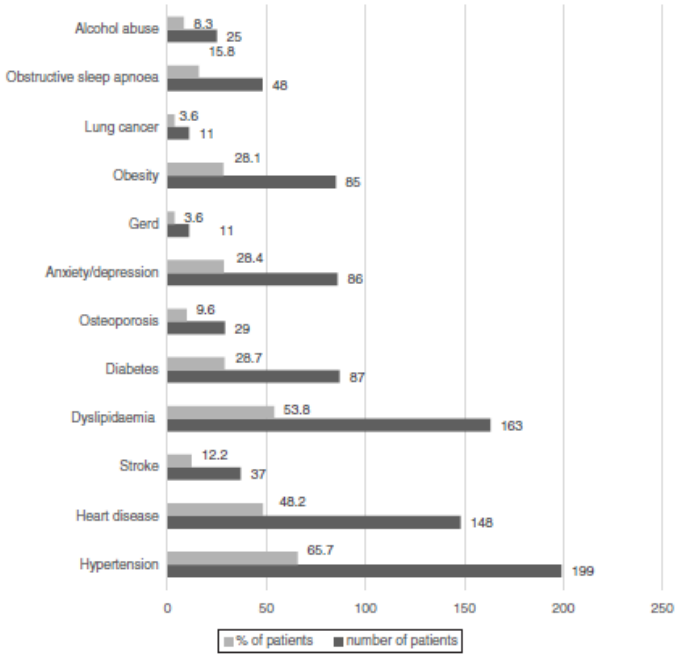

Figure 1 Common comorbid conditions. *Notes and abbreviations*: Heart disease: ischemic heart disease, heart failure or atrial fibrillation; GERD, gastroesophageal reflux disease; Stroke, history of stroke. Obesity: BMI $\geq$30 kg/m^2.

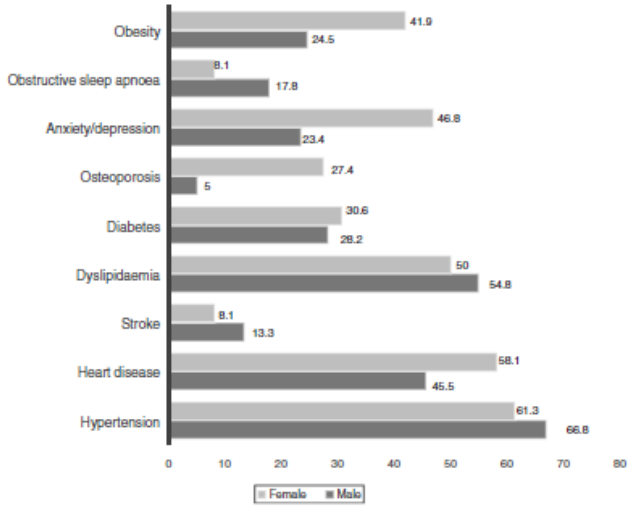

Figure 2 Common comorbid conditions by gender. *Notes and abbreviations*: Heart disease: ischemic heart disease, heart failure or atrial fibrillation; Stroke, history of stroke. Obesity: BMI $\geq$30 kg/m^2. Results presented as % of patients.

income, education level, symptoms and airflow limitation. (4) FEV_1 was significantly related both to symptoms and exacerbations.

In the present study, as expected, tobacco smoking was the most commonly identified exposure, but a significant proportion of patients (26%) was never-smokers who self-reported significant indoor exposure to household air pollution or occupational exposure to dust, gas or fumes relevant to COPD. COPD is known to be predominantly a disease of cigarette smokers. However, international variation in the prevalence of COPD cannot be explained solely by different rates of smoking in the community, and some authors

Table 2 Relationship between different variables.

Comparison by gender	Male gender	Female gender	*p*-value
Mean age	67.4	67.6	0.886
Mean FEV_1%	53	53.8	0.770
CAT ≥10	68.5%	88.1%	**0.007**
mMRC ≥2	59%	72.1%	0.400
ECOPD ≥2	34.0	53.2%	**0.005**
Comparison by symptoms	**CAT <10**	**CAT ≥10**	***p*-value**
Mean age	67.9	64.7	**0.035**
Mean FEV_1%	64.0	48.4	**0.001**
ECOPD ≥2	10.3%	46.1%	**0.001**
Comparison by dyspnoea	**mMRC <2**	**mMRC ≥2**	***p*-value**
Mean age	67.8	67.2	0.639
Mean FEV_1%	63.5	46.6	**0.001**
ECOPD ≥2	16.5	51.9	**0.001**

Note and abbreviations: Data shown as mean±SD or *n* (%); mMRC, Medical Research Council Dyspnea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.
Bold values indicate the statistical significance.

Table 3 Binary logistic regression.

	Wald	df	Sig.	OR	95% C.I.for OR	
					Lower	Upper
Predictors of CAT						
Smoking history	1.409	1	.235	2.167	.604	7.769
Gender	3.770	1	.052	4.414	.986	19.757
Age (≥65)	2.241	1	.134	.546	.247	1.206
Monthly income	.009	1	.924	1.040	.468	2.312
Education level	.031	1	.859	1.098	.392	3.071
FEV_1%	18.775	1	**.000**	.957	.937	.976
Asthma	.748	1	.387	1.460	.619	3.445
CB	5.382	1	**.020**	3.974	1.239	12.746
Constant	4.554	1	.033	9.497		
Predictors of mMRC						
Smoking history	.000	1	.989	.994	.437	2.261
Gender	.525	1	.469	1.376	.580	3.261
Age (≥65)	.649	1	.420	.775	.416	1.442
Monthly income	.786	1	.375	.765	.423	1.384
Education level	5.092	1	**.024**	.461	.235	.903
FEV_1%	32.916	1	**.000**	.955	.940	.970
Asthma	.328	1	.567	1.206	.636	2.287
CB	7.014	1	**.008**	2.679	1.292	5.555
Constant	21.587	1	.000	31.181		

Abbreviations: mMRC, Medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; Asthma, previous history of asthma before 40th years; CB, chronic bronchitis.
Bold values indicate the statistical significance.

Table 4 Relationship between ECOPD and other variables.

	ECOPD ≥2	*p*-value
Education level ≤3 years	51.7	
Education level >4 years	32.2	0.001
Monthly income <530 Euros	44.2	
Monthly income ≥530 Euros	26.2	0.002
Male gender	34	
Female gender	53.3	0.005
mMRC ≥2	51.9	
mMRC <2	16.5	0.001
CAT ≥10	46.1	
CAT <10	10.3	0.001

Note and abbreviations: Data shown as %; mMRC, Medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations.

Table 5 Binary logistic regression – predictors of exacerbation (ECOPD).

	Wald	df	Sig.	OR	95% C.I. for OR	
					Lower	Upper
mMRC grade	1.348	1	.246	1.650	.709	3.842
CAT score	6.015	1	**.014**	4.058	1.325	12.429
FEV_1%	8.207	1	**.004**	.968	.947	.990
Gender	3.706	1	.054	2.845	.981	8.249
Monthly income	.618	1	.432	.727	.329	1.609
Education level	1.848	1	.174	.531	.213	1.322
Asthma	1.966	1	.161	.580	.271	1.242
CB	.474	1	.491	1.337	.585	3.055
Age (≥65)	3.583	1	.058	2.106	.974	4.554
Smoking history	3.159	1	.076	.367	.121	1.109
Constant	.692	1	.405	2.426		

Abbreviations: mMRC, Medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; Asthma, previous history of asthma before 40th years; CB, chronic bronchitis.
Bold values indicate the statistical significance.

estimated that at least one fourth of patients with COPD are never-smokers.[11] A COPD prevalence of 9.2% was found in never-smokers in Lisbon region, but we have no information about the rate of never-smokers in COPD cases.[12] In a recent analysis of data from 14 countries participating in the BOLD study, never-smokers comprised 23.3% of COPD patients classified as GOLD stage II+ and NHANES III data in US populations showed that about one-fourth of COPD cases occurred in non-smoking subjects.[13] The analysis of BOLD data in Tunisia shows that non-smokers account for 45% of COPD cases,[14] and a recent Korean study reported never-smokers accounting for 31.7% of all COPD patients.[15] In the present study, never-smoking COPD patients were more symptomatic than patients with a smoking history, and contrasts with other published studies.[16] This is an intriguing issue, and may partly be due to not having been considered as exclusion criteria in the present study, features that could suggest airway hyperreactivity. We found no association between smoking history and degree of airflow limitation. This also contrasts with previous studies.[17]

In our study, occupational exposure was self-reported and dichotomised as regularly-exposed and not-regularly exposed, because there was a significant lack of power in the information related to time and type of exposure.[18] It was reported by 55.5% of patients, significantly overlapping with tobacco exposure. Occupational exposure as a COPD risk factor has long been recognised.[19] The contribution of occupational exposure to the burden of COPD is estimated to

be of 15%[20,21] to 20%,[13] but as much as 31% of COPD in never-smokers may be attributed to occupational exposure.[22] Although population specific job exposure matrices (JEMs) perform better than the self-reported method in assessing the risk of developing occupational COPD,[23] many epidemiological studies have relied on self-reported exposure,[19] which can be subject to recall bias. Mineral dust exposure is a well-known cause of COPD, but a significant risk of COPD is associated to occupational exposure to biological dust,[19] especially for women.

Indoor air pollution due to solid fuel combustion is an important risk factor for COPD,[24] particularly in non-smoking women of middle and low-income countries.[25] In this study, self-reported exposure to household air pollution from coal and biomass fuel combustion for cooking, both in the past and present, was reported by 63.8% of women. It was the most important exposure identified among women suffering from COPD. They were more symptomatic and more frequent exacerbators. Whether this represents a true gender characteristic or a greater tendency for women to report symptoms and exacerbations cannot be answered in the present study. Anxiety/depression, obesity and osteoporosis were more prevalent in the female gender. Some of this data is supported by previous studies.[26] Being older was not related to airflow limitation, symptoms or acute exacerbations. These findings are in contrast with some other observational studies.[27]

ECOPD were defined according to GOLD, but also as requiring an unplanned medical visit. Therefore, our ECOPD definition fails to capture unreported and untreated minor or even moderate exacerbations. Probably unreported cases were less severe, self-limited and self-managed. Nevertheless, according to current literature, less than one third of exacerbations are estimated to be reported,[28] but the unreported also have impact on patients' health status. On the other hand, sudden respiratory symptoms due to comorbidities like congestive heart failure, pulmonary embolism or pneumonia can mimic ECOPD or even trigger a COPD acute exacerbation, leading to a real possibility of misclassification of some reported ECOPD. The clinical tools used in the present study were not calibrated to discriminate with high precision the causes of exacerbations or accurately distinguish ECOPD from other clinical situations. In our study, 38% of patients, more often women, were frequent exacerbators. As in other populations studied, low educational level and low monthly income were also associated with a history of previous acute exacerbation.[29] The prognosis of COPD is closely related to the severity and frequency of acute exacerbations[30]: they influence the overall severity of the disease, impair quality of life, and worsen the pulmonary function and the underlying co-morbidities.[28] Our study also failed to capture the aetiology and severity of COPD exacerbations. There is currently no consensual classification of exacerbation severity, and in one-third of cases the aetiology cannot be identified.[31] However, different aetiologies and severity of acute exacerbations have different impact on health status, respiratory function and quality of life.

There was a positive association between airflow limitation and both symptoms and a history of frequent acute exacerbations. When controlling all variables associated with symptoms and exacerbations, only FEV_1 was significantly related to mMRC, CAT and ECOPD. This is consistent with other published studies, and it is well-known that exacerbations are significantly associated with worsening lung function, and become more frequent and more severe as the severity of the underlying disease increases.

In the present study, 27.4% of COPD patients reported a previous diagnosis of asthma before 40, usually in childhood. Because of the possibility of confusion between COPD and asthma, in which dyspnoea is also a cardinal symptom, many studies on COPD exclude participants with a prior history of asthma.[20] Because it is a well-known risk factor for COPD, we did not exclude those patients from the present study. They were younger, reported less tobacco consumption and more symptoms. As asthma and COPD are different conditions, features of both diseases can be present in the same patient. This is currently referred to as Asthma-COPD overlap (ACO). The definition, the clinical characteristics, the course and the phenotypes of ACO are still controversial.[32] The diagnostic criteria changed during the period our study was designed and data collected and interpreted.[33] Because neither the term nor the diagnostic criteria are universally accepted,[34] and the Portuguese consensus on ACO was only recently published,[35] ACO was not included for analysis.

COPD is widely recognised as a heterogeneous disorder with many systemic features and medical comorbidities occurring across the spectrum of disease severity.[36] As in previous studies, our COPD patients present many different comorbidities, such as hypertension and heart diseases.[1] The prevalence of diabetes, anxiety and depression was higher than in other studies.[37] Gastroesophageal reflux disease (GERD) was present in only 3.6% of patients. Although we expected a higher prevalence, this is not surprising, because there are many different definitions of GERD based on different diagnostic models.

Significant and relevant differences in demographic and clinical characteristics and exposures relevant for COPD have been described in different countries. We recruited a convenience sample of COPD outpatients in the respiratory clinic of a single hospital, though middle-sized one, as the reference population. Nevertheless, the descriptive and analytic characteristics of most of the demographic variables and some clinical and functional ones show that the sample is representative of the studied population.[38] As expected, descriptive and analytic characteristics of some variables differ from populations in other studies. This is due both to the fact that we included only outpatients recruited in a hospital setting, and because we studied a clinical sample.

Conclusions

Our data confirms COPD as a complex and heterogeneous disorder with significant morbidity due to the nature of symptoms, frequent comorbidities and exacerbations. Our data also confirms previous evidence that a substantial proportion of COPD patients, mainly women, are non-smokers. This calls attention to the need for COPD recognition among never-smokers, particularly women. COPD in female gender, in never-smokers and patients with a previous diagnosis

of asthma presented some specific characteristics. Some patients' characteristics are associated with frequent acute exacerbations. FEV_1 was strongly related to both symptoms and acute exacerbations.

Author contributions

Duarte-de-Araújo conceived and developed the study, carried out acquisition and interpretation of data, 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 the authors approved the final manuscript.

Conflicts of interest

The authors have no conflict of interest to declare regarding the present study.

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Symptoms irregularity and increased risk of COPD acute exacerbations

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Symptoms irregularity and increased risk of COPD acute exacerbations

Chronic Obstructive Pulmonary Disease (COPD) is a complex and heterogeneous disease. Acute exacerbations are trajectory-changing events in the natural history of the disease and are also an important cause of morbidity and the main cause of mortality, during and after hospitalization.[1] Some demographic, clinical or functional characteristics displayed by some individuals may allow the identification of groups of patients with different risk of acute exacerbation. This may be crucial for the busy clinician, facilitating the choice of the best therapeutic approach from the beginning. We present the preliminary results of a cross-sectional study aimed at evaluating whether some patients' characteristics can predict an increased risk of acute exacerbations of COPD (ECOPD), and thus influence therapeutic options.[2] The variables under study were age, gender, education level, income, smoking status, airflow limitation, symptoms and symptoms irregularity.

COPD out-patients over 40 years old, diagnosed according to GOLD criteria,[3] were recruited consecutively between March 2016 and May 2017, and all gave their written informed consent. Exclusion criteria were refusal to participate and inability to understand simple questionnaires. The study was approved by the hospital de Guimarães Ethics Committee, the Research Ethics Committee of Minho' University and by the Portuguese data Protection Agency. A survey of demographic and clinical data was applied, and the assessment of symptoms was done using the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). ECOPD were defined as a worsening of one or more major respiratory symptoms, requiring an unplanned medical visit that led to any extra treatment or to a treatment change. Symptom irregularities were defined as a worsening of one or more respiratory symptoms in winter and/or with changes in weather that led to the use of rescue medication but did not require an unplanned medical visit. A statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

We studied 310 COPD patients, all Caucasian, 79.4% males (mean age = 67.66 years), 84.4% retired and 79% urban inhabitants. Low education level ($\leq$6 years at school) was declared by 87.8%, very-low education level ($\leq$3 years) by 29.7%, and low income (<530 €) by 65.2% of subjects. The majority of patients (59.8%) declared low socioeconomic status (Graffar social classification score 4 and occasionally 5). Tobacco smoking was the most common exposure identified in 74.8% of patients. 5.2% were modest smokers, defined, according to previous literature, as <10 pack-years,[4] and 17.7% were current smokers. The mean tobacco amount was 48.7 ± 32.6 pack-year. Self-reported occupational exposure to dust, gas or fumes relevant to COPD, and sustained indoor exposure to household air pollution from coal and biomass fuel combustion was stated by 55.5% of patients and by 62.5% of women, respectively. Eighty-three patients (27.1%) had a history of childhood asthma or a previous diagnosis of asthma before age 40 years. A history of frequent ($\geq$2) treated exacerbations was recorded by 38.4% of patients in the previous year. The mean FEV_1 was 1.37 L or 53.4% of the predicted values (GLI 2012 Spirometry reference Equations [5–7]). An mMRC grade $\geq$2 was observed in 62.6% and a CAT score >10 by 72.8% of the responders. The distribution of patients according to GOLD 2017 stage and classification were 10%, 41.9%, 35.2% and 12.9% stage 1 to 4, and 22.9%, 39.4%, 2.3% and 35.5% GOLD A to D.

We found a significant association between the risk of exacerbations and both education level ($p = .020$) and income ($p = .007$). Binary logistic regression indicates an odds ratio of 1.9 times more risk of ECOPD for very-low education level ($\leq$3 years of school) and 2 times more risk of exacerbations for lower income, when controlling for age and gender.

Age was also not related to an increased risk of exacerbation ($p = .153$) nor with GOLD 2017 stage or classification ($p = .637$ and $p = .528$, respectively). We found no association between age and clinical worsening of the disease (CAT < 10, mean age = 67.9 years; CAT $\geq$ 10, mean age = 64.9 years; mMRC < 2, mean age = 67.9 years; mMRC $\geq$ 2, mean age = 67.5 years). There was no association between age and airflow limitation ($p = .545$, being the correlation coefficient between age and $FEV_1\% = .034$).

We found no significant differences between genders related to age (mean age of men and women were 67.5 years and 68.1 years, respectively) and to airflow limitation (mean $FEV_1\%$ was 53.1 in man and 54.3 in women). CAT score and mMRC grade was higher in women ($p = .004$ and $p = .026$, respectively). Female gender was also related to an increased risk of exacerbation ($p = .003$).

Patients with a smoking history are mainly male. Current smokers have a significantly lower mean age than ex-smokers or never-smokers (61.2, 67.4 and 72.8 years, respectively, $p = .000$). Current smokers, ex-smokers and the never-smokers reporting significant occupational or in-door exposure relevant to COPD, present comparable airflow limitation ($p = .511$) and risk of exacerbation ($p = .150$). Never-smokers have significantly higher CAT score ($p = .013$) and mMRC grade ($p = .025$). We found also no association between pack-years smoking history and GOLD stage (GOLD 1–4: 43.7; 43.8; 55.6 and 47.6 average number of pack-year, $p = .103$).

Patients with mMRC grade $\geq$2 ($p = .000$) or CAT score $\geq$10 ($p = .000$) were at increased risk of acute exacerbation. Patients with higher airflow limitation, according to GOLD stage, were also at increased risk of acute exacerbation ($p = .000$). We found a strong association between airflow limitation, according to GOLD classification, and mMRC grade ($p = .000$) or CAT total score ($p = .000$). Many patients (62.3%) report irregularity of symptoms. We found a significant association between symptom variability and a history of frequent ($\geq$2) treated exacerbations ($p = .004$), when controlling for gender, previous history of asthma and $FEV_1\%$ (Table 1). This was expected, since acute exacerbations are major forms of symptoms' irregularity.

Different COPD previous exposure factors often overlap in the same patient. In never-smoking patients, and in the absence of measurable exposure data, the risk of COPD may be overestimated. However, many epidemiological studies have relied on self-reported exposure,[8] and this is how, in clinical practice, the risk of developing COPD is assessed. In contrast to other studies, never-smoking COPD patients are more symptomatic than patients with a smoking history,[9]

and we found no association between the degree of airflow limitation and different COPD risk factors or smoking history.[10] Smoking history was also not related to risk of ECOPD. Probably because patients are being treated, aging was not related to airflow limitation, symptoms or acute exacerbations. These findings are in contrast with some observational studies.[11] Women are more at risk of ECOPD. As in other populations studied, very-low education level and low income were also related with an increased risk of acute exacerbation.[12] Patients with higher airflow limitation are more symptomatic. They are at increased risk of ECOPD. Patients recording irregularity of symptoms also seem to be more prone to acute exacerbations of COPD. Because of the greater tendency to exacerbate, more attention needs to be paid to these patients. A ''hit hard'' approach and a closer follow-up would be a good therapeutic option.[13] A trial of inhaled corticosteroids association in symptomatic patients despite optimized bronchodilation is also recommended.[14]

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Table 1: Symptoms instability and ECOPD

Dependent Variable: ECOPD - 12 Months

Variable	Sum of squares	D F	Quadratic mean	F	P value	h^2 Pa
Model	40,013[a]	8	5,002	6,883	,000	
Intercept.	74,604	1	74,604	102,664	,000	
FEV1%	20,084	1	20,084	27,638	**,000**	
Symptoms Instability	6,053	1	6,053	8,330	**,004**	
Asthma	2,220	1	2,220	3,055	,082	
Gender	2,812	1	2,812	3,869	,050	
IS* Asthma	,054	1	,054	,074	,786	
IS* Gender	,105	1	,105	,145	,704	
Asthma * Gender	,977	1	,977	1,345	,247	
IS* Asthma * Gender	,170	1	,170	,234	,629	
Error	172,950	238	,727			
Total	466,000	247				
Corrected Total	212,964	246				

a. R^2 = ,188 (R^2 adjusted= ,161)

Understanding patient adherence to inhaled medication: The social representations of COPD

(Rev Port Pneumol. 2017; 23(6):358-359.)

Understanding patient adherence to inhaled medication: The social representations of COPD

Adherence to medication is a complex phenomenon that may vary in form and intentionality. In COPD, as in many chronic diseases, poor adherence behaviors are a well-known factor of therapeutic failure.[1] The patients' understanding of their disease and therapy are constructs based on social and cultural factors,[2] and health-related beliefs will influence the patient adherence to therapy. In the evaluation of adherence, self-reported questionnaires are currently the most widely used tools.[3] The 7 items Measure of Treatment Adherence (MTA) is a validated tool for studying the adherence to medication,[4] and the Beliefs about Medicines Questionnaire (BMQ) is useful for exploring the relationship between beliefs and adherence.[5,6] However, to understand this complex and subjective phenomena, qualitative methods have also been used in production of knowledge,[7,8] complementing quantitative studies. We present the preliminary results of an ongoing study aimed at understanding the patterns and reasons for non-adherence and how the patients' representation of COPD influence adherence to inhaled medication.

Participants over 40 years old diagnosed as suffering from COPD according to GOLD criteria were included. The MTA, the BMQ, and a demographic, socioeconomic, clinical and an easy-to-answer survey on COPD were used. After completion of the questionnaires, semi-structured interviews were carried out. Participants were encouraged to justify their opinions and behaviors, according to Grounded Theory qualitative methodology. The objective was to obtain new information from patients themselves. Field-notes were made during the interview, and each interview was analyzed before the next one. A quantitative and qualitative analysis of the variables was then performed.

Of the 174 participants (mean age = 67.8 years), 78.2% were males, the majority (85.1%) living in predominantly urban spaces, 85% were of low educational level (≤4 years of school) and 66.1% low income (≤530 €). The mean FEV_1 was 52.1% ± 19% and 36.7% of patients mentioned ≥2 exacerbations in the previous year. A total of 163 participants completed the MTA questionnaire: 50 referred to one or more poorly adherent behaviors, but only 25 (15.3%) were considered non-adherent. The relationship between adherence, beliefs about medication, and GOLD stage and classification is shown in Table 1. Some participants reported forgetting to take the medication, carelessness with schedules or letting the medication run out. Others reported complete withdrawal, usually for economic reasons. Other patterns of non-adherence were, when less symptomatic, suspension of all medication, reduction in the number of inhalations, suppression of one dose, usually at night, use of the medication only in exacerbations, and suppression of one of the inhalers. In case of worsening of symptoms, the two patterns of incorrect adherence were the increased frequency of the number of inhalations and anticipation of the schedule of prescribed inhalations. The reasons for non-adherence were: use according to need, economic reasons, confusion or misunderstanding of therapy, fear of side effects, and dependence on others. Only 4 patients experienced unpleasant side effects of medication. There were 4 domains of poor adherence: health-related experiences, economic, behavioral, and health-related beliefs. The reasons given for good adherence behaviors were discipline in medication compliance, daily routines, having a caregiver, the use of rapid relief medication, confidence in the physician or in the medication, having reserve medications, previous negative experiences and ease of medication acquisition. We found 3 domains of good adherence: health-related behaviors, health-related experiences and health-related beliefs. The majority of participants recognized COPD as a chronic disease and a serious illness (88.6% and 78.6%, respectively). Some justified the severity

Table 1 Adherence to inhaled medication.

Relationship between adherence and beliefs		
	BMQ necessity	BMQ concerns
Adherent patients	Score = 21.08 ± 3.882	Score = 10.13 ± 4.323
Non-adherent patients	Score = 14.65 ± 6.011	Score = 9.90 ± 4.166
	$p = .000$	$p = .841$

Relationship between adherence and GOLD 2016 stage and classification				
	GOLD			
	I	II	III	IV
Patients (%)	8.6	40.8	35.6	15
Non-adherent (%)($p = .039$)	25	23	9.8	4
	GOLD			
	A	B	C	D
Patients (%)	15.5	22.4	9.8	52.3
Non-adherent (%)($p = .025$)	40	16.2	11.7	10.1

because of their symptoms (41.3%) or limitations (22.4%), being incurable (7.7%) and because of recreational limitations (3.4%). Paradoxically, only 4 participants mentioned fear of dying. However, only 11.7% of patients referred to the disease by its correct name, 41% attributed other names to it, 15.5% did not know what they were suffering, 16.6% referred not to the disease but to the affected organ or function, 12.3% to symptoms, and 3% to its etiology.

COPD is represented by patients as a chronic and severe disease, since it is symptomatic and limiting. Fear of hospitalization or death was not valued by the participants in this study. In many chronic diseases, non-adherence appears to depend on the balance between perceived necessity and specific medication concern, but in our survey only necessity beliefs are associated with adherence. Compliance is also related with the clinical and functional severity of the disease. In fact, the evaluation of treatment necessity is based in the perception of the necessity. Concerns about inhaled medication are not related to side-effects, and do not appear to significantly affect adherence. MTA was chosen because it is validated by the Portuguese population. However is not specific for inhaler devices nor to COPD, and when compared to the Test of Adherence to Inhalers[9] or the Morisky Medication Adherence Scale,[10] may not be able to capture some patterns of non-adherence. This may, to some degree, justify the low level of non-adherence. However, recently published studies reported variability in the prevalence of poor adherence, when using different methods or instruments, and different populations.[11]

New information obtained was related to the patterns and reasons for non-adherence, and to behavior actions that reinforce compliance. The more important practical differences between patient and doctor cultural perception about the treatment lies in its usefulness in prevention of exacerbations and disease progression.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL RESEARCH

COPD: understanding patients' adherence to inhaled medications

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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 FEV_1% (P=0.000). The mean BMQ Necessity score was higher in adherent patients (P=0.000), but the 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

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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 FEV_1%. Regression also reveals a statistically significant negative association between FEV_1% 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 FEV_1% 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 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

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
X^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
X^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

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 FEV_1%. However, we found the association between adherence and FEV_1% 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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COPD: Misuse of inhaler devices in clinical practice

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COPD: misuse of inhaler devices in clinical practice

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Background and objectives: Inhalers mishandling remain an important clinical issue worldwide. The aim of this study was to evaluate inhalation technique in stable COPD out-patients. The variables under study were type of inhaler device (ID), patients' preference for an inhaler, number of IDs used by each patient, beliefs about inhaler medication and some demographic, clinical and functional patients' characteristics. We aim to assess how they are related to inhalation technique.

Methods: A cross-sectional study was conducted in a hospital outpatient respiratory care. COPD patients over 40 years old, diagnosed according to GOLD criteria, and using IDs were included consecutively. The Beliefs about Medicines Questionnaire (BMQ), a demographic and a clinical survey were applied. The number of IDs used by each patient and the patients' preference for some IDs were recorded. Patients were asked to demonstrate the use of their prescribed inhalation devices, and inhaler technique was assessed by using previously defined checklists, including essential steps and critical errors. A statistics analysis was then performed.

Results: We studied 300 subjects performing a total of 521 inhalation manoeuvers with 10 different IDs. At least one step incorrectly performed was found in 48.2% of demonstrations and in 29.9% critical errors were observed. Misuse was related to priming/loading in 6.9%, to inhalation manoeuver in 13.1% and to both in 10%. There was a statistically significant association between critical errors and type of ID ($P<0.001$). No significant relationship was found between correct performance of key manoeuvers and patients' preference or number of inhalers used per patient. Misuse due to critical errors was observed in 39.3% of patients and was positively related to female gender, age ≥65, lower education level and lower socio-economic status (higher Graffar classification score), but not to patients' clinical or functional characteristics. In the sub-group of patients presenting critical errors when using IDs, there was a statistically significant inverse association between BMQ Necessity score and number of critical errors.

Conclusions: Inhalers mishandling remains disappointingly common. A good inhalation technique depends on the type of ID, and failure of inhalation manoeuver was the main cause of ID misuse. It was not associated to multiple inhalers' use nor to patient's preference, but to the patient's beliefs about the necessity to use them. Elderly patients, women and those with lower education level or lower socioeconomic status demonstrate a worse inhalation technique.

Keywords: COPD; Inhalation technique; Inhaler devices

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Background and objectives

COPD currently represents one of the most significant health problems at an international level. Inhaled medication is the mainstay of COPD management,

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and therapeutic success depends on the maintenance of a correct inhalation technique. There is a growing evidence concerning inhalers misuse as a common problem worldwide.[1,2] It can be associated with increased rate of severe COPD exacerbations (ECOPD),[3] but the impact of inhalers misuse on COPD outcomes remains currently unknown. In a country where patients have a good access to health-care services and to effective treatment, any development in treatment outcomes must address the improvement of inhalation technique. This can be one of the main cost/benefit measures improving healthcare in COPD patients.

In 1965, Saunders published in the *BMJ* the first paper describing the misuse of inhaled medication.[4] In fact, misuse of inhaler devices (IDs) in obstructive airway diseases is an old problem, and has not improved over the past 40 years, despite the progressive technical improvement of IDs.[5] Currently, up to 94% of patients have demonstrated inhalers' mishandling in clinical studies.[6] Teaching and maintaining a correct inhalation technique has a positive impact on disease and patient outcomes.[7] It should remain a constant concern of any health professional involved in the management of COPD patients.[8,9]

The knowledge of difficulties and barriers that hinder a correct inhalation technique is of paramount importance to develop any educational intervention regarding the correct use of IDs. However, this can be a very difficult task. Assessment of inhalation technique is complex and always somewhat subjective, and consensus is lacking between researchers regarding the definition of critical errors and standardization of inhaler technique checklists.[7]

The aim of this study was to evaluate the inhalation technique in stable COPD outpatients, because there was a gap of information in Portuguese population. We intended assessing whether the type of ID, the preference or number of IDs used by each patient, the demographic, clinical or functional characteristics of patients, and the patients' beliefs about inhaled medication are associated with a correct inhalation technique. This last aspect was never studied, to the best of our knowledge.

Materials and methods

A cross-sectional study was conducted in the outpatient respiratory care of Guimarães hospital, between March 2016 and May 2017. COPD patients over 40 years old diagnosed according to GOLD criteria, without acute exacerbations for >4 weeks and using inhalation devices were consecutively included. Exclusion criteria were refusal to participate and an inability to understand simple questionnaires. No participants were at the same time enrolled in another different studies, and all gave their written informed consent. The study was approved by the Guimarães Hospital Ethics Committee, the Research Ethics Committee of Minho's University and by the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[10]

A survey of demographic and clinical data, the Graffar Social Classification,[11] validated for use in Portuguese population and the cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese were applied.[12] Patients' beliefs about inhaled medication can influence adherence to medication but we suspect they can also motivate patients to learn the correct use of inhalers. BMQ is an 11-item questionnaire with a five-item Necessity scale and a six-item Concern scale. The Necessity and the Concern scales assess, respectively, the beliefs about the necessity and the beliefs about concerns related to side-effects, dependence and toxicity of the medication. 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 in the Necessity scale and 6 to 30 in the Concern scale. It was clearly detailed that questions referred to the inhaled medication, and not to the device itself. The number of ECOPD referred in the last year was evaluated. We defined ECOPD according to GOLD as an acute worsening of respiratory symptoms that results in additional therapy,[13] but also requiring an unplanned medical visit, because patients have difficulty in remembering unreported exacerbations. Evaluation of symptoms was done using the Portuguese versions of the COPD assessment Test (CAT) and the Medical Research Council Dyspnoea Questionnaire (mMRC). All subjects performed spirometries according to ERS/ATS criteria, and referenced according to the Global Lung Function Initiative predict equations (GLI 2012).[14,15] Inhalation technique was assessed by using previous defined checklists, as presented in Tables 1 and 2.

They were developed according to the instructions provided by the manufactures and to previous literature,[16] and included essential steps and critical errors. Errors are considered critical when they can substantially affect drug delivery to the lungs, and are related to priming/loading or inhalation manoeuver. The definition of critical errors when using inhalers is of great importance. However, there is currently a lack of consensus on their definition, deserving discussion.[7]

Table 1 Checklist of steps for a correct inhalation technique

1	Correct priming or loading (Incorrect priming or loading were considered critical error).
2	Exhalation before inhalation.
3	Correct inhalation (Incorrect inhalation were considered critical error).
4	Hold the breath a few seconds after inhalation (except when using a pMDI + spacer).
5	Finalization (clean the mouth-piece, remove used capsule after verifying that no powder remains, check color changing in control window, close ID and wash the mouth if necessary).

Table 2 Critical errors in different IDs

1	Aeroliser®, Breezhaler®, and Handihaler®: failure to insert the capsule, failure to press and release buttons, powder remaining in the capsule after inhalation.
2	Diskus®: failure to open the cover, to slide the lever until it clicks, or not keeping inhaler horizontally.
3	Ellipta®: failure to slide cover down until a click is heard or block air vent with fingers.
4	Genuair®: failure to remove the cap, to press and release the button until the control window has changed to green, not holding inhaler horizontally, and not changing control window to red after inhalation.
5	pMDI: failure to remove cap, not shaking the inhaler (suspensions only), not holding the inhaler in the upright position, poorly synchronized hand actuation and inhalation (except using a spacer), inhalation through the nose, actuation against teeth, lips or tongue.
6	Respimat®: lack of cartridge in the device, failure to open the cap, twisting the base or pressing the dose-release button, poorly synchronized hand actuation and inhalation.
7	Spiromax®: failure to hold the inhaler in upright position, failure to open mouthpiece cover until a click is heard or blocking air vent with fingers.
8	Turbuhaler®: failure to remove cover, to hold the inhaler upright when twisting the grip (tolerance ±45°) until a click is heard.

Abbreviation: ID, inhaler device.

Participants were asked to demonstrate the use of their prescribed ID just as they do it at home, but demonstrations were done with inhalers containing placebo medications. Assessment of patients handling of IDs, by recording the correct steps and critical errors, were done by a single trained senior pulmonologist, to avoid inter-observer variability. The number of IDs simultaneously in use by each patient was recorded. Patients using two or more inhalers were inquired for device preference, and invited to justify their answer, clearly stated that the question is related only to inhalers' aspects. This was an open question. Answers were then collected in 5 groups: more practical to use, easier to use, ID characteristics, accustomed to using, and others. Because of the difficulty to distinguish between "being more practical" and "easier", these two answers were later analyzed together.

The variables under study, evaluated for potential association with incorrect inhalation technique, were the type of ID, patients' preference, use of multiple devices, beliefs about inhaled medication and some patients' characteristics: age, gender, monthly income, social classification, education level, CAT score, mMRC grade, number of ECOPD referred in the last year, FEV_1%, and GOLD 2017 stage and classification. Because patients were using 1–4 IDs at the same time, to assess inhalation technique three different outcomes, exhibiting different aspects of the same reality were defined. Correct use rate (CUR) was defined as the ratio between the sum of the number of correct steps in all IDs used by each patient and the total possible number of steps. Critical errors rate (CER) was defined as the ratio between the sum of the number of critical errors done with all the IDs and the total number of possible critical errors. The patients' ability (ABL) to use inhalers was defined as the ratio between the number of IDs without any critical errors and the total number of IDs used. Data were compiled in Microsoft Office Excel 2013 (Microsoft Corporation, Redmond, WA, USA).

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp., Armonk, NY, USA). Group differences in the sample were analyzed with Student's *T* test and Chi-square independence test. Multivariate ANOVA modeling was used to identify differences among sample groups in: CUR, CER and the patients' ability to use inhalers. Spearman's correlation was used to explore the association between patients' beliefs (BMQ) and

CER or the patient's ability to use inhalers. Statistical significance was considered when $P<0.05$.

Results

Sample characteristics

We studied 300 subjects performing a total of 521 inhalation manoeuvers with 10 different IDs in a total of 69 (13.2%) pMDI, 132 (25.3%) single-dose inhalers (sDPI), 239 (45.8%) multiple dose inhalers (mDPI) and 81 (15.5%) SMI-Respimat®. Only 12 pMDIs (17.4%) were used together with a spacer. All participants referred using inhalers for over a month, regardless of having received prior instructions for the correct inhalers' use. The main demographic, clinical and functional characteristics of patients are described in Table 3.

89.7% of patients referred living with the family, but 23.2% of women and 5.6% of men ($P<0.001$) referred living alone. Tobacco smoking was the most common exposure identified and 16.4% of subjects were current smokers. Participants were currently using one (38.9%), two (49.5%), three (10.6%) or four inhalers (1%). The main reasons for an ID preference were the ease of use (65.9%), ID characteristics (24.6%) and being accustomed to using (2.9%). Devices' characteristics were frequently reported as pleasant because of the small size and feedback provided by some inhalers. Powder's bad taste and a significant effort needed during inhalation were frequently referred as unpleasant.

Table 3 Demographic, clinical and functional characteristics of COPD patients

Characteristics	*n*=300
Male gender	231 (77.0)
Mean age (years) Total/ male / female	 67.6 / 67.4 / 68.3
Age ≥65 years	188 (62.7)
Education level ≤3 school years Total; male; female	 89 (29.7); 58 (25.1); 31 (44.9)
Very low monthly income (<530 Euros) Total; male; female	 199 (66.8); 146 (63.5); 53 (77.9)
Graffar social classification	
I – 2 (0.7); II – 13 (4.4); III – 102 (34.5); IV – 175 (59.1); V – 4 (1.3)	
Mean smoking amount (pack/years) mMRC grade ≥2 CAT score ≥10 Frequent ECOPD (≥2 / last year) Post-bronchodilator FEV_1L (%)	49.2±32.9 189 (64.3) 156 (75.4) 119 (39.7) 1.35 (53.0)
GOLD 2017 stage and classification	
I – 30 (10.0); II – 123 (41.0); III – 108 (36.0); IV – 39 (13.0) A – 62 (20.7); B – 121 (40.3); C – 7 (2.3); D – 110 (36.7)	

Note: Data shown as mean or *n*° (%).
Abbreviations: mMRC, Medical Research Council Dyspnea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations.

Inhalation misuse by IDs

At least one incorrect step was found in 48.2% of inhalations. In 156 (29.9%) demonstrations, critical errors were observed: 53.6% with pMDIs, 24.2% with sDPIs, 26.8% with mDPIs and 28.4% with the soft-mist inhaler. There was a statistically significant association between critical errors and the type of ID ($P<0.001$). Misuse was related to priming or loading in 6.9%, to inhalation manoeuver in 13.1% and to both in 10%. In mDPI group, critical errors ranged from 16.1% with Ellipta® to 35.1% with Turbohaler®. No significant relationship was found between correct performance of key maneuvers and patient's preference: 26.3% of preferred and 28.1% of non-preferred IDs presented incorrect use ($P=0.120$). No significant relationship was found between the correct performance of key manoeuvers and the number of inhalers currently used by patients (the incorrect use was 31.6% with one inhaler, 24.8% with two, 33.4% with three and 66.7% with four inhalers, $P=0.739$). The relationship between IDs and critical errors/inhalation technique is presented in Table 4. Participants showed more difficulty in inhalation maneuver with pMDI, in priming when using a Turbuhaler® and in both loading and inhalation maneuver when using the Handihaler®.

Inhalation misuse by patients' characteristics

Misuse due to critical errors was observed in 52.1% of women and 35.4% of men, in a total of 39.3% patients. The statistically significant relationship between the studied outcomes, as referred in the section on materials and methods, and patients' characteristics are presented in Table 5.

A statistically significant association was also found between CUR and age <65 (<65 years: mean score=0.8264, ≥65 years: mean score=0.7581, $P=0.026$). No statistically significant association was found between the studied outcomes and ECOPD, CAT score, mMRC grade, FEV_1% and GOLD stage or classification.

Table 4 Inhalation misuse by inhaler devices

Critical errors (%)[a]	n°	% of incorrect use	1	2	3
pMDI (12 with spacer)	69	53.6	5.8	30.6	17.4
SMI	81	28.4	0	16	12.3
sDPI	132	24.2	9.1	5.3	9.8
Breezhaler®	72	19.4	6.9	5.6	6.9
Handihaler®	51	37.3	13.7	5.9	17.6
Aeroliser®	9	0	0	0	0
mDPI	239	26.8	8.4	11.3	7.1
Diskus®	75	29.3	2.7	16	10.7
Genuair®	53	22.6	11.3	5.7	5.7
Spiromax®	43	25.6	0	20.9	4.7
Turbuhaler®	37	35.1	29.7	2.7	2.7
Ellipta®	31	16.1	3.2	6.5	6.5
	(*P*<0.001)		(*P*<0.001)		

Notes: [a]Critical errors related to: 1=priming/loading; 2=inhalation maneuver; 3=1+2. [b]Incorrect use=presence of critical errors.

Table 5 Inhalers misuse by patients' characteristics

	CUR	*P*-value	CER	*P*-value	ABL	*P*-value
Male gender	0.8116		0.1618		0.7454	
Female gender	0.6899	0.001	0.3284	0.001	0.5616	0.001
Education level <4 years	0.7171		0.2591		0.5991	
Education level ≥4 years	0.8117	0.003	0.1753	0.026	0.7470	0.004
Graffar 4+5	0.7264		0.2472		0.6269	
Graffar 1+2+3	0.8654	0.001	0.1308	0.001	0.8180	0.001

Note: Data shown as mean score.
Abbreviations: CUR, correct use rate of inhalers; CER, critical errors rate; ABL, patients' ability to use inhalers; Graffar, Graffar social classification.

Inhalation misuse by patients' beliefs about medicines

Only 59 (85.5%) women and 191 (82.7%) men (*P*=0.364), in a total of 250 (83.3%) participants were able to understand and respond to the BMQ questionnaire. Misuse due to critical errors was observed in 92 (36.8%) of them. We found no significant association between the BMQ concern score and CER or the ability to use inhalers. However, in this sub-group of patients (*n*=92) there was a statistically significant correlation between the BMQ Necessity score and CER (Spearman's rho =−0.294, *P*=0.004) or the ability to use IDs (Spearman's rho =0.248, *P*=0.017). The patients' beliefs about the necessity to use IDs were, respectively, significant direct and inverse predictors of ability to use inhalers (β=0.310; *P*=0.003; r^2=0.096) and misuse due to critical errors (β=−0.289; *P*=0.005; r^2=0.084). In this group of patients, the beliefs about inhalers' need account for 9.6% of the observed variance in the ability to use IDs. Nevertheless, there is an interaction effect between education level and response to BMQ, because responders had a significantly high education level compared to non-responders (*P*=0.001). Necessity beliefs as a predictor of critical errors and as a predictor of ABL to use IDs are presented in Figures 1 and 2.

Discussion

In our study, the majority of patients was treated by pulmonologists for COPD, even if they were simultaneously being cared by their family physician for other co-morbidities. Even so, inhalers' misuse was disappointingly common. This is consistent with other published

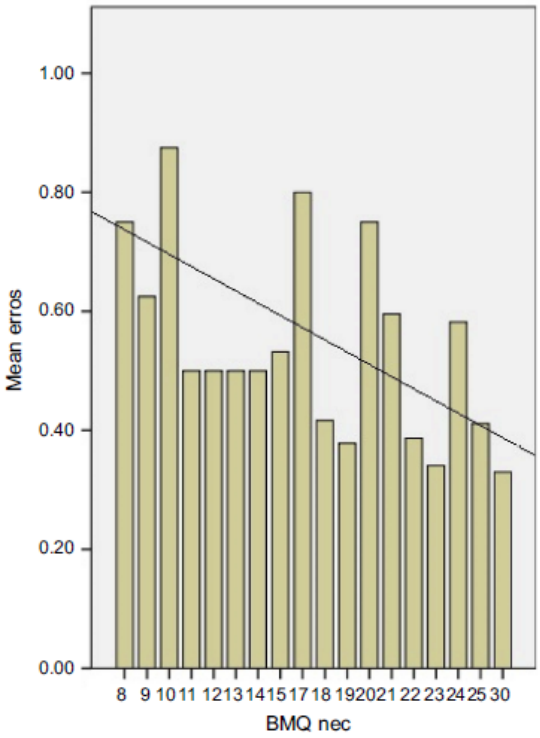

Figure 1 Necessity beliefs as a predictor of errors.

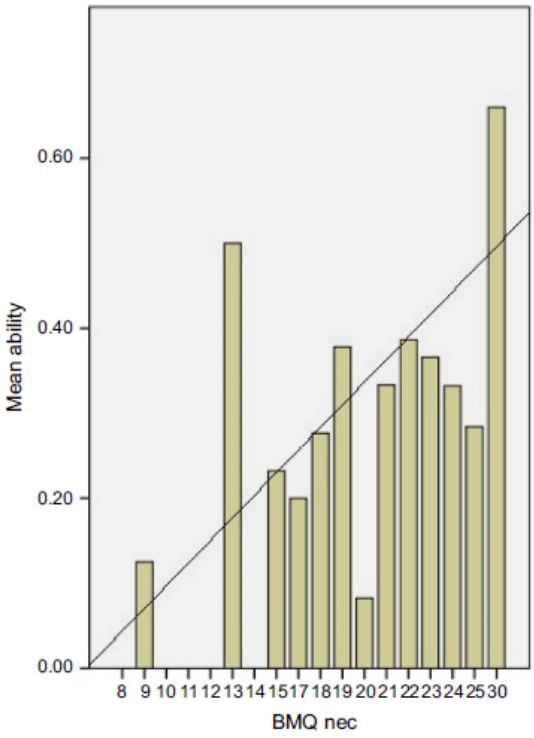

Figure 2 Necessity beliefs as a predictor of patients' ability.
Abbreviation: BMQ, Beliefs about Medicines Questionnaire; Nec, Necessity Score.

studies. In a recent study on 2,935 patients, handling errors were observed in over 50% of demonstrations.[3] Different studies reported different rates of misuse, using different methods and studying different populations.[17] A good inhalation technique depends on the type of ID. Critical errors were observed regardless of the inhaler used, but their proportion is different according to ID. Failure of inhalation maneuver was the main cause of ID misuse. However, evaluation of inhalation maneuver was the most difficult and subjective step to evaluate, especially when using a DPI, because we do not have measure inhalation parameters. This could favor some DPIs, mainly the Turbuhaler®, Diskus®, Ellipta® and Spiromax®, for which poor inhalation flow cannot be evidenced by lack of changing of control window's color or by powder remaining in the device. Therefore, there is a possibly a greater rate of misuse than we actually described. In patients needing >1 ID, whenever possible, we suggest the prescription of inhalers of the same type. Although differences were found between all types of inhalers, misuse related to inhalation manoeuver when using a pMDI was the most common reason for any inhaler misuse. This can be related to ID characteristics or to insufficient teaching or training. This group of inhalers is usually considered the most difficult to use, despite requiring a minimum inspiratory flow for correct airway deposition.[18] Poor coordination and failure to inhale slowly and deeply are well-known causes of pMDI misuse. Their use together with a spacer, although somewhat unpopular in practice, has been recommended in certain circumstances, and may overcome some difficulties.[19] In our study, only a small number of patients used pMDIs together with a spacer, which is insufficient to draw any conclusions. The soft-mist inhaler represents a more recent category of a liquid ID that can lead to high lung depositions in patients with low inspiratory flow. In our study, they represent 15.5% of the IDs evaluated, with a rate of misuse significantly lower than pMDI and comparable to DPIs. They can be a good therapeutic option, limited by the reduced number of drugs available on a SMI. DPIs were the most popular inhalers used in our study, probably because they deliver a large

range of different drugs. The sub-group of sDPI presented the better rates of correct use, and Ellipta® was the mDPI easier to use.

In our survey, a good inhaler technique was not associated with patient's preference nor to multiple inhalers' use, unlike in previous studies.[20,21] A previous study referred the importance of patients' confidence on the use of their inhalers to improve treatment adherence.[22] In our study, in the group of patients presenting critical errors when using their inhalers, the patients that believe less in the need for medication were more prone to make a higher number of critical errors. This is a new information and needs to be interpreted with caution. This is a cross-sectional study and there is an interaction effect between education level and response to BMQ.

Some patient's characteristics are significantly related to misuse of IDs. Being older, having lower education level or lower socio-economic status was significantly related to an incorrect inhalation technique, as in other published studies.[6] Therefore, the large rate of inhalers misuse in our study is not surprising, especially after considering the overall education level and socioeconomic background of the studied population. As in previous published studies,[6,23]females are also more prone to inhalers misuse. However, there is an interaction effect between gender and education level in the sample. Possibly, the effect observed in gender difference (ie, higher proportion of female with critical errors) may be associated with lower education level in the women subgroup. Women also exhibit a lower socioeconomic status and are more prone to live alone, without any help from family members in the use of IDs. All of this can justify the higher proportion of IDs misuse in female gender. We suggest that educational interventions could be reinforced in such patients. In our study, patients' clinical or functional characteristics were not related to inhalers' misuse. Again, this is consistent with other published studies.[18]

Although it would be expectable, the impact of inhalers misuse on ECOPD is currently unknown, and probably difficult to be proved, given the small number of studies reporting significant association between critical errors and COPD outcomes.[7] We also failed to demonstrate a significant association between inhalers' misuse and COPD acute exacerbations. Both COPD and aging process reduces inspiratory muscle function and the ability to generate sufficient inspiratory flow to allow significantly lung deposition. This is usually the limiting factor for the proper use of an inhaler, but it was not objectively measured in the present study. We understand that it could, by some extent, explain the lack of association found between inhalers' misuse and COPD acute exacerbations. However, the aim of this study was the patient's ability and knowledge to use IDs, and not the patient's capacity to generate sufficient inspiratory flow.

Our study was conducted in a 'real word' setting, but in a single institution. Patients were mostly treated by pulmonologists and were recruited sequentially, so we cannot exclude selection bias. This may limit the generalization of results to other populations.[24] However, we have studied a significant number of patients using a wide range of IDs. Subjects were recruited without prior notification and were invited to demonstrate the use of their prescribed ID by using placebo inhalers, to facilitate the evaluation of the inhalation technique. Assessing inhalation technique by using checklists is somewhat subjective, but currently, there is no 'best' method. Some authors suggest the need of studies based on generally accepted checklists of maneuvers affecting drug delivery, to facilitate comparisons of results.[5] Previous published studies measured inhaler technique by counting the number of correct steps, counting the number of critical errors or essential steps, or classifying the quality of the inhaler technique.[6,20,25–27] Our checklists were designed with full of steps and critical errors, to minimize subjective evaluation, and inhalation technique was evaluated by a single trained pulmonologist, to avoid inter-observer variability. The definition of critical errors is of great importance, because they are likely to significantly decrease delivery of medication to the lungs, impairing health-related outcomes. Nonetheless, there is currently a wide variation and a lack of consensus on their definition.[7] Therefore, our defined checklist of steps for a correct inhalation technique and the choice of critical errors, although based on previous literature, deserves discussion.

Very few original studies have been developed in Portuguese populations of COPD patients, regarding misuse of IDs,[23,28] and to the best of our knowledge, this is the first study relating inhalers misuse to the patients' beliefs about inhaled medication. A correct understanding of the relationship between inhalers and some specific patient-related characteristics can be useful in clinical practice, adding value in a resource-limited community. Nevertheless, matching the adequate medications with the adequate devices for each patient will always be a challenging issue.

Conclusions

Despite significant developments in device engineering, inhalers mishandling remains an important clinical problem. A good inhalation technique depends on the type of ID. Some inhalers are more prone to critical errors, and different inhalers are susceptible to different types of critical errors. Elderly patients, women, patients with lower education level, lower socioeconomic status or less believers in the need of inhaled medication demonstrate a worse inhalation technique. Therefore, any educational intervention should be reinforced in patients with these characteristics. This knowledge can be important in clinical practice by helping the choice of IDs, in predicting difficulties and in planning educational interventions regarding the correct use of inhalers.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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Teaching inhalation technique in COPD- outpatients: Can a sustained improvement be achieved?

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did not perform the technique, peripheral hospitals were the most eager to develop it in the future. This seemingly growing interest in pleuroscopy by peripheral hospitals was also reported in the UK survey[5] and though the reasons behind this are out of the scope of our work, a possible explanation can reside in the lesser need of pleuroscopy felt by central hospitals that are in close proximity with thoracic surgery departments. One indirect data retrieved from our survey that can corroborate this suspicion was the referral pattern of the different hospitals. Among hospitals that did not offer pleuroscopy, most level I referred their patients to other pulmonology departments while none of the level II and above did so, preferring to refer their patients to video-assisted thoracic surgery (VATS) instead.

Concerning the types of devices, the semiflexible pleuroscope seemed to be more appealing to peripheral hospitals, and those using it seemed to be performing a larger number of exams, as compared to those that used the rigid pleuroscope. This can add on the notion that the wider familiarity with this type of equipment (more similar to a classical videobronchoscope) can actually contribute to increase the utilization of pleuroscopy,[8] namely at peripheral settings as we recently reported in a previous publication.[9]

Our results also raise the question of training in this technique. Almost all our responders obtained additional training to perform pleuroscopy, which can lead us to question if the training that is currently being offered during standard pulmonology residencies is sufficient to prepare our future generation of pulmonologists in this specific context.

Finally with an exceeding number of centers performing less than 15 procedures per year, training, proficiency and ongoing competence issues should be discussed.[10]

Conflicts of interest

The authors have no conflicts of interest to declare.

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Teaching inhalation technique in COPD outpatients: Can a sustained improvement be achieved?

Inhalers mishandling remains an important clinical problem.[1] However, a large proportion of patients refer to a lack of effective training from their health care professionals and inhaler technique is seldom systematically checked up on during medical visits.[2] Actually, even after being learned correctly, inhaler technique can deteriorate over time. The aim of this study was to evaluate if educational intervention with COPD outpatients on the correct use of inhaler devices (IDs), can sustain long-term improvement in inhalation technique and to assess the inhaler and patient-related characteristics that are associated with some improvement in inhalation technique.

An interventional study was conducted in the outpatient respiratory care of Guimarães hospital. Stable COPD patients $\geq$ 40 years diagnosed according to GOLD criteria were evaluated in two different medical visits,[3] with a 10–12 months interval between them. They were recruited consecutively

Table 1 Demographic, clinical and functional characteristics of COPD patients.

Characteristics	$n = 170$
Mean age (years)	66.8
Age ≥65 years	102 (60.0)
Male gender	133 (78.2)
Education level ≤3 school years	49 (28.8)
Education level ≤6 school years	152 (89.4)
Very low monthly income (<530 Euros)	119 (70.0)
Graffar social classification 4 + 5	105 (62.5)
mMRC grade ≥2	107 (62.9)
CAT score ≥10	100 (78.7)
ECOPD ≥2 (last year)	70 (41.2)
Post-bronchodilator mean FEV_1%	52.8
GOLD 2017 stage and classification (n; %): I – 18 (10.6); II – 66 (38.8); III – 64 (37.6); IV – 22 (12.9) A – 32 (18.8); B – 69 (40.6); C – 3 (1.8); D – 66 (38.8)	

Note: Data shown as mean or *n* (%).
Abbreviations: mMRC, modified Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; ECOPD, chronic obstructive pulmonary disease acute exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

and evaluated on a first medical visit between March 2016 and May 2017. Refusal to participate and inability to understand simple questionnaires were the exclusion criteria. In the first visit, a survey of demographic and clinical data and the Portuguese versions of the Graffar social classification and the Beliefs about Medicines Questionnaires were conducted.[4] The BMQ has a Necessity and a Concern scale, assessing respectively the beliefs about the medication necessity and concerns about the side-effects of medication. Symptom evaluation was done using the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaires (mMRC). The number of acute exacerbations of COPD in the previous year was recorded. All participants performed at least one spirometry according to ERS/ATS criteria and referenced according to the Global Lung Function Initiative prediction equations (GLI 2012).[5,6] Participants were then invited to demonstrate the use of their prescribed IDs, and the inhaler techn que was accessed by using p evious defined checklists of essential steps and critical errors. All the participants received face-to-face demonstration and training with inhalers containing placebo medications, until correct usage was achieved. After 10–12 months, participants were invited by mail for a second medical visit, and a re-evaluation of inhalers' technique was conducted. The difference in number of critical errors between the two visits, expressed as qualita ive, was defined as outcome. A statistical analysis was then performed.

Only 201 patients ag eed to participate in the second medical visit. From these, 31 were excluded because they were using different IDs. We evaluated 170 participants performing 266 inhalation manoeuvres. The main demographic, clinical and functional characteristics of patients are described in Table 1. Ten different IDs were examined, in a total of 31 (11.7%) pMDI, 63 (23.7%) single-dose inhalers (sDPI) 136 (51.1%) multiple dose inhalers (mDPI) and 37 (13.9%) SMI-Respimat®. An improvement in number of critical errors was observed in 50 (18.8%) and a worsening in 21 (7.9%) demonstrations, and critical errors were more often related to inhalation manoeuvres than to priming/loading. There was a general improvement in critical errors in all types of IDs, but with different statistical significances (Table 2). A worsening in the total number of critical errors was observed in 20 (8.8%) patients and an improvement in 47 (25.9%). Improvement was significantly related to CAT score (CAT < 10: 22.2% worsened and 22.2% improved inhalation technique; CAT ≥ 10: 6% worsened and 25% improved inhalation technique, $p = 0.037$), but not to any other demographic, clinical or functional characteristics of patients. In the subset of patients who improved their inhalation technique, males had a higher average BMQ Necessity score than females (mean BMQ Necessity score were respectively 21.97 and 17.88, $p = 0.017$).

A significant number of papers explore the effects of educational intervention on frequency of inhaler errors,[7] and a significant improvement of inhalation technique is usu-

Table 2 Variation on critical errors in the different groups of inhaler devices.

				Error M1				McNemar test
			No Error	Error	Total	Worsened	Improved	P-value
mDPI		No error	92	20	112	8.1%	14.7%	
	Error M2	Error	11	13	24			0.150
		Total	103	33	136			
pMDI		No error	12	7	19	3.2%	22,6%	
	Error M2	Error	1	11	12			0.070
		Total	13	18	31			
sDPI		No error	48	10	58	1.6%	16.1%	
	Error M2	Error	1	3	4			0.012
		Total	49	13	62			
Softm		No error	23	8	31	8.1%	21,6%	
	Error M2	Error	3	3	6			0.227
		Total	26	11	37			

Note and abbreviations: Error Moment 1: first assessment; Error Moment 2: 2nd assessment; errors shown as number of demonstrations; Worsened/Improved described as % of demonstrations.

ally reported. In a recent systematic review of inhalers' critical errors, 11 out of 21 studies exploring the relationship between previous inhaler instructions and frequency of inhaler errors found a positive association between previous instructions and a better inhaler technique.[8] In the present study, some improvement in inhalation technique was achieved after a single education intervention in all types of IDs, with statistical significance in the group of inhalers with an easy feed-back to the patient that a significant amount of medication had been inhaled. It appears that these devices attributes, by improving patient confidence in their use, improve the maintenance of a correct inhaler technique. We found a significant positive association between symptoms and improvement of the inhaler technique. We hypothesized that more symptomatic patients can be more motivated to learn how to use inhalers properly. We also found that male patients who improve their inhalation technique seem to greater belief in need for medication than women. Probably men, but not women, have to believe in the need of medication to improve their learning of correct inhalation techniques. This information is new and needs to be confirmed by other studies.

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 text. Pedro Teixeira carried out the statistical analysis, contributed to the section on methods and results, and collaborated in the final writing. Venceslau Hespanhol reviewed the final draft. Jaime Correia-de-Sousa reviewed all the drafts and collaborated in the final writing. All the authors approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Should tobacco interventions be different in men and women?

Men and women differ in their smoking behaviour: women smoke fewer cigarettes per day, their consumption is more related to sensory effects, mood and negative emotions, they start smoking later with a lower cumulative consumption and tend to use cigarettes with lower nicotine content, show lower dependency scores than men, become dependent earlier and have greater difficulty quitting smoking experiencing more severe nicotine withdrawal symtoms.[1]

We conducted an observational, multicenter study of consecutive patients who attended several smoking clinics to stop smoking between October 2014 and October 2015. We wanted to know if there were differences between men and women in terms of tobacco consumption. To investigate this we included qualitative variables (questionnaires to measure motivation to quit and nicotine dependence) and quantitative variables (age, tobacco consumption, num-

Variation on critical errors in the different groups of inhaler devices

		Error M1					McNemar test
		No Error	Error	Total	Worsened	Improved	p-value
mDPI	No error	92	20	112	8.1%	14.7%	
Error M2	Error	11	13	24			0.150
	Total	103	33	136			
pMDI	No error	12	7	19	3.2%	22,6%	
Error M2	Error	1	11	12			0.070
	Total	13	18	31			
sDPI	No error	48	10	58	1.6%	16.1%	
Error M2	Error	1	3	4			0.012
	Total	49	13	62			
Softm	No error	23	8	31	8.1%	21,6%	
Error M2	Error	3	3	6			0.227
	Total	26	11	37			
sDPI + Genuair	No error	76	14	90	1.04%	14.6%	0.001
Error M2	Error	1	5	6			
	Total	77	19	96			

COPD: analysing factors associated with a successful treatment

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COPD: Analysing factors associated with a successful treatment

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KEYWORDS
COPD;
Inhalation technique;
Adherence;
Prescriber disagreement;
Clinical outcomes

Abstract
Objectives: To evaluate if non-adherence to inhaled medications, inhalers mishandling or the prescribers' non-adherence to GOLD strategy are associated with mMRC grade, CAT score, COPD acute exacerbations or FEV_1%.
Methods: A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães. Patients ≥40 years diagnosed according to GOLD criteria were recruited consecutively. A survey of demographic and clinical data was used. Adherence was assessed by using the Measure of Treatment Adherence (MTA) questionnaire. Inhalation technique was evaluated by using checklists of correct steps and critical errors, and inhalers' misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use. To evaluate the prescriber non-adherence to GOLD strategy, the patients' current medication was compared with therapeutic standards proposed by the GOLD 2017 strategy for the same ABCD groups. A statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.
Results: We studied 303 participants, 79.5% males, mean age = 67.5 years. A total of 285 completed the MTA questionnaire. Non-adherence was referred by 47 (16.5%) patients, and a significant negative association was found between adherence and CAT score and FEV_1%. 285 patients performed 499 inhalations manoeuvres with 10 different IDs. Inhaler misuse was observed in 113 (39.6%) patients, and was not associated with CAT score, mMRC grade, ECOPD or FEV_1%. We found deviations from the GOLD strategy in 133 (44.3%) patients, which were negatively related to CAT score, mMRC grade and ECOPD.

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Conclusions: In the present study we failed to prove a positive association between non-adherence to medication, inhalers mishandling or prescribers' non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients were more adherent to medication, previous ECOPD seems to improve prescribers' adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

Background and objectives

Chronic Obstructive Pulmonary Disease (COPD) is the only leading cause of death with rising mortality and morbidity,[1] and currently represents one of the most significant health problems at international level. It is a chronic and incurable disease, but symptoms significantly improve with inhaled therapy, even though it is unlikely that most patients remain asymptomatic. Lung function also improves with medication, and acute exacerbations can be prevented or mitigated. Symptoms, acute exacerbations and airflow limitation are important treatment outcomes. Treatment can be described as successful if an appropriate change is measured in an appropriate outcome.[2] Some factors relying on patients, on health-care providers or on the physician–patient relationship can be significantly related to poor clinical outcomes. Some of them are common and modifiable. Non-adherence to medications in COPD has been related to mortality, poor disease control and poor quality of life. In the LASSYC study,[3] poor adherence was associated with more exacerbations. Vestbo et al., using data from the TORCH study, also found significant differences in survival and risk of severe exacerbations according to the degree of patient adherence.[4] Inhaled medication is the mainstay of COPD management. Inhaler misuse has been associated with increased rate of severe COPD exacerbations,[5] but the overall impact on clinical outcomes remains currently unknown. It would appear to be predictable that poor clinical outcomes is related to non-adherence to guidelines, but the relationship between adherence to guidelines and some clinical outcomes, such as the number of acute exacerbations, may be different than expected.[6,7]

The objective of this study was to assess whether non-adherence to inhaled medications, inhaler mishandling or prescriber non-adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy are associated with medical Research Council Dyspnoea Questionnaire (mMRC) grade, COPD Assessment Test (CAT) score, COPD acute exacerbations and FEV_1%.

Methods

Study design and population

A cross-sectional study was conducted in the outpatient respiratory care of Hospital de Guimarães, Portugal, between March 2016 and May 2017. Stable patients over 40 years old and diagnosed as suffering from COPD according to the GOLD criteria were consecutively included, after having given their written informed consent. Exclusion criteria were the refusal to participate and the inability to understand simple questionnaires. The study was approved by the Hospital's Ethics Committee, the Research Ethics Committee of Minho University and the Portuguese Data Protection Agency. We followed the STROBE guidelines for reporting observational studies.[8]

Demographic and clinical characteristics

A questionnaire of demographic and clinical data was used. Symptoms were evaluated using the Portuguese versions of the CAT questionnaire and the mMRC scale. Results were later dichotomised according to GOLD thresholds for considering more or less symptomatic impact of COPD. A variable''symptoms'' was created and dichotomised into fewer symptoms (mMRC <2 and CAT <10) or more symptoms (mMRC $\geq$2 and/or CAT $\geq$10). The number of COPD acute exacerbations (ECOPD) registered in the previous year was evaluated. We defined ECOPD according to GOLD, as an acute worsening of respiratory symptoms that result in additional therapy,[9] but also requiring an unplanned medical visit, whatever the severity of symptoms. The number of ECOPD were also dichotomised according to GOLD as <2 exacerbations and $\geq$2 exacerbations or $\geq$1 hospitalisation. All participants performed spirometry according to the American Thoracic Society and the European Respiratory Society recommendations for standardised lung function testing,[10,11] and referenced according to Global Lung Function Initiative prediction equations (GLI 2012).[12] The diagnosis of ACO was not considered in the present

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study, because neither its definition nor the clinical characteristics or diagnostic criteria are universally accepted, and they changed during the period the project was conceived and developed, and data was collected and interpreted.[13]

Adherence to medication

Adherence to inhaled medication was assessed using the Measure of Treatment Adherence (MTA), a psychometric tool validated for the Portuguese population in 2001, with a reported Cronbach's alpha of 0.74. It consists of a seven items questionnaire, reflecting common patterns of non-adherent behaviours. 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, and total scores range from 6 to 42, with higher scores indicating higher self-reported adherence. Non-adherence was defined by a score $\leq$5, after dividing the total score by the number of questions. This cut-off was validated by the MTA authors.[14]

Inhaler technique

Inhaler technique was assessed using previously defined checklists developed according to the instructions provided by the manufactures and to previous literature,[15] and also including essential steps and critical errors (Table 1). Errors considered critical were related to priming/loading or the inhalation manoeuvre, and could substantially affect drug delivery to the lungs. These included lack of inhalation through the mouthpiece for all devices, slow and not forceful inhalation for dry powder inhalers (DPI) and rapid or forceful inhalation for pressurised metered-dose inhalers (pMDI) or soft-mist inhalers (SMI). Device-dependent critical errors are listed in Table 2.

Participants were invited to demonstrate the use of their prescribed inhaler devices, just as they do it at home, and the correct steps and critical errors were recorded. Inhaler misuse was defined when one or more critical errors were made, whatever the number or types of inhalers in use.

Adherence to guideline

The prescribers' adherence to GOLD 2017 strategy was assessed by comparing the patient's current medication with the therapeutic standards for the same ABCD groups. Current medication was evaluated using the hospital data base, the health data platform, or patient self-reported information. Patients were categorised as GOLD-concordant or GOLD-discordant based on criteria presented in Table 3.

Statistical analysis

The statistical association between dichotomous variables was assessed with the Chi-square test and intensity of linear association with the Pearson's correlation coefficient. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Table 1 Check-list of steps and critical errors.

1.Correct priming or loading
(Incorrect priming or loading were considered critical error)
2.Exhalation before inhalation
(No-exhalation before inhalation was not considered critical)
3.Correct inhalation
(Incorrect inhalation were considered critical error)
4.Hold the breath a few seconds after inhalation (except when using a spacer)
(Not holding the breath or exhalation through the mouthpiece was not considered critical)
5.Finalisation (clean the mouth-piece, remove used capsule after verifying that no powder remains, check colour changing in control window, close ID and wash the mouth if necessary)

Table 2 Critical errors in different IDs.

1. Aeroliser®, Breezhaler®, and Handihaler®: failure to insert the capsule, failure to press and release buttons, powder remaining in the capsule after inhalation.
2. Diskus®: failure to open the cover, to slide the lever until it clicks, or not keeping inhaler horizontally.
3. Ellipta®: failure to slide cover down until a click is heard or block air vent with fingers.
4. Genuair®: failure to remove the cap, to press and release the button until the control window has changed to green, not holding inhaler horizontally, and not changing control window to red after inhalation.
5. pMDI: failure to remove cap, not shaking the inhaler (suspensions only), not holding the inhaler in the upright position, poorly synchronised hand actuation and inhalation (except using a spacer), inhalation through the nose, actuation against teeth, lips or tongue.
6. Respimat®: lack of cartridge in the device, failure to open the cap, twisting the base or pressing the dose-release button, poorly synchronised hand actuation and inhalation.
7. Spiromax®: failure to hold the inhaler in upright position, failure to open mouthpiece cover until a click is heard or blocking air vent with fingers.
8. Turbuhaler®: failure to remove cover, to hold the inhaler upright when twisting the grip (tolerance $\pm 45^{\circ}$) until a click is heard.

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Table 3 Type and number of deviations from the GOLD strategy.

Type of deviations	Number of deviations
1. Underuse	
1.1. Absence of medication (in B, C and D groups; in A group if symptoms or exacerbations)	3
1.2. Under-medication (under-therapeutic bronchodilation; only SAMA or SABA as need in B, C or D groups)	13
2. Overuse	
2.1. Doubling medication (2 or more different LAMA, LABA or ICS)	8
2.2. Overuse of bronchodilators (LABA + LAMA in A group)	34
2.3. Inhaled corticosteroids overuse (in A or B groups)	98
3. Inappropriate bronchodilation (only LABA in C or D groups)	1

Note: A total of 157 deviations from GOLD guideline were found in 133 patients: occasionally different deviations overlap in the same patient.

Results

Adherence to medication

A total of 303 COPD outpatients were included in the study. The most important demographic, clinical and functional characteristics of the patients are presented in Table 4.

A total of 285 participants completed the MTA questionnaire, and 47 (16.5%) were considered non-adherent to inhaled medications. The distribution of non-adherent patients were respectively 17.0%, 53.3%, 25.5% and 2.1% from GOLD I to IV ($p = 0.002$) and 34.0%, 36.2%, 4.3% and 25.5% from A to D of GOLD 2017 classification ($p = 0.53$). No association between adherence and mMRC score was found; an association between non-adherence and CAT score was found (26.5% of patients with CAT score <10 and 12.8% ≥10 were non-adherent, $p = 0.023$). A significant relationship was found between non-adherence and FEV_1% (the mean FEV_1% of non-adherent and adherent patients were respectively 62.3 and 49.9, $p < 0.001$). Non-adherence was respectively found in 19.3% and 12.4% of patients reporting <2 and ≥2 ECOPD, however without statistical significance ($p = 0.087$). When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, FEV_1% was the only variable significantly associated with adherence (Table 5).

Inhaler technique

285 patients carried out 499 inhalations manoeuvres with 10 different IDs (Aeroliser®, Breezhaler®, Diskus®, Ellipta®, Genuair®, Handihaler®, pMDI, Respimat®, Spiromax® and Turbuhaler®) in a total of 66 (13.2%) pMDI, 128 (25.7%) single-dose inhalers (sDPI), 228 (50.8%) multiple dose inhalers (mDPI) and 77 (15.4%) SMI-Respimat®. Misuse due to critical errors was observed in 113 (39.6%) patients. It was significantly related to the type of inhaler device and was observed respectively in 53.6%, 28.4%, 26.2% and 24.2% demonstrations using a pMDI, SMI, mDPI or sDPI ($p < 0.001$). Neither was any statistically significant association found between inhaler misuse and CAT score, mMRC grade, FEV_1% and ECOPD. When controlling for age, gender, education level, monthly income, Graffar classification, active smoking, symptoms and FEV_1%, only age, gender and Graffar classification were significantly associated with inhaler technique (Table 5). There was also no statistical relationship

Table 4 Demographic, clinical and functional characteristics of COPD patients.

Characteristics	$n = 303$
Male gender	241 (79.5)
Mean age (years)	67.5 ± 10.2
Age ≥ 65 years	186 (61.4)
Very low education level ≤ 3 school years	89 (29.4)
Graffar social classification	
Graffar 1	2 (0.7)
Graffar 2	13 (4.3)
Graffar 3	106 (35.5)
Graffar 4	174 (58.2)
Graffar 5	4 (1.3)
Very low monthly income (<530 Euros)	197 (65.7)
Mean smoking amount (pack/years)	49.3 ± 32.4
mMRC grade ≥ 2	185 (61.1)
CAT score ≥ 10	152 (72.4)
Frequent ECOPD (≥2/last year)	115 (38.0)
Post-bronchodilator mean FEV_1%	53.2 ± 19.7
GOLD stage	
I	30 (9.9)
II	127 (41.9)
III	106 (35.05)
IV	40 (13.2)
GOLD 2017 classification	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)

Note: Data shown as mean ± SD or *n* (%).
Abbreviations: mMRC, medical Research Council Dyspnoea Questionnaire; CAT, COPD Assessment Test; ECOPD, COPD exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

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Table 5 Predictors of adherence and inhalers misuse.

		Logistic regression – predictors of adherence							
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.499	.405	1.518	1	.218	1.648	.745	3.647
	Age	.022	.019	1.472	1	.225	1.023	.986	1.061
	Ed. level 0/1	.349	.466	.560	1	.454	1.417	.569	3.532
	Gender	−.386	.425	.825	1	.364	.680	.295	1.564
	Curr. smok.	−.715	.432	2.730	1	.098	.489	.210	1.142
	FEV_1%	−.029	.010	9.367	1	.002	.971	.953	.990
	Income 0/1	.248	.382	.423	1	.515	1.282	.607	2.708
	Graffar 0/1	−.179	.413	.188	1	.665	.836	.372	1.878
	Constant	1.371	1.608	.727	1	.394	3.940		
		Logistic regression – predictors of inhalers misuse							
		B	S.E.	Wald	df	Sig.	Exp(*B*)	95% C.I. for Exp(*B*)	
								Lower	Upper
Step 1	Symptoms 0/1	.366	.343	1.139	1	.286	1.442	.736	2.827
	Age	.039	.015	6.811	1	.009	1.039	1.010	1.070
	Ed. level 0/1	.084	.341	.061	1	.806	1.088	.557	2.123
	Gender	.736	.325	5.132	1	.023	2.087	1.104	3.946
	Curr. smok.	.266	.370	.519	1	.471	1.305	.632	2.696
	FEV_1%	−.002	.007	.044	1	.833	.998	.984	1.013
	Income 0/1	.215	.290	.547	1	.460	1.239	.702	2.190
	Graffar 0/1	−.775	.318	5.951	1	.015	.461	.247	.859
	Constant	−3.272	1.271	6.632	1	.010	.038		

a. Variable(s) entered on step 1: Symptoms 0/1 (symptoms = 0: mMRC <2 and CAT <10; symptoms = 1: mMRC ≥2 and/or CAT ≥10), age, education level 0/1 (<4 years at school = 0; ≥4 years = 1), gender, current smoking 0/1, FEV_1%, monthly income 0/1 (<530 Euros = 0; ≥530 euros = 1), Graffar social classification 0/1 (4 and 5 = 0; 1,2 and 3 = 1).

between inhaler technique and adherence to medications ($p = 0.328$).

Adherence to guideline

We found deviations from the GOLD 2017 therapeutic strategy in 133 (44.3%) patients, and they are described in Table 3. The most frequent deviations were related to the overuse of inhaled corticosteroids in GOLD A and B groups and the overuse of bronchodilators in the A group. Overuse of ICS and/or bronchodilators accounted for 88% of total prescriber deviations. It should be noted here that during the period of patient recruitment the 2017 GOLD version was published and 24,4% of patients moved from C and D to A and B groups. In the historical context in which they were treated, medications now considered excessive, could then have been appropriate. Table 6 describes the type of prescriber lack of agreement by GOLD 2017 ABCD groups.

We found no association between deviations from the GOLD guideline and FEV_1. However, 78.8% of the patients medicated according to GOLD and 62.2% of those not according to GOLD had a CAT score ≥10 ($p = 0.023$), and 68.5% of patients medicated according to GOLD and 53.0% of those not according had an mMRC grade ≥2 ($p = 0.024$). 58.7% of those who were medicated according to GOLD and 12.8% of patients medicated not according to GOLD referred to frequent exacerbations in the previous year ($p < 0.001$).

Discussion

Patient non-adherence to medications, inhaler mishandling and prescriber disagreement to therapeutic standards are common and modifiable factors which are likely to be related to poor clinical outcomes. Lung function, symptoms and acute exacerbations are important clinical outcomes among COPD patients, and they were measured in the present study. We found a negative association between adherence and the clinical or functional severity of the disease. No significant association was found between inhaler misuse and ECOPD, symptoms or FEV_1%. Lack of agreement with the GOLD strategy was more frequent than poor-adherence to medication or inhaler misuse, and previous ECOPD seems to improve prescriber adherence to treatment guidelines.

In the present study, adherence was significantly related to the clinical and functional severity of the disease. Patients who complained of more symptoms or airflow limitation adhered better to inhaled medications. This may be due to the fact that patient adherence to medication is based on their perceptions of symptoms severity. A positive association between poor-adherence behaviours and

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Table 6 Prescribers disagreement to GOLD 2017 strategy by ABCD groups.

	Group A	Group B	Group C	Group D
Guide-line concordant	26 (37.7)	44 (37.3)	5 (71.4)	92 (86.8)
Overuse	43 (62.3)	70 (59.3)	1 (14.3)	4 (3.8)
Underuse	0 (0)	4 (3.4)	0 (0)	10 (9.4)
Inadequate bronchodilator	0 (0)	0 (0)	1 (14.3)	0 (0)

Note: Results presented as number (%) of patients. $p < 0.001$; in 3 patients there was no information related to current medications.

poor treatment outcomes has been described in previous papers.[16,17] A previous study reported that patients are likely to alter the recommended medication based on how they feel,[18] and that the sentence ''I vary my recommended management based on how I am feeling'' was a significant predictor of non-adherence to medications.

We found inhaler mishandling disappointingly common but not related to patient clinical or functional characteristics. This is consistent with other published studies.[19,20] However, it was expectable a significant impact on clinical outcomes, such as symptoms and acute exacerbations. This is a surprising issue, and may be both because we have not analysed the specific medication affected by inhaler misuse and because of the substantial overuse of ICs and/or bronchodilators by a significant number of patients. In medical literature, a small number of studies report an association between critical errors and COPD outcomes.[21] In a recently published study the authors found inhaler misuse associated with an increased rate of severe COPD exacerbations,[22] and in two different cross-sectional studies inhaler misuse was related to increased risk of hospitalisation and emergency room visits.[23,24]

Prescribers not respecting guidelines was common in the present study and more frequent than poor-adherence or inhaler misuse, but there is currently no standard threshold of satisfactory adherence.[25] The most frequently found deviations were related to overuse of inhaled corticosteroids. This was to be expected because the diagnosis of ACO was not considered in the present study and the GOLD 2017 report was published while data was being collected, with many patients shifting from high to low risk groups. The overall non-adherence to GOLD guidelines seems to be very common, even though varying from country to country.[26] In previous studies, overuse of ICS was also the most common recorded deviation to international standards of therapy.[27,28] A previous published study found that exacerbations-related hospitalisations lead to improved adherence to GOLD guidelines.[6] In the present study, previous ECOPD seems to improve prescriber adherence to treatment guidelines, and patients medicated in non-agreement with the GOLD were less symptomatic and had fewer exacerbations. This is an intriguing issue, and can partly be due to fact that the present study did not control for features suggestive of airway hyperactivity. Moreover, because overuse of ICS and/or bronchodilators accounted for 88% of prescriber deviations, there were no reasons for patients medicated in non-agreement with guidelines to present more symptoms or more airflow limitation.

The present study draws attention to the choice of significant outcomes to evaluate responsiveness to treatment, and to the appropriate instruments to measure them.[29] Lung function, symptoms and acute exacerbations are important treatment outcomes in COPD. FEV_1 is a highly reproductive measurement strongly related to mortality. Dyspnoea is an important patient-centred outcome. However, it is very subjective, and the level of breathlessness depends on the level of patient activity. The mMRC scale, an instrument that has stood the test of time,[30] measures mainly dyspnoea-related disability, and, like other tools, may be not useful in evaluating responsiveness to treatment.[31] CAT has strong measurement properties in the overall impact of the disease, and the GOLD recommends its routine use in clinical practice. COPD exacerbations are the single most important feature of COPD, they indicate clinical instability and progression, and are related to increased mortality. It is an important outcome both from the physicians' and patients' perspectives. However, there is no standardised definition, and unreported exacerbations, not evaluated in the present study, have the same clinical relevance. A measure of self-reported adherence, the Test of the Adherence to Inhalers (TAI),[32] specifically designed to identify non-adherence to inhalers in asthma and COPD patients, is presently available in Portuguese-Brazilian language. To the best of our knowledge, MTA was the only validated instrument to measure adherence in the Portuguese language at the time patients were recruited for the present study. However, we acknowledge that factors related to adherence with inhaler therapy in COPD present some unusual features which makes the use of many unspecific questionnaires less appropriate.

Conclusions

In the present study, done in a real world context, we failed to prove a positive association between non-adherence to medication, inhaler mishandling or prescriber non-adherence to GOLD strategy with symptoms, exacerbations and airflow limitation. Conversely, more symptomatic and more obstructed patients adhered better to medication, previous ECOPD seems to have improved prescriber adherence to treatment guidelines, and symptoms, ECOPD and FEV_1% were not significantly associated with inhaler technique.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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DISCUSSION

Overview

The present thesis comprises four main surveys and three complementary studies published as research letters. The thread connecting all the studies is the identification and understanding of factors whose correction can be translated into improved care for patients with COPD, centred on adherence to medication, prescribers' adherence to GOLD strategy and adequate use of inhalers. The internal validity and the main limitations of each study have been discussed in their appropriate section. However, some issues will be discussed here in more detail. The external validity of the four surveys has also been discussed in their proper section, with comparison of the presented findings with that of different studies. Because some papers have been published in medical literature since the submission of the articles, reporting new and relevant findings which can enrich the present discussion, an updated comparison of results will be carried out here in this section.

Most of the objectives of the thesis were reached in the present work. Non-adherence to inhaled medications, prescribers' non-adherence to GOLD strategy and inhalers misuse were chosen because they are modifiable factors usually related to poor clinical outcomes. However, the present study failed to prove a direct association between them and CAT score, mMRC grade, ECOPD and FEV_1%. Inversely, some features, like symptoms and airflow limitation, usually considered to be consequences and directly associated with non-adherence behaviours, were actually contributory of a better adherence profile, and a history of frequent exacerbations encouraged prescribers to follow the GOLD strategy. This can be justified by some limitations of the present study. The type of study design, the outcomes chosen and the tools used were previously discussed in the proper section of the works that comprises the thesis and yet elsewhere in this thesis. However, a direct relationship between an accurate inhaled medication and a successful treatment, defined by a significant change in important and measurable outcomes, can be arguably in a real-world context. Patients always present a sort of characteristics that modulate the interaction between the prescribed therapy and the outcomes intended to be achieved. The patient's beliefs related to the disease and medication can influence adherence and inhaler technique. Patients' behaviours also influence adherence and inhaler technique. The social representations of health, disease and medications can modulate the way how patients feel and understand the disease, and influence adherence, the ability to use inhaler devices and the motivation to learn how to use them. Some demographic characteristics as older age, low socioeconomic level and low education level

influence patients' health literacy, limiting the ability to understand instructions. The severity of COPD, the way how patients feel and understand the disease, and the way COPD is valued by patients in the context of several comorbidities, can in fact modulate adherence, inhaler technique and even influence physicians' decisions.

Major findings. Their clinical and scientific implications.

1- Our data confirms COPD as a very complex and heterogeneous disorder, more prevalent in the elderly and people with low socioeconomic level.
2- A substantial proportion of COPD patients were never-smokers, mainly women. We emphasises the need for COPD recognition among never-smokers, particularly women.
3- COPD in women, in never-smokers and in patients with a previous diagnosis of asthma presented some specific characteristics.
4- Patients suffering from COPD usually present a set of different comorbidities that have to be taken in account.
5- A low education or socioeconomic level should be understood as a feature of severity, when treating patients suffering from COPD.
6- FEV_1 was strongly related to symptoms and exacerbations.
7- Predictors of ECOPD were gender, monthly income, education level and FEV_1.
8- Patients referring irregularity of symptoms are more prone to acute exacerbations.
9- Adherence to inhaled medication is related to the need perception and to the functional severity of the disease: symptoms and airflow limitation can influence how patients feel the need to comply with prescribed medications. We emphasises that adherence should be reinforced in less symptomatic COPD patients, chiefly in the frequent exacerbator phenotype.
10- Patients´ beliefs regarding disease treatment were the most powerful predictors of adherence to inhaled therapy. Past experiences and health-related behaviours are also adherence predictors.
11- Patients and physicians' cultural perception about the necessity of the inhaled medications differs on its usefulness in preventing exacerbations and disease progression. There is a need to reinforce patients' beliefs about the necessity of taking their inhaled medications as prescribed, clearly stated that medication is useful not only to ameliorate symptoms but also to prevent acute exacerbations.

12- COPD patients exhibited different patterns and reasons for different adherent behaviours.

13- Inhalers mishandling depends on the type of ID; it was not associated to multiple inhalers use nor to patients' preference, but to the patient's beliefs about the necessity to use them. Patients less believers in the need of medication demonstrated a worse inhalation technique. We acknowledge that patients need to believe in inhaled medication to use inhalers correctly.

14- Elderly patients, women and those with lower education level or lower socioeconomic status demonstrate a worse inhalation technique. The teaching of a correct inhalation technique should be reinforced in such patients.

15- Some inhaler devices, by giving an easy feed-back to the patient that a significant amount of medication have been inhaled, improve the maintenance of a correct inhaler technique.

16- More symptomatic patients and men who belief in the need of medication are more prone to learn and improve their inhalation technique.

17- Prescriber disagreement with the GOLD strategy was found more frequently than poor-adherence or inhalers misuse.

18- Previous ECOPD seems to improve prescribers' adherence to treatment guidelines.

19- It was not possible to prove non-adherence to medication, inhalers mishandling and prescribers' non-adherence to GOLD strategy related with poor clinical outcomes such as worsening of symptoms and airflow limitation, or increased number of acute exacerbations.

20- Patients always present characteristics that modulate the interaction between the prescribed therapy and the desired outcomes. In stable COPD patients, there is a need to acknowledge patients' perspectives related to behaviours, beliefs and demographic characteristics limiting their ability to understand instructions and deal with the disease.

21- We emphasizes that stable COPD should be managed taking into account the severity of the disease but also the personal and cultural perspective of each person.

Internal validity and comparison of results with different published works

The present study used data generated during routine clinical practice so it can be defined as a 'real world' observational, cross-sectional study. Observational studies are an important type of study design. They are more representative of usual clinical practices than randomized controlled trials (RCTs).[137] With 'real world' observational studies, investigators can evaluate a wide range of

outcomes, opening an important window to daily medical practice. Some features intended to be studied, as adherence to inhaled medications, prescribers' adherence to guidelines or patients' ability to use inhaler devices, were only possible to be evaluated in such a design study.[138] However, they present several limiting factors, and investigators can only prove associations between variables rather than a causal relationship.

A large convenience sample recruited in one single medical centre was the solution found in the absence of resources either for a correct randomisation or for the accomplishment of a multicentre survey. Exclusion criteria in the present study were only the refusal to participate and the inability to understand simple questionnaires. This allowed investigators to include the wider range of diversity elements of the population from which the sample was taken. Many studies on COPD exclude participants with a prior history of asthma, because the possibility of confusion between asthma and COPD. They were not excluded in the present study, as childhood asthma is a well-known risk factor for COPD. The number of patients included in the several studies that comprises the thesis were between 300 and 319. This is a small study. However, there is nothing wrong with small studies provided they are well-designed and interpreted carefully. They may, ultimately, inspire larger confirmatory studies.

The diagnosis of COPD and the patients' evaluation were done according to GOLD criteria. The main questionnaire used in the present study was specifically created for this purpose. However, the questionnaire was not validated. This can be a source of bias, especially the easy-to-answer questionnaire on COPD, relating to the patient's knowledge of their disease, used to help understanding the social representations of COPD. However, all of the surveys of COPD have used ad hoc developed questionnaires.[139] The Graffar Social Classification, used in Portugal for many decades, was adapted to the changes in Portuguese population characteristics, related to education level and monthly income. Evaluation of symptoms was done using the Portuguese versions of the mMRC and CAT questionnaires. The CAT is translated but not validated for the Portuguese population, however it is commonly used in clinical practice for many years. Adherence to inhaled medications was assessed using the Measure of Treatment Adherence (MTA). MTA was validated for the Portuguese population in 2001, but it is not specific for COPD or inhaled medication. Previous to the application of MTA patients were clearly informed that the questions were only related to inhalation therapy, and in all the questions the term *medication* («medicação») was changed to *inhaled medication («medicação inalatória, inaladores, bombinhas para inalação»).* This change was done with the knowledge and agreement of the authors of MTA. To

the best of our knowledge, it was the only instrument to measure adherence validated to Portuguese language by the time the project of this thesis was designed, and patients' recruited. However, we acknowledge that factors related to adherence with inhaler therapy in COPD present some particularities making the use of unspecific questionnaires less appropriate. Some specific factors, related to the disease, demographic characteristics of patients and type of medications, are:

- the patients' mean old age,
- mean low socioeconomic and mean low education level,
- dyspnoea, as a bothersome symptom and some amelioration following a bronchodilator inhalation (although less than is asthma patients).

Specific factors related to inhalation therapy are:

- patients' beliefs about inhaled medications,
- the social representations of inhalation therapy, and
- the difficulty in using inhalers.

This could be a source of bias, when studying patient's adherence to medications. Non-adherence was defined by a score ≤5, as previously described. This cut off was validated by the MTA authors. However, when compared with other different tools studying adherence, as the more recently described TAI questionnaire, a significant lower score has to be reached, to define non-adherence. These two last issues can in part justify the low rate of non-adherent patients found in the present study. For this reason, and because the words adherence and non-adherence cannot fully describe the complexity of adherence-related behaviours, poor-adherence was also defined, but this cut off was not validated. The cross sectional adaptation of the BMQ-specific into Portuguese was validated as an interviewer-administered questionnaire in 2013. Participants were clearly informed that the questions referred to inhalation medication, used to treat the respiratory disease, and not to other used medications nor to the device itself. The BMQ has been widely used in the understanding of patients' beliefs about their disease or medication, in many diseases other than COPD. This enable a comparison of results with other populations suffering from COPD. Inhalation technique was assessed by using previous defined checklists, developed according to the instructions provided by the manufactures and to previous literature, as described in the respective studies. The internal validity and the main limitations have also been discussed in their appropriate section.

All the studies related to this thesis were published recently, and the comparison of their findings with other published studies were fully discussed in their external validation section. However, some important and recently published studies must be referred in this section.

A questionnaire designed to identify non-adherence to inhalers in asthma and COPD patients, the Test of Adherence to Inhalers (TAI) was developed in Spain, and published in 2016. The validation study, conducted in 1009 patients, 410 of them suffering from COPD, showed a good internal consistency (Cronbach's alfa of 0.883) and a good test-retest reliability (0.883). The TAI consists of two complementary questionnaires, the 10-items TAI, completed by the patient, and the 12-items questionnaire, completed by the patient and the health-care professional. The TAI holds good psychometric properties and seems to be able to recognise the predominant pattern of non-adherence. The TAI test, in a cross-sectional multicentre study in 910 Spanish patients suffering from asthma and COPD, found that 62.5% of patients were non-adherent to inhaled medications. This study also found that the non-adherence erratic pattern was more common than the deliberate or the unwitting patterns.

The 10-item TAI was used to assess the adherence profiles to inhaled therapies in 795 patients of seven Latin American countries. The LASSYC study was published in 2017, and found a prevalence of good-adherence to inhaled medications in approximately 50% of participants. TAI also found that more severe patients are more adherent to medication. However, a low adherence was associated with lower smoking history, lower education level, worse health status and more exacerbations.

Some authors have considered electronic monitors the gold standard for objective quantifying adherence to therapy.[73, 140] Sulaiman I et al published in 2017 an objective assessment of adherence to inhalers in COPD, using an inhaler compliance assessment (INCA audio recording device) attached to a salmeterol/fluticasone Diskus.[86] More than the quantification of adherence and inhaler technique, this paper calls attention to the characterisation of the inhaler errors made by COPD patients using the same device as intermittent, frequent and persistent. This new information is important to understand the relationship between inhalers misuse and COPD outcomes. Using check-lists to study patients' inhaler technique one can have only a snapshot, and inhaler technique can be significantly different in different moments. Moreover, the presence of an external observer, especially when analysing the inhaler proficiency in older persons with very low education level and not familiarised to being evaluated or observed, can interfere with the very demonstration of the inhaler technique. This is another limitation of the study that may have limited an association between inhaler technique and COPD outcomes.

Celli B et al,[139] in 2017, published the MIRROR study. It's objective was to compare potential differences between the perceptions that COPD patients have of their disease to the physician's perception about the way how COPD affect their patients. As expectable, the study shows significant gaps between this two groups, particularly important in areas related to quality of life and symptoms. Moreover, 89% of patients stated that they "lied" or were "not honest" when interacting with their physician, during clinic visits. This two issues must be considered when interpreting adherence to medications and when valued clinical outcomes less objectives than FEV_1%.

CONCLUSIONS

A previous section named "*Major findings. Their clinical and scientific implications"* can be understood as a point-by-point summary and conclusions of the several works comprised in the thesis, open to clinical practice, pointing ways and suggesting strategies to deal with patients suffering from COPD. It is itself a conclusion of the present thesis. Instead, the present section is an integration of the conclusions of the different works included in the thesis into the current clinical and scientific trends to understand COPD.

COPD is the most common chronic respiratory disease. Every day people suffer and die from this disease. We are currently facing a revolution in the understanding of what a disease is. This new understanding of the disease in the framework of human biology have been catalysed by systems biology and its new concepts of scale-free networks and systems emerging properties. The application of this network science to human biology, both in health and in disease, will lead to a different nosology and to a new definition of the disease expression, in which the molecular signature will replace histopathology in the diagnosis and in the prediction of outcomes. In the era of genomics and proteomics, Mark Fitzgerald referred the need to understand the behavioural perspective, best described as a *humanomics* perspective,[3] a term previous coined to bring a human focus to some economic concepts. The way how clinicians understand and treat COPD is usually based in three dimensions, the pulmonary function, symptoms and the risk of exacerbations. In the present work, COPD was recognised as a very heterogeneous disorder, but with some specific characteristics in women, in never-smokers and in patients with a previous diagnosis of asthma. Symptoms irregularity was related to the risk of exacerbations, and a low education or socioeconomic level emerged as a feature of severity. We have demonstrated that other dimensions related to persons must be also taken in account to accomplish a successful treatment in COPD. Disease management should be viewed through the patients' perspective. It modulates the relationship between medications and the outcomes intended to be achieved. Hence, the present work found that the relationship between adherent to medications, inhaler' technique or prescribers' adherence to GOLD strategy and COPD outcomes can present an opposite direction than was previously expected. Symptoms and airflow limitation can influence the way patients feel the need to comply with prescribed medications.The way patients understand their disease, value their symptoms in a context of multiple co-morbidities and believe in the need for medication can influence adherence and inhaler technique. The beliefs related to the need of

medication were found to be the most powerful predictor of adherence. Past experiences and health-related behaviours were also predictors of adherence to prescribed medication. Inhalers mishandling depends on the type of inhaler device and on patients' beliefs about the necessity to use them. By having confidence in the inhalation manoeuvre, patients improve the maintenance of a correct inhaler technique. A correct medical decision depends on an accurate patient evaluation and on robust scientific information, but a successful treatment is also modulated by some patients' characteristics, and by their behaviours and beliefs related to the disease and the medication. Some dimensions related to persons must be taken in account to accomplish a successful treatment. Clinical expertise has been defined by the ability to integrate scientific evidence and patients' circumstances and preferences.[141] Clinical expertise can be understood as the art of Medicine. Probably the present study, designed in the perspective of a better knowledge of the patient with COPD, can give some contribution to the understanding of the art of Medicine, beyond an inappropriate standardization and industrialization of Medicine or a reductionist biology-based approach.

SUGGESTIONS FOR FUTURE RESEARCH

The objective of this thesis was to understand the factors whose correction could be translated into improved care for patients with COPD. It was focused on patients' adherence behaviours, inhalation technique and treatment deviations from GOLD strategy. Most of the specific objectives have been fulfilled. However, we failed to prove non-adherence to medication, inhalers' mishandling and non-adherence to GOLD strategy related to poor clinical outcomes. This may be due either to the cross-sectional design of the work or to a complex interaction between the different variables and the studied outcomes. A significant number of new questions emerged during the present work. One of them, related to the understanding of reasons for poor-adherence to guidelines in COPD, lead the authors to conduct a study aimed to understand how evidence from randomized clinical trials apply to patients treated in routine clinical practice. The estimated global prevalence of COPD is currently around 11.7% in persons 40 years and older, and asthma affects an estimated 300 million individuals worldwide. They are the most prevalent airway diseases. The first diagnostic approach is clinical. Nonetheless, clinical diagnosis has little robustness. To diagnose airflow limitation that is not fully reversible, spirometry should always be performed. Many patients suffering from chronic asthma also present airflow limitation that is not fully reversible. Spirometry give more robustness to diagnosis, but is frequently not enough. COPD is considered a disease of smokers, but a significant portion of COPD may be attributed to occupational exposures and to indoor air pollution from biomass fuel combustion. Nonetheless, many asthmatic patients also smoke or report the same occupational and indoor exposures. COPD is commonly known as a disease of the elderly. However, with the progressive knowledge of genetic factors associated with early abnormal lung development, and the understanding of the influence of environment factors in different life stages, including pre and early postnatal exposures, physicians will be faced with a diagnosis of COPD at a much earlier age. We understand that, in clinical practice, airway disease should be approached in an integrated way, beyond the artificial duality of asthma or COPD diagnosis. The focus will not be centred in diagnosing asthma or COPD, but in the understanding what must be treated in a given patient. In this new paradigm, some clinical questions should be asked:

- In this given patient, how can physicians support preventing exacerbations? How can physicians help to prevent disease progression? How can social, occupation and family

problems be prevented? How can physicians improve patients' symptoms, quality of life and physical activity, helping patients live with the disease?

And some research questions should also be asked:

- Are these important clinical or patients-centred outcomes? What really matters to the patient suffering from airway diseases? How can it be measured? What are there determinants, and how can they be measured?

Ongoing studies

1- *Prevalence of abdominal aortic aneurysm (AAA) in patients with chronic obstructive pulmonary disease.*

Objectives:

To compare the prevalence of AAA in COPD patients and in community, after adjustment for age, gender, tobacco amount and cardiovascular comorbidities.

2- *Exploring clinical predictors of COPD exacerbation in a community cohort (study proposal).*

Scientific Rationale:

A- COPD exacerbations, by definition, are acute events. They are usually associated with increased dyspnoea, increased sputum volume and purulence, decreased exercise capacity and worsening of respiratory function that frequently takes a long time to recover. Patients with COPD often wait and do not react in time to signs of disease deterioration, which results in progressive worsening and in treatment delay.

B- We hypothesise that progression of acute exacerbations can be prevented or delayed at an individual level early enough to avoid significant worsening of respiratory function, hospitalisation or visits the emergency room. Enabling patients to self-monitor their disease and react in time to prevent further deterioration can prevent significant ECOPD related morbidity and mortality, and decrease costs related to hospitalisations and visits to emergency rooms.

FINAL NOTES

Being an academic clinician in a research-friendly environment was the main self-proposed objective, defined at the beginning of this long journey. In the last four years, completing the studies that are comprised or related to the thesis, and undertaking different oral communications, also mostly related to the thesis, I have learned the basis of scientific rigor. First, I learned how to ask a pertinent research question. It must be useful in clinical practice, and the work that will respond to it must be feasible with the available resources. Second, I learned how to collect current and high-quality information that supports the research question and allows a later discussion of results. Third, I learned how to collect high-quality data from patients, and how to select the suitable tools to measure both the variables under study and the defined outcomes. The question to be answered must be translated from clinical language to a query that can be answered using statistical methods and the results once again translated into clinical language. Fourth, I learned how to develop a suitable study design that answers the research question, and using appropriate statistical techniques. Finally, I have learned how to report clinical and scientific research, using adequate international guidelines, and how to select the adequate journal for publishing it, within the established time boundaries.

An amount of different studies related to the thesis were conducted on a cohort of COPD outpatients. COPD has been for a long time recognised as a complex and heterogeneous disorder. However, the present studies allowed both to understand this reality but also to understand patients' complexity and heterogeneity. As a pulmonologist, I always treated patients suffering from airway diseases, and a correct medical decision had always relied on an accurate patient evaluation and on robust scientific information. COPD patients have been mainly treated according to their severity. However, a new understand has recently emerged: some dimensions related with the patients themselves must be taken in account. A successful treatment is arbitrated by some patients' characteristics, by their behaviours and beliefs related to the disease and medication, and by their personal and cultural perspectives. Non-adherence was known to be unfortunately common, now it starts being understood. Inhalers' mishandling was known to be frequent, but never understood by me, a person with a high degree education and accustomed to handling small objects and gadgets from the earliest childhood. However, that was not the patients' background. COPD patients are not familiarised to being taught, to learning and mostly to being evaluated. A new understanding related to the difficulty of using inhaler devices has also emerged. COPD can

be currently best understood by incorporating the experiential and social perspectives defining what a disease is.

No hay asuntos agotados, solo hombres agotados en ciertos asuntos."

("There are no exhausted matters, but only exhausted men in certain matters.")

Ramon y Cajal (1852-1934)

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ATTACHMENTS

Other published papers related to thesis

DPOC: estamos a tratar os doentes conforme o *estado da arte?*

António Manuel S. Duarte de Araújo*

RESUMO

A DPOC é a doença respiratória crónica mais comum, com uma prevalência estimada em 7,6 a 8,9% da população adulta e representando hoje a quarta causa de morte a nível mundial. A sua elevada mortalidade é essencialmente devida às agudizações que requerem internamento hospitalar. Dada a dificuldade clínica em prever, quer as exacerbações quer os doentes com maior propensão a agudizar, e a elas nos anteciparmos, o correto tratamento da DPOC e uma boa adesão à terapêutica são fatores essenciais. Apesar de isoladamente terem baixa sensibilidade, questionários e escalas de avaliação da adesão, bem como instrumentos de avaliação de crenças dos doentes sobre medicamentos, poderão ser ferramentas importantes, ajudando a encontrar barreiras práticas à adesão. O êxito terapêutico está também dependente de uma boa técnica inalatória, já que quando o doente os usa corretamente, os diferentes dispositivos inalatórios tem efeitos terapêuticos semelhantes. Um correto conhecimento das normas terapêuticas por parte do médico, uma boa adesão à terapêutica e a manutenção de uma correta técnica inalatória, por parte do doente, parecem dever ser os principais motivos de preocupação do médico que trata doentes com DPOC.

Palavras-chave: DPOC; Tratamento; Recomendações.

A patologia obstrutiva das vias aéreas representa um conjunto de doenças respiratórias crónicas, de elevada prevalência na população e, por isso, com um peso significativo tanto nas consultas hospitalares, como no âmbito dos cuidados primários. Para além dos crescentes e elevados custos, direta ou indiretamente relacionados com a saúde, e suportados pelos doentes, pelas suas famílias ou pelo Estado, muitas destas patologias vão acompanhar o doente ao longo de toda a sua vida, com significativo impacto na sua qualidade de vida e no seu rendimento profissional. É, por isso, natural que a comunidade médica se preocupe com o seu adequado tratamento, sendo uma das preocupações atuais da Direção-Geral da Saúde,[1-3] em sintonia com os relatórios e preocupações da Organização Mundial da Saúde (OMS).

A doença pulmonar obstrutiva crónica (DPOC) é a doença respiratória crónica mais comum a nível mundial. Com uma prevalência estimada em 7,6 a 8,9%[4] da população adulta, variável de país para país, é claramente uma patologia subdiagnosticada e por isso subtratada. Em Portugal, a sua prevalência poderá ser tão elevada quanto 14,2% em adultos com mais de 40 anos, segundo um estudo efetuado numa amostra representativa da população da área metropolitana de Lisboa e integrado no estudo BOLD.[5] Em Espanha, a sua prevalência está estimada em 9%,[6-7] sendo causa de 35% das consultas externas de pneumologia. A DPOC representa hoje a quarta causa de morte a nível mundial e na União Europeia responsabiliza-se por 56% dos custos com saúde atribuíveis às doenças respiratórias. Em Portugal, entre 2000 e 2008, o número de internamentos por DPOC aumentou cerca de 20%, representando um custo superior a 25 milhões de euros, com um aumento de 39,2%. De todas as enfermidades respiratórias é a de maior impacto socioeconómico e representa hoje um dos grandes desafios em saúde pública.

A DPOC é atualmente definida como uma doença comum, passível de prevenção e tratamento, caracte-

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rizada por uma obstrução brônquica persistente e habitualmente progressiva, associada a uma resposta inflamatória crónica do pulmão e das vias aéreas, secundária a uma agressão externa por gases ou partículas.[8] A gravidade funcional apresenta pouca relação com a sintomatologia e, por isso, com a autoperceção. A DPOC é uma doença heterogénea, com grande variedade de fenótipos clínicos, como vem refletido nas últimas atualizações do *Global Initiative for Chronic Obstructive Lung Disease* (GOLD). Os principais aspetos da heterogeneidade são os valores espirométricos, a sintomatologia e a frequência de agudizações. Sendo a obstrução persistente das vias aéreas a sua marca fundamental, não admira que seja a espirometria a principal ferramenta diagnóstica e o FEV_1/FVC obtido após a manobra de broncodilatação o melhor indicador de obstrução do fluxo aéreo, sendo o *cut-off* de 0,7 o mais aceite. O FEV_1 é uma medida espirométrica objetiva, reprodutível e com relação significativa com a mortalidade. A dispneia é o sintoma principal da doença, ainda que possa ser percebido de forma desigual por doentes diferentes e até com o mesmo grau de obstrução. Existem vários instrumentos de medida e valorização da dispneia, mas, pela sua sensibilidade e facilidade de registo, recomenda-se habitualmente a escala mMRC, o *Medical Research Council Dyspnoea Questionnaire*, com adaptação transcultural para a população portuguesa. Sendo a DPOC uma doença crónica, progressiva e multissistémica, importa também conhecer o seu impacto na qualidade de vida do doente e no seu bem-estar quotidiano, tendo sido o *COPD Assessment Test* (CAT) desenhado para o medir e recomendado o seu uso pelas *guidelines* internacionais.[8]

Relativamente à DPOC, como de resto em muitas outras situações clínicas, as *guidelines* são uma ajuda significativa na orientação terapêutica, permitindo-nos encontrar respostas na medicina baseada na evidência. Não substituem, no entanto, a experiência do médico, tendem a igualar doentes e situações clínicas em si muito diversas e são frequentemente de difícil aplicação na prática clínica. Apesar de serem hoje cada vez mais discutíveis as bases científicas e clínicas de algumas *guidelines*,[9] elas representam um padrão de tratamento e, apesar de se assumirem como recomendações, não podem ser ignoradas, sob o risco de má prática médica. Para além dos seus reflexos no bem-estar do doente, no que se refere aos custos, um estudo de 2013[10] observou um impacto económico negativo quando as *guidelines* do GOLD (2007), num estudo levado a cabo em Espanha, não eram seguidas no tratamento da DPOC ao nível dos cuidados de saúde primários. Interessa, por estas razões, um conhecimento rigoroso das normas internacionais de tratamento e orientação destes doentes, pelo que a melhoria do acesso à espirometria por parte dos cuidados de saúde primários, no nosso país, é uma condição fundamental.

A DPOC responsabiliza-se por elevada morbilidade, que habitualmente se mede através da sintomatologia, número de agudizações, de recorrências a serviços de urgência ou a consultas não programadas e de internamentos. O objetivo do tratamento é a melhoria sintomática, que proporciona maior bem-estar e maior tolerância ao exercício e a diminuição dos riscos futuros, evitando a progressão da doença e as agudizações, reduzindo a mortalidade. A cessação tabágica, no doente fumador, é a intervenção com maior capacidade para alterar o curso natural da doença[8] e a terapêutica farmacológica assenta nos fármacos broncodilatadores, isolados ou em associação, preferencialmente por via inalatória, podendo-se associar os corticoides inalados.

Para além da elevada morbilidade e de elevados custos económicos, diretos e indiretos, a DPOC responsabiliza-se por elevada mortalidade, sendo as agudizações a sua principal causa: as agudizações estão na origem da recorrência frequente dos doentes ao hospital, dos internamentos e reinternamentos e contribuem para uma elevada mortalidade intrahospitalar após a alta.[11] O diagnóstico das exacerbações é clínico, à falta de biomarcadores de agudização. Uma exacerbação de DPOC pode ser definida como um evento agudo, caracterizado por um agravamento dos sintomas respiratórios em relação à situação de base, levando necessariamente a uma alteração da medicação. A prevenção das agudizações passa pela vacinação antigripal, prevenção da doença pneumocócica, pela manutenção da atividade física e pelo correto tratamento da DPOC. Assim, dada a dificuldade clínica em prever quer as exacerbações, quer os doentes com maior propensão a agudizar, a identificação dos fatores, associados ao doente e aos cuidados de saúde que, pela sua correção, se possam traduzir em melhoria dos cuidados presta-

dos ao doente deve ser a principal preocupação do médico que se dedica ao tratamento de doentes com esta patologia.

O êxito terapêutico na DPOC depende de múltiplos fatores, mas é essencial uma terapêutica adequada, uma boa adesão (ou concordância, no sentido de aliança terapêutica) e uma correta técnica inalatória. Mas, para além da dificuldade de aplicação das normas internacionais na prática clínica, por parte do médico, há uma multiplicidade de fatores, por parte do doente, ou que radicam na relação médico-doente, e que condicionam a eficácia terapêutica: o doente desconhece o que é a DPOC e desvaloriza os sintomas e a gravidade da doença, aderindo mal à terapêutica. Parece também persistir um conjunto de crenças ou conceitos, tendo por pano de fundo caraterísticas socioculturais e relacionadas com a medicação inalatória que podem constituir fatores de má adesão.

A OMS reconhece a não adesão[12] à medicação como fator de insucesso terapêutico de grande magnitude e um problema comum a vários tipos de situações clínicas. No que se refere à adesão do doente à terapêutica prescrita na DPOC não são conhecidos dados no nosso meio e o conhecimento da adesão é tanto mais importante quanto a DPOC é uma doença crónica. A cronicidade é um fator há muito reconhecido de redução da adesão à terapêutica, estimando alguns estudos que se possa situar nos 50% para algumas situações clínicas.[13] Rand, em 2005,[14] fez uma revisão exaustiva da literatura no que respeita à adesão à terapêutica no doente com DPOC e concluiu que a evidência clínica sobre este tema é muito pouco robusta, mas parece, no entanto, ser pobre e influenciada mais pelas crenças dos doentes sobre medicamentos do que pela gravidade da doença ou por fatores demográficos. Posteriormente, em 2013, Bryant e colaboradores,[15] após uma extensa revisão da literatura sobre este tema, consideraram o conhecimento da adesão ao tratamento, e a sua melhoria, um ponto crítico no tratamento do doente com DPOC e a merecer mais investigação. Em 2014, Boven e colaboradores,[16] numa análise custo-eficácia, concluíram que melhorando a adesão à terapêutica inalatória no doente com DPOC se diminuem os gastos com esta patologia. A adesão à terapêutica pode ser definida como o grau de concordância entre o recomendado pelo prestador de saúde e o comportamento do doente em relação ao regime terapêutico proposto. É um fenómeno complexo e habitualmente visto como um contínuo entre duas atitudes comportamentais extremas, o cumprimento total e a completa recusa, podendo variar na forma e na intencionalidade. Não há consenso sobre o que é uma ótima aderência, uma aderência adequada ou até uma aderência aceitável, nem mesmo um *cut-point* para definição dos aderentes. Se este é um conceito de difícil definição, mais difícil é medir a adesão, até por não existir um "melhor método". À falta deste *Gold-Stardart*, métodos subjetivos *(self-reported)*, como questionários e escalas, são atualmente os mais usados. Apesar de isoladamente terem baixa sensibilidade, parecem ser os mais eficientes e de maior relação custo/benefício de avaliação da adesão, neste caso da *adesão referida*, sobretudo em estudos populacionais. Por este motivo tem sido desenvolvidas medidas psicométricas para este fim. O MAT – Medida da Adesão aos Tratamentos – é uma escala de sete itens, validada para a população portuguesa em 2001,[17] com boa consistência interna, sensível, com boa relação com medidas objetivas de adesão e, respondida numa escala de *Likert*, parece ser um útil instrumento para a sua medida.

Apesar da importância do conhecimento da adesão através do recurso a medidas psicométricas, estas pouco ou nada nos dizem sobre as razões da não adesão e tão pouco se conhece, no nosso meio, o papel desempenhado pelas crenças relacionadas com a medicação inalatória na adesão do doente. Mas a adesão depende primariamente da forma como o paciente acredita no tratamento. Simon[18] estudou os fatores que influenciavam comportamentos relacionados com a saúde, de acordo com o *Health Belief Model*, em doentes asmáticos e com DPOC, tendo verificado que metade cumpria irregularmente a medicação, que a maioria obtinha informação sobre a sua doença e tratamento junto do seu médico, apesar de a Internet desempenhar um papel importante no caso dos doentes asmáticos e que as variáveis sociodemográficas se relacionavam de uma forma pobre com as variáveis comportamentais. Barnestein-Fonseca e colaboradores propuseram um protocolo de estudo,[19] de modo a compreender melhor os fatores relacionados com a adesão e a sua medição para intervir positivamente na adesão ao tratamento no doente com DPOC, explorando os aspetos motivacio-

nais, os aspetos cognitivos e a técnica inalatória. Um instrumento de avaliação de crenças sobre medicamentos, a Escala de Crenças Acerca de Medicamentos, adaptação transcultural da BMQ *(Beliefs About Medicines Questionnaire)*,[20] demonstrou boa consistência interna e estrutura idêntica à versão original. Esta ferramenta, com aplicabilidade à população geral de utilizadores de medicamentos, poderá ajudar a encontrar barreiras práticas à adesão, já que as representações sociais da doença e da terapêutica, nomeadamente a inalatória, são conhecidos fatores funcionais de não adesão intencional.

O êxito terapêutico está também dependente de uma boa técnica inalatória. Várias meta-análises demonstraram que, quando o doente os usa corretamente, os diferentes dispositivos inalatórios (DI) têm efeitos terapêuticos semelhantes. É, assim, importante conhecermos se o doente com DPOC usa corretamente os dispositivos inalatórios e como isso se relaciona com a adesão e com a morbilidade, apesar de não se conhecer um "melhor método" na avaliação da técnica inalatória. Sobre este assunto, mais que a DPOC, tem sido estudada a asma brônquica, e a maioria dos estudos reportam-se apenas à corticoterapia inalatória. Alguns estudos referem-se apenas a um tipo de DI ou comparam um grupo limitado de DI, habitualmente apenas dois. Outros estudos analisam o conhecimento dos DI por parte dos próprios profissionais de saúde. Correia e colaboradores mostraram que uma percentagem significativa de profissionais de saúde, nos Açores, tinha um conhecimento pobre sobre técnica inalatória, falhando muitas etapas imprescindíveis à eficácia terapêutica dos fármacos inalados.[21] Há trabalhos que estudam a intervenção educacional como forma de melhorar a adesão e a técnica inalatória, propondo até o uso de uma *checklist* orientadora da prescrição inalatória. Outros estudos analisam os erros mais comuns com o uso de DI, ou centram a sua atenção no doente idoso com DPOC, mas os trabalhos mais frequentes são sobretudo artigos de opinião, baseados apenas na experiência pessoal e na revisão bibliográfica.

Assim, à falta de um conhecimento robusto que nos permita prever as agudizações da DPOC e a elas nos anteciparmos, o correto tratamento da doença, de acordo com as *guidelines* internacionais, a boa adesão à terapêutica e a manutenção de uma correta técnica inalatória, parecem dever ser os principais motivos de preocupação do médico que trata doentes com DPOC, de modo a reduzir a elevada mortalidade e morbilidade desta doença crónica com tão elevada prevalência na nossa população.

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CONFLITO DE INTERESSES
Os autores declaram não ter conflitos de interesses.

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ABSTRACT

DOES OUR CURRENT TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE REPRESENT THE STATE OF THE ART?

Chronic obstructive pulmonary disease (COPD) is the most common chronic respiratory disease in adults, with an estimated prevalence from 7.6 to 8.9% of the adult population. It is the fourth most common cause of death worldwide. The high mortality from COPD is mainly due to exacerbations requiring hospitalization. We lack robust knowledge allowing us to predict exacerbations of COPD and when and in whom they will occur. Correct treatment, based on the best medical available evidence and knowledge of the reasons for non-adherence, can improve adherence and promote correct inhaler technique. These goals represent the best way to treat patients with COPD and should be the physician's first concern.

Keywords: COPD; Treatment; Guidelines.

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LETTERS TO THE EDITOR

COPD: Evidence-based medicine or the patient-centered medicine?

COPD is the most common chronic respiratory disease. Today it is the 4th highest cause of death worldwide and therefore it should always be considered when a patient has chronic dyspnea, cough with or without sputum production, and a history of exposure to risk factors. The diagnosis always requires a spirometry and the ratio FEV1/FVC (or FEV1/VC) is what is normally accepted as the index that defines airway obstruction.[1] Airflow limitation that is not fully reversible is defined by the Global Initiative for Obstructive Lung Diseases[2] (GOLD) as a post-bronchodilator FEV1/FVC < 0.7, and by the ATS/ERS Task Force position paper[3] as a ratio ≤0.7. However, this diagnostic criterion has been increasingly questioned. Although simpler and easier to use in primary care settings worldwide, some authors have claimed that it can miss the diagnosis in younger, predominantly female individuals where an early diagnosis brings the greatest benefit, and can lead to over-diagnosis of COPD in older men, missing a heart disease diagnosis, or even an asthma diagnosis, which require a different approach. So, they argue that the lower limit of normal (LLN) criterion (FEV1/FVC < LLN) should be used instead. Some authors also propose a low FEV1/FVC ratio in any criteria, coupled with a FEV1 <0.8 of the predicted value.[4] In fact, there is currently no consensus about the best criteria to be used in COPD. In 2010, 150 international experts and 12 international organizations asked GOLD to change its definition of airflow obstruction to LLN criterion,[5] and, in relation to the use of LLN, a recent editorial in the ERJ stresses the need to improve the diagnosis of early COPD.

The goals of the treatment are symptomatic improvement and prevention of disease progression and exacerbations. The high mortality of COPD is mainly due to exacerbations requiring hospitalization. Exacerbations are in COPD what myocardial infarctions are in coronary artery disease[6]: acute, disease modifying, causing high mortality during hospitalization and in the first year after discharge, and decreased quality of life. At present there is neither a good definition nor an agreed classification of exacerbation. Some authors propose 3 levels of exacerbation; home treated, requiring hospitalization and leading to respiratory failure. Others suggest a mild level, requiring no change in treatment or only short-acting bronchodilators, a moderate level, requiring systemic corticosteroids/antibiotics and a severe level, requiring hospitalization. In addition, the usual definition of exacerbation as an event characterized by a change in the patient's baseline dyspnea, cough or sputum beyond day-to-day variability, that needs a change in medication, is difficult to use in clinical practice and other definitions are needed, for operational reasons, such as clinical trials.

For therapeutic success in COPD an appropriate therapy is essential, combined with a good level of adherence and correct inhalation technique. Although the clinical and scientific bases of some guidelines are now increasingly debatable,[7] they represent a standard of care, allowing us to find answers in Evidence Based Medicine and therefore cannot be ignored. However there are numerous other factors[8] relating to the patients themselves or to the doctor–patient relationship, which determine the therapeutic efficacy: the patient is unaware of the nature of COPD,[9] plays down symptoms and the severity of the disease, and a set of sociocultural beliefs or concepts seem to persist in relation to inhaled medication, which can constitute poor adherence factors.

Rand CS[10] did an exhaustive review of the literature with regard to adherence to therapy in patients with COPD, and concluded that the clinical evidence on this topic is not very robust, in fact it seems very poor, and more influenced by the beliefs of patients about the medicines, than by disease severity or demographic factors. Bryant and colleagues[11] consider that knowledge about adherence to treatment, and its improvement is critical in the treatment of patients with COPD. But if adherence is a difficult concept to define, it is even more difficult to measure, because there is no "best way". As well as inadequate knowledge about adherence, little is known regarding the patient's beliefs[12] about medicines, in COPD.

Therapeutic success is also dependent on a good inhaler technique, but we do not know how the patient uses the delivery devices, nor is there a "best method" for assessing the inhalation technique, and there is little evidence about the choice of the optimal delivery method or device for each patient.[13]

Thus, in clinical practice, knowing the best medical evidence, although mandatory, is currently not enough, and

we have to focus heavily on patient education, with respect to illness and treatment, and participation in clinical decisions, allowing for patients' perspectives, their medicine and inhalation device preferences, and also their disease and therapeutic related beliefs. We also need to know the physical and emotional needs of the patients, and to treat the comorbid conditions, in order to achieve a better control of COPD. For this purpose, we emphasize the key role of the patient's family or caregivers, and the importance of a multidisciplinary team in patient-centered medicine. More than the diagnosis and treatment, patient centered COPD care involves working with the patient to provide the best care possible and improvement in their quality of life.

Conflicts of interest

The author has no conflicts of interest to declare.

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Spontaneous pneumomediastinum in pregnancy: A case report

Dear Editor-in-Chief,

Postpartum spontaneous pneumomediastinum (Hamman's Syndrome) is a well-known but rare complication of pregnancy which is potentially lethal. However, current international pneumothorax guidelines do not give any advice on the management of this life-threatening event.[1–4]

We report the case of a 30-year-old woman who came to our attention at the 40th week of her pregnancy. She was a non-smoker and had no history of pulmonary diseases.

During the later part of labor, she suddenly developed facial edema, subcutaneous thoracic emphysema and dyspnea.

Arterial blood gas analysis revealed severe hypoxemia and hypocapnia.

Blood pressure and cardiac rate were normal and sensorium was intact (Kelly score= 1).

Chest CT scan showed a large pneumomediastinum with bilateral pneumothorax (Fig. 1).

The patient was submitted to cardio-respiratory monitoring and treated with oxygen and conservative therapy.

Within five days of hospitalization, the patient's condition improved with complete resolution of the subcutaneous emphysema and a partial reabsorption of both pneumomediastinum and pneumothorax.

After a follow-up of two weeks, chest X-ray turned out to be normal.

Patho-physiologically, the development of pneumomediastinum during spontaneous delivery is linked to the sudden laceration of the alveola due to the increase of intrathoracic and intra-abdominal pressure caused by repeated Valsalva maneuvers (Fig. 2).

The main physiological alterations of the respiratory system that occurred during the last part of pregnancy are mainly the consequence of the progestin stimulation of the respiratory drive and consist of a reduction in the functional

COPD: From the stethoscope to the spirometer

Letter to the editor:

In the world, about 3 billion of people, predominantly women, young girls and small children, are exposed to household air pollution, secondary to indoor cooking with biomass and coal.[1] Because the combustion of solid fuels produces a mixture of air pollutants, from respirable particles to gases, this exposure is associated with chronic obstructive pulmonary disease (COPD), and this association is well documented.[2] During their lifetime, some women can be exposed to biomass smoke for 30–40 years, or 60,000 h of exposure.[3] This can be the biggest risk factor for COPD in the world, even predominates in developing countries.[4] In rural areas, 90% of households continue to use this highly polluting biomass fuel. In 2008, in the Portuguese region of Lisbon, the BOLD study showed a GOLD stage 1 or higher COPD prevalence of 9.2% in never-smokers.[5]

Despite the fact that, within never-smokers, COPD has been neglected and excluded in the majority of large studies,[6] the association observed between the exposure to biomass smoke and COPD is as great as the risk of active smoking. The prevalence of COPD among never-smokers varies widely across the countries, but at least one fourth of patients with COPD are never-smokers. Many are women, in whom this disease is understudied.[7] But cooking with biomass and coal, rather than a recent phenomenon, is an old problem, still persisting in rural areas of many developed countries, as in Portugal, Spain, Canada, Australia or US. Thereby, we wonder why COPD is a disease only recently concern, and usually associated with tobacco epidemic.

In fact, the recognition of emphysema and chronic bronchitis, and the evolution of their knowledge, cover nearly four centuries, since the Bonets's description of ''voluminous lungs'', in 1679.[8] In 1821, Laënnec, the inventor of the stethoscope, describes the emphysema as a disease that was ''very little known'' and ''completely overlooked''.[8] However, since the discovery and use of the stethoscope, he wrote, he believed to be a much more common problem. With Laënnec begins the modern era of COPD. In that time smoking was rare, but urban atmospheric pollution, in particular coal smoke, and domestic pollution from open fireplaces, in houses with poor ventilation, was a well-known phenomena, as was the conditions of work in cotton factories. In 1868, Manchester's first Medical Officer of Health said that the normal condition of the working man of middle age in Manchester was bronchitic.[9] Occupation, domestic pollution and atmospheric pollution were, in the 19th century, well known risk factors for chronic bronchitis and emphysema.

Until recently, the diagnosis of emphysema and chronic bronchitis was based on symptoms of dyspnea, cough and expectoration, and on physical examination of an enlarged chest. The diagnosis of emphysema, according to Ronald Christie, in 1944, should be considered certain in the presence of dyspnea on exertion and of insidious onset, not due to bronchospasm or left ventricular failure, in a patient with physical signs of emphysema. But by the time clinical signs are present, COPD is in a moderate or advanced stage,[10] and we miss not only the early diagnosis but most diagnosis. Furthermore, before the CIBA Guest Symposium,

in 1959, and the American Thoracic Society Symposium, in 1962, there was much confusion regarding the diagnosis of chronic bronchitis and emphysema, and the concept of airflow obstruction was only introduced at that time.[11] Gradually, doctors and scientists concern with the pathology and the clinic moved toward the pathophysiology, giving rise to the actual concept of COPD.

Cigarette mass production began circa 1880, and their consumption has increased until now, but the association with COPD was only established once the latent effects of cigarettes became apparent, in the second half of the 20th century. With the progressive increase of smoking, initially solely in the developed countries, an easier access to the quantification of exposure, and a well-documented association to COPD, tobacco smoking became the most important risk factor for COPD. But COPD, even under the old label of emphysema or chronic bronchitis, was probably very common before tobacco smoking was widespread, although little recognized.

In 1846 Hutchinson invented the spirometer, so important to the diagnosis of COPD, but only recently the industry and technology made possible the emergence of handheld spirometers, accurate and inexpensive, and their spread in the primary care medicine, although there is a lack of accessibility in our country, as suggested by the BOLD study in Lisbon.[5] FEV_1/FVC, more than defining obstruction, is a sensitive test for early stages of airflow limitation, and, when <70%, heralds the onset of rapid decline in FEV_1. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, and the first report issued in 2001.[12] Rather than a new disease, the generalization of these two tools, the spirometer and the GOLD consensus report, enabled showing COPD as a common disease and a leading cause of morbidity and mortality worldwide, giving to COPD importance and visibility.

However, the term COPD is more than a new label for an old disease: is a new concept, as proposed by the GOLD working definition; is chronic and common; is preventable and treatable; is a complex disease based on inflammation, his pathological hallmark; is a heterogeneous disorder, and also heterogeneous in its presentation. And exacerbations and comorbidities contribute to the overall severity. Any individual patient may have emphysema, or peripheral airways disease, or chronic bronchitis, or all of these conditions,[13] but the dominant clinical feature is persistent and usually progressive airflow limitation, that is the hallmark of COPD.

Conflicts of interest

The author has no conflicts of interest to declare.

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COPD: Are we using all the tools we have?

COPD is the most common chronic respiratory disease and represents today the 4th cause of death worldwide; it has an estimated prevalence of 14.2% in Lisbon adult (over 40 years) population.[1] The high mortality of COPD is mainly due to exacerbations requiring hospitalization, and in patients with hypercapnia and respiratory acidosis, the mortality reaches 10%, increasing to 40% in the first year after hospital discharge. The goals of the treatment are symptomatic improvement, and preventing disease progression and exacerbations.

Dyspnoea is the main symptom of the disease, there are several possible measuring instruments but the Medical Research Council Dyspnoea Questionnaire (mMRC) with cross-cultural adaptation to the Portuguese population is the one usually recommended because of its sensitivity and ease of registration. As COPD is a chronic, progressive and multisystem disease, it is also important to understand its impact on patient quality of life and well-being, and so the CAT (COPD Assessment Test) was designed to measure these, and its use is recommended by international guidelines.[2] These tools cannot be ignored in daily clinical practice.

Adherence to treatment, and its improvement, is a critical issue in the treatment of patients with COPD. In the absence of a "best way" to measure adherence, subjective or self-reported methods, such as those exemplified by the MAT – Measurement of Treatment Adherence, validated for the Portuguese population in 2001,[3] should be more widely used. MAT is a psychometric measure which is easy to use in clinical practice providing good sensitivity and specificity.

Despite the importance of knowing about adherence, some psychometric measures say little or nothing about the reasons for non-adherence. An instrument of evaluation of the beliefs about medicines, Escala de Crenças Acerca de Medicamentos, cross-cultural adaptation of the BMQ-Specific (Beliefs About Medicines Questionnaire)[4] into Portuguese for the general population of medicine users, can help discover practical barriers to adherence to inhaled therapy. The BMQ, an eleven-item questionnaire with a five-item Necessity scale and a six-item Concerns scale, essentially studies intentional non-adherence, and it is easy to use in clinical practice.

Therapeutic success is also dependent on a good inhaler technique, it has been demonstrated by meta-analysis that when the patient uses them correctly, the various inhaler devices have similar therapeutic effects.[5] We need to demonstrate at all medical visits how to use the inhaler devices correctly, but we have also to check how the patient uses it. Checklists[6] with the number of steps for the correct use of devices, including a critical step which if not performed would result in no drug delivery, can be useful in clinical practice. The choice of the inhaler device is so important that some authors propose a single algorithm or checklist to guide selection[7] in primary care practice.

The role of pulmonary rehabilitation in COPD has been carefully evaluated, with some benefits showing an A level of evidence. Pulmonary rehabilitation improves exercise capacity and health-related quality of life, reduces the exacerbations requiring hospitalizations and improves recovery after hospitalization. In fact, pulmonary rehabilitation is regarded as one of the most effective non-pharmacological treatments.[8] However, according to GOLD guidelines, physical activity is recommended for all patients with COPD only because it seems intuitively correct, but without COPD-specific evidence to support any recommendations. The 2015 CHEST and CTS Guideline,[9] a document fully describing the current state of knowledge regarding the prevention of acute exacerbation of COPD, like many other papers, do not include any recommendations regarding physical activity in COPD. So, for therapeutic success we also need evidence concerning the importance of regular physical activity in all stages of COPD, outside the context of pulmonary rehabilitation, and how to get patient adherence, which can a difficult task.

Thus, in the absence of robust knowledge that would allow us to predict exacerbations, the main cause of mortality of COPD, using these tools gives the physician guidance about correct treatment according to the best medical evidence, and can improves adherence, aid device selection and correct inhalation technique.

Conflicts of interest

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Dogmas and Medical Beliefs in COPD☆

Dogmas y Creencias Médicas Acerca de la EPOC

To the Editor,

Physicians who spend their lives treating patients have always lived with the social representations of health, disease, and medication. These social representations are construct images of a natural reality and are as old as the disease itself. Based on affective and cognitive predispositions, and often inhabited by fears, beliefs, and magical and supernatural elements, the function of social representations is to make something unusual and unknown familiar to the patient.

Chronic obstructive pulmonary disease (COPD) and inhaled medications do not escape these social representation systems. The theory of social representations was first formulated by social psychologist Serge Moscovici in a paper published in France in 1961.[1] I wonder, however, if COPD is not itself also represented in doctors who usually treat this complex disease in hospitals or in primary health care, and if their representation is haunted by dogmas and medical beliefs.

In COPD, as in many other chronic diseases, non-adherence to medication is a critical issue.[2] Non-adherence to inhaled therapy in COPD has been called a high magnitude problem and a major factor of therapeutic failure, but only a limited number of studies have specifically examined adherence in patients with COPD therapy, and most research was conducted before the widespread availability of inhaled medications taken once or twice daily. In some original articles, many patient characteristics, such as the degree of bronchial obstruction or symptoms like dyspnea, are missing. However, it is well known that dyspnea, fear of dyspnea, and feelings of vulnerability contribute to better adherence to medication. Poor adherence to therapy, therefore, does not seem to make much sense from a clinical point of view, especially in these very symptomatic patients with COPD Gold stage B or D. Poor medication adherence in COPD has become a dogma that may well not correspond to reality, at least in patients with greater severity, and as such remains an open issue that merits further investigation.[3]

Another persistent dogma is the belief that once-daily medication is the best alternative for all COPD patients,[4] because it is easier to use and improves compliance. As effort dyspnea is the main symptom of COPD, the most commonly recommended schedule for bronchodilator therapy administration is early morning. Many patients, however, experience an evening aggravation or at least a fear of a nocturnal aggravation of dyspnea. Patients use inhalers because they feel relief from their dyspnea. As therapy in COPD is to some extent driven by symptoms, a twice-daily bronchodilator regimen may be more suitable in certain patient groups, such as those with exacerbating phenotypes or asthma-COPD overlap syndrome (ACOS).

The introduction of inhaled corticosteroids (ICs) to COPD therapy has been widely debated in medical and scientific communities. Weaning from ICs in COPD, and 4 other important randomized trials that evaluated the effect of IC discontinuity (COPE, COSMIC, INSTEAD, and WISDOM), have also created considerable controversy.[5] However, ICs in association bronchodilators have long been a mainstay of treatment for COPD. It was only the recent introduction of new long-acting bronchodilators, specifically developed for the treatment of COPD, and new fixed combinations of LABA-LAMA that led to the current debate in the medical community.[6] There is now enough clinical evidence to challenge the widespread use of IC in COPD in patients who do not suffer from exacerbations and who have not shown any benefit with ICs.[7]

The science of medicine is characterized by its evidence-based approach and its revisibility. As a human activity, it is necessarily subject to dogmas and beliefs. Whether it was the medical representation of COPD as an inflammatory disease or the medical belief of a real benefit to the patient that led to the widespread use of ICs in COPD is still unclear. However, the medical community must wonder how real-life patients in real-life situations are represented in large randomized studies (often double-blind, placebo-controlled trials) supporting evidence-based medicine.

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COPD: A controversial disease?

COPD is today the most common chronic respiratory disease and a growing cause of worldwide morbidity and mortality, with many cardiovascular, musculoskeletal, metabolic and mental sequelae, some usually referred to as comorbidities. According to some authors, chronic obstructive pulmonary disease is not a disease in the true sense of the word, but a very popular acronym.[2] The defining characteristics of a disease are clinical symptoms and signs, structural abnormalities, function disorders, and causation or etiology,[3] but COPD is a heterogeneous collection of different pathophysiological processes that result in the development of chronic and usually progressive airflow limitation,[4] as defined by GOLD.[5] Poor lung development, excess lung damage, airway remodeling and deficient lung repair are different processes affecting the development and progression of COPD. The Fletcher–Peto curve remains a landmark reference for the natural history of COPD, but because of the heterogeneous nature of the disease, several natural histories are possible, and there may be patients progressing on different natural history trajectories, from slowly progressive to rapidly progressive natural histories.[6] Now we recognize that the term COPD brings together a number of entities with different clinical and pathophysiological features, hence the emphasis given to the great diversity of phenotypes of COPD.[7] This emphasis in COPD phenotypes was born both from the current trend of doing a patient-centered medicine and from the need to understand the disease in its heterogeneity.

COPD is characterized by persistent airway limitation that is not fully reversible and is usually progressive.[8] Obstruction is defined by the GOLD as a post-bronchodilator $FEV_1/FVC < 0.7$, but this criterion of obstruction has been increasingly questioned, and because there is currently no consensus about the best criterion to be used in COPD,[9] this remains a matter of continuous debate in literature.[10] Furthermore, even though obstruction is a landmark of the disease, some authors wonder if obstruction does always need to be present in early stages, or if emphysema, in the absence of obstruction, represents COPD.[4] However, in any stage of the disease, and despite obstruction not being fully reversible, bronchodilators remain the cornerstone of the treatment, since they usually cause a significant clinical improvement, even without significantly modifying FEV_1.[11]

Inflammation plays a central role in the pathogenesis of COPD, and keeps on after smoking cessation, but there still persists the concept of COPD as a steroid-resistant disease.[12] Conflicting with this, clinical evidence shows an effect of inhaled corticosteroids (ICS) on the rate of COPD exacerbations and in quality of life,[13] and consensus was reached regarding the indication of ICS in ACOS and frequent exacerbating phenotypes.[14] ICS have some adverse effects, the increased incidence of pneumonia being the best-documented treatment risk,[15] but, paradoxically, the risk of dying is not higher in ICS treated patients. Nevertheless, ICS have been widely used, with more than 70% of COPD patients being treated with ICS,[16] and observational studies have shown the persistence of an excessive use of ICS in

mild COPD. This extensive use is discrepant from treatment guidelines, but the use of ICS in COPD is still an important matter of debate, as is the question of the effects of discontinuation of ICS.

In the general population, the benefits of physical activity are well documented. Physical inactivity is a central problem in COPD patients in all severity stages of the disease, it plays a crucial role in the development of COPD comorbidities and it is the best predictor of all-cause mortality in these patients.[17] Physical activity can be, along with smoking cessation, the best cost-benefit measure to prevent disease progression, comorbidities and mortality. As decreased physical activity is already present early in the development of the disease, the implementation of regular physical activity should be an important secondary prevention strategy. However, GOLD and many other guidelines do not include any recommendations regarding physical activity in COPD, which take into account the physical exercise requirements in relations to duration, frequency and intensity. The recently published ATS/ERS statement,[6] regarding the types of research which will have the greatest impact on patient-centered outcomes in COPD, does not refer to any research recommendation regarding physical exercise, except for pulmonary rehabilitation.

Despite all these controversies, COPD is a disease defined by a function disorder. Although heterogeneous and associated with a chronic inflammatory response in the airways and lungs, COPD is an obstructive disease; the airflow limitation is chronic, not fully reversible and usually progressive. In medical discourse, a disease is a sum of abnormal phenomena that place a living organism in a biological disadvantage, and its defining characteristics may only be pathophysiological.[18] The name of a disease is a conclusion of a diagnostic process, the purpose of which is more to simplify and clarify the medical discourse than to decide a treatment for a given patient. In pulmonary medicine, it is important to distinguish between the connotation of the word obstruction as a function disorder, or a disease like COPD.

Conflicts of interest

The author has no conflicts of interest to declare.

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Lungs and Breathing

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COPD or functionally COPD?

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The recent paradigm shift in the treatment of COPD has led many physicians to withdraw inhaled corticosteroids to a significant group of patients with obstructive airways disease with no recent history of exacerbations. Many of these patients, until then symptomatically stabilized, became more acute, and this persistence in ICs withdrawing seems to be justified by complying with international guidelines. The basis of this problem seems to lie in the chronic confusion between COPD and non-reversible or only partially reversible obstruction of the airways, that is, a functionally COPD. Moreover, safe withdrawal or deprescribing of ICS in patients with COPD should be done according to sound criteria [1].

In medical discourse, the name of a disease refers to a set of abnormal phenomena, exhibited by a group of individuals in such a way as to place them at a biological disadvantage [2]. The diagnostic process is the objective assessment of this biological disadvantage, the conclusion of which is the name of the disease. Disease is thus an intellectual elaboration, since it does not exist separately from the subject who suffers from it. Its main function is to facilitate the communication within the medical and scientific community.

The definition of any disease may be based on aetiology, on a clinical description, on a structural abnormality, or on a disorder of function. According to GOLD, updated in 2018, COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases [3]. This consensus definition contains all the defining elements of a disease. However, the significant overlap between the clinical, functional, and structural characteristics of patients with asthma diagnosis, leads to difficulty in differential diagnosis.

A persistent obstruction of the airways is essential for the diagnosis of COPD and is also the easiest feature to document in clinical practice. However, it is not pathognomonic of COPD. In asthma patients, the airway inflammation and airflow limitation may lead to lung remodelling, resulting in irreversible airflow obstruction [4]. Because of that, some authors refer a significant association between active asthma and the subsequent development of COPD [5]. More recently, this association or progression is called Asthma COPD Overlap (ACO). Patients with fixed airflow limitation show distinct pathologic and functional characteristics, depending on a history of either COPD or asthma [6]. They also have a different response to steroids and a different prognosis. In fact, different airways diseases may exhibit a chronic airflow limitation, and chronic obstructive lung disease, as defined, is more than a disorder of function.

A definition of a disease is an important matter in medicine, but the role of medicine is mainly to help patients. Patients with airway disease seek medical attention not because of asthma, COPD or airflow limitation. Some patients have respiratory symptoms with significant variability, although they have periods in which they feel completely well. Some other patients seek medical attention because, although their symptomatology is stable, their dyspnoea is such that it severely impairs their quality of life. Many patients, however referring variation or instability of symptoms beyond physical exertion, are always more or less symptomatic. In any group of individuals with airway disease we should question about the severity of the disease and its impact on well-being; the activity level of the disease; the treatable traits in as particular patient or group of patients [7]; and which should be treated or prevented. Patient health status is what matters in medicine, and the added value are the interventions in order to improve patient's health status. Guide-lines are important tools, based in the best medical evidence, but should be questioned, as should the current diagnosis. After all, we currently have only three major groups of drugs to treat COPD patients: muscarinic antagonist bronchodilators, β-agonist bronchodilators, and inhaled corticosteroids. And these three groups are the same ones we use to treat asthma.

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The etiopathogenesis of OFTP remains unclear, and multiple hypotheses have been proposed. Sehgal and colleagues retrospectively analyzed a series of 54 cases, and found most pseudomembranes to be located in the subglottic region, the narrowest part, where the mucosa is most sensitive during intubation. However, not all cases are located below the glottis.[3] Deslee and colleagues suggest cuff-induced ischemic damage as a possible cause, althought his theory does not explain cases in which high-volume low-pressure tubes were used.[4] In 2013, Alvarez-Maldonado and colleagues reported a case of pseudomembrane formation following percutaneous dilatational tracheostomy (PDT).[5] In our case, OFTP occurred after silicone stent insertion. Both cases show that various factors may be related to OFTP, including mechanical stimulus and local aseptic inflammation. To sum up, OFTP is an uncommon complication after silicone stent insertion, and can be fatal if not diagnosed promptly. Bronchoscopy is essential in the management of OFTP.

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Is COPD Control a Useful Concept? Assessing Treatment Success by Evaluating COPD-Related Health Status☆

¿Es útil el concepto de control de la EPOC?: evaluación del éxito terapéutico a partir de la valoración del estado de salud en relación con la EPOC

To the Editor,

In most chronic diseases, treatment decisions are usually based on whether control has been achieved in a given patient. This concept can have some clinical utility in COPD. However, there is currently no definition of well-controlled disease, and no objective criteria to define control in COPD or any objective tools to measure it.[1] In fact, it is still unclear how to evaluate response to treatment in COPD.[2]

In asthma, control is an important concept, because severity is assessed retrospectively from the level of treatment required to control the disease.[3] However, in asthma, the concept of control is easily confused with the concept of severity, as they represent overlapping dimensions.[4] This is not the case in COPD, and GOLD 2016, unlike previous versions, recommends using the Clinical COPD Questionnaire[5,6] in addition to CAT and/or mMRC as a tool for evaluating symptoms and assessing COPD health status, not as a direct measure of COPD control.[7]

Patients with COPD seek health care mostly due to exertional dyspnoea and limitation of physical activity: breathlessness is the most common symptom limiting exercise capacity, and exercise intolerance or decreased physical activity are present from the beginning of the disease.[8] The degree of physical activity is the best predictor of all-cause mortality,[9] and COPD can be understood as an exercise intolerance disease that can impact daily activities. From the patient's point of view, there should be several therapeutic successes in COPD, given the different perceptions of dyspnoea, variability in physical activity and general well-being.

COPD is characterised by persistent airway limitation that is usually progressive and not fully reversible. The term COPD brings together a number of entities with different clinical and pathophysiological features, and the treatment goals are symptomatic improvement, prevention of exacerbations and disease progression. The high mortality associated with COPD is mainly due to exacerbations requiring hospitalisation. Acute exacerbations also contribute to worsening of pulmonary function, change the trajectory of the disease, and contribute to impairment of health-related quality of life. Indeed, control will always be a difficult concept to define in COPD. However, based on the definition of the disease and the goals of treatment, there are probably two main domains in COPD control: a functional domain, focussed on FEV1, and a clinical domain, focussed on exacerbations.

Nevertheless, the therapeutic definition of success should not only be based on control as a biomedical concept, but rather on a multidimensional dimension, a general COPD-related health status, that should incorporate the patient's perspective, considering also the "quality of life" dimension.

As control of symptoms is insufficient to control the disease and its progression, the patient has a limited capacity to define therapeutic success in order to participate in clinical decision-making: control is thus a limiting biomedical concept. To define therapeutic success, therefore, we also need to take in account the idea of patient well-being.

COPD is a chronic and incurable disease, and although it is unlikely that most patients will remain asymptomatic, their symptoms improve with continuous bronchodilator use. The best possible improvement in symptoms and lung function, and the absence of exacerbations, seems to be more similar to the notion of controlled disease, but it is certainly part of therapeutic success. The idea of therapeutic success is useful, because it is linked to the concept of value.[10] Value in medicine must be defined in terms of the patient: it is the patient's health outcomes that matter. In

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clinical practice, however, it is important to define and manage the determinant factors of therapeutic success in COPD. There is a need to personalise treatment strategies,[11] and four goals must be achieved. First, we have to assess the patient in a multidimensional way, according to the severity of the disease, its activity, future risk and impact on the patient, including their well-being. This allows us to define treatable clinical characteristics and assess future risk, and helps us tailor treatments to individual patients.[12,13] Second, we have to evaluate the patient's perspectives and beliefs about the treatment and the disease.[14] Third, it is important to prescribe the correct treatment, based on the best medical evidence, taking in account pulmonary and extra pulmonary factors, the patient's perspective and their behaviours/lifestyle. And fourth, we should monitor the treatment, assess and improve adherence, ensure correct inhalation technique and monitor the patient's well-being.

Rather than assessing treatment success based merely on the level of control that has been achieved, we should move to a more comprehensive concept by assessing COPD-related health status and evaluating the changes or the maintenance of a certain level of quality of life based on pre-established treatment goals. Deciding which tool or set of tools to use is another matter and should be discussed in another paper.[15]

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Pulmonary Mucormycosis at Onset of Diabetes in a Young Patient☆

Mucormicosis pulmonar en paciente joven con inicio de diabetes mellitus

To the Editor,

Mucormycosis is an infection caused by filamentous fungi that presents in different forms: rhinocerebral, pulmonary, renal, cutaneous, and gastrointestinal. The species *Rhizopus oryzae*, responsible for 70% of cases, is the most frequently isolated organism.[1] Risk factors for developing mucormycosis include blood diseases, diabetes mellitus with poor metabolic control, solid organ or hematopoietic transplantation, neutropenia, injury, iron overload, and severe burns. It is unclear whether the chronic use of corticosteroids predisposes patients to developing mucormycosis. In recent years, we have witnessed an increase in the incidence of this entity due to population aging, which goes hand in hand with an increase in the above-mentioned risk factors.[2,3]

We report the case of a 29-year-old woman, smoker of 10 pack-years, with recent onset of diabetes mellitus type 1 (ketoacidosis the week before presentation of this clinical episode). She consulted due to a few hours history of dyspnea, fever 38 °C, pain in the right flank, cough and rust-colored expectoration. Auscultation revealed crackles in the right lung base. Clinical laboratory tests showed significant leukocytosis (30 100/μl) and elevated CRP (224 mg/l). Consolidation of the right lower lobe was observed on chest radiograph. The patient was diagnosed with community-acquired pneumonia, and empirical antibiotic therapy was started. The chest computed tomography (CT) scan showed consolidation of the pulmonary parenchyma in the right lower lobe, with the formation of a thick-walled hypodense lesion containing air bubbles, with axial diameters measuring 6.1 cm×4.2 cm, consistent with an abscess (Fig. 1A). During hospitalization in the general

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and the blind pleural biopsy revealed nonspecific pleuritis. Due to symptomatic persistence and pleural thickening causing pulmonary restriction, she underwent pulmonary decortication and parietal pleurectomy. Pleural histological examination revealed epithelioid cells proliferation with atypia and positive for the CD34 marker, favoring the diagnosis of epithelioid hemangioendothelioma (Fig. 1D). The thoraco–abdominal–pelvic CT did not show other alterations. Chemotherapy was initiated with Doxorubicin but the patient died after the first cycle, 6 months after admission.

Primary thoracic sarcomas are tumors derived from mesenchymal cells, they represent 5% of all thoracic neoplasms and may involve lung, pleura and mediastinum.[2] The leiomyosarcoma and epithelioid hemangioendothelioma with pleuropulmonary origin are two extremely rare types of these tumors that, due to the clinical and histological similarity to other pleural neoplasms, are often difficult to diagnose, with most of the cases diagnosed by surgical biopsy.[3,4] The pleuropulmonary leiomyosarcoma usually presents as a nonspecific pleural mass and/or effusion with pulmonary involvement as a well defined nodule with smooth margins, necrotic mass or endobronchial lesions.[2,3] Some risk factors have been identified, namely previous chemotherapy or radiation therapy and environmental or occupational exposure.[2] It is characterized by malignant spindle cells with immunohistochemical staining for smooth muscle actin, vimentin and desmin.[2,3] The treatment of choice in the limited disease is surgical resection associated with chemotherapy and/or radiation assessed on a case-by-case basis, depending on the histological grade and the clinical stage.[2,3] In the advanced disease only chemotherapy is recommended.[3] The median survival for patients with extensive disease is about 12 months.[3] The pleural epithelioid hemangioendothelioma has vascular origin and usually is manifested by unilateral pleural effusion and nodular pleural thickening.[4,5] The clinical presentation is variable, however, chest pain, dyspnea and cough are consistent symptoms.[4] Although risk factors are unclear, cases have been described that follow exposure to occupational contaminants, such as roofing material, industrial exposures, cheese making, and asbestos.[6] It is characterized by cords and nests of epithelioid cells similar to endothelial cells, associated with a myxohyaline matrix and immunoreactive for CD34, CD31, vimentin and factor VIII.[2,4] Surgical resection is recommended but, when impracticable, chemotherapy has been used, although not uniformly.[4] Compared to the pulmonary form, the pleural epithelioid hemangioendothelioma usually has an aggressive clinical course and a poor prognosis.[5,7] The authors describe two patients with rare causes of pleural effusion, illustrative of the diagnostic difficulty and aggressiveness of these tumors.

Conflicts of interest

The authors have no conflicts of interest to declare.

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COPD and physical activity

In the general population, the benefits of physical activity (PA) are well documented, and include primary prevention and control of many chronic diseases, such as metabolic or cardiovascular disease. Being physically active preserves bone mass and muscle strength, promotes well-being, cognitive function and quality of life. The American College of Sports Medicine states that healthy adults aged 18–65 years[1] need a minimum of 30 min of moderate aerobic exercise per day, five days a week, and the British Association of Sport and Exercise Sciences advises at least 150 min of moderate-intensity aerobic activity each week, or 75 min of vigorous-intensity aerobic activity per week.[2] Adults not meeting these values should be considered as insufficiently active. However, according to GOLD guidelines,[3] PA is recommended for all patients with COPD just because it seems intuitively correct, given the overall population benefits, but without COPD-specific evidence to support any recommendations. On the other hand, pulmonary rehabilitation (PR) has been carefully evaluated: it improves exercise capacity, recovery after hospitalization and reduces the

exacerbations requiring hospitalizations. The 2015 American College of Chest Physicians and Canadian Thoracic Society Guideline,[4] the ALAT – 2014 COPD Clinical Practice Guidelines,[5] and many other papers, do not include any recommendations regarding physical activity in COPD. However, for primary prevention, treatment and control of many other diseases, such as cardiovascular diseases or hypertension, recommendations have been developed, taking into account the physical exercise requirements in relation to duration, frequency and intensity. For COPD patients there is an emerging need not only for recommendations, but for practical interventions that would increase physical activity which, combined with smoking cessation and pharmacological treatment, could prevent disease progression, comorbidities and exacerbations.

Physical inactivity is a central problem in COPD patients and plays a crucial role in the development of COPD comorbidities. Being physically active is associated with a reduced risk of hospital admission and mortality,[6] and this is the best available evidence, although moderate, concerning PA and COPD. More low-intensity physical activity reduces the risk of hospitalization, but daily high-intensity PA does not generate additional benefits.[7] Because of the increased exertional dyspnea due to pulmonary function and gas exchange abnormalities, the patients decrease their physical activity, and deconditioning and muscle weakness are physiological consequences. Patients with severe and very severe COPD carry out their daily activities in fewer and shorter bouts than those in mild and moderate stages.[8] However, PA is a multidimensional issue and it is the result of a complex interaction of many factors, such as socioeconomic status, more or less sedentary occupation or patients living alone or with family members.[9]

A sedentary lifestyle is present in all stages of severity of COPD. Decreased PA is already present in the early stages of the disease development, and worsens as the disease severity progresses. Many patients with COPD (30%) did not achieve 30 min of walking time per day, and are effectively housebound. They not only walk for less time per day, but they also walk 25% slower than healthy people, and they spend 12% of the day-time lying down, compared to 4% for healthy elderly people.[10] But COPD patients are capable of bouts of moderate-to-vigorous physical activity. The decline in PA level is associated with increasing airflow limitation, but it is not significantly associated with changes in exercise capacity: avoiding activities is a strategy for avoiding symptoms. These two observations make the improvement of PA feasible in clinical practice.

Patients with COPD are less physically active than healthy subjects, but it is unclear which are the determinants and outcomes of this reduced activity.[11] Comorbidities contribute to impaired functional exercise capacity,[12] but we were not able to establish age, socioeconomic or cultural status, dyspnea, FEV1 or BMI as determinants of reduced activity, nor dyspnea, FEV1, exercise capacity or exacerbations as outcomes of reduced activity. The second question is how much physical activity is needed to obtain health benefits in sedentary patients with COPD, but individualized physical activity recommendations will probably be more suitable for these patients, adapting the intensity to the patient's aerobic fitness level.[13] A third question, and challenging one, is whether the decline in PA can be reversed in patients with COPD.[14] A final problem is the lack of knowledge about the daily PA in the real life of stable COPD patients, and the lack of knowledge about the best tools for PA assessment: self-report, like the Minnesota Leisure Time Physical Activity Questionnaire, or objective measures, such as the use of a pedometer or accelerometry-based motion sensor.

Pulmonary rehabilitation (PR) is regarded as one of the most effective non-pharmacological treatments in COPD patients,[15] with clear benefits in the pre/post-exacerbation setting, but acceptance and uptake of pulmonary rehabilitation following an acute exacerbation are very poor, and many patients refuse referral to post-acute exacerbation PR because of practical or psychosocial barriers.[16] Instead, regular PA is available to all patients. Physical activity, objectively measured,[17] is the best predictor of all-cause mortality in patients with COPD, with a linear association between PA and mortality. As a predictor of mortality, PA is better than BODE or ADO indexes, malnutrition, muscle wasting, healthy status, cardiac function, depressive symptoms or dyspnea. Physical Activity, outside a pulmonary rehabilitation program, such as domestic, occupational and everyday activities for independent living, and physical exercise, inside and outside their homes, in light, moderate or vigorous intensity, can, together with smoking cessation, become the best way of preventing disease progression, comorbidities and exacerbations of COPD. We need pharmacological and nonpharmacological strategies to overcome the difficulties in the implementation of regular physical activity, but improving the patient's self-management education and the relationship of trust between the patient and the physician[18] may be the most important of all.

Conflicts of interest

The author has no conflicts of interest to declare.

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Discordance between old and new criteria for stratifying patients with COPD

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TO THE EDITOR:

Medical decisions must be based on accurate patient evaluations and on robust scientific information. The objective of clinical guidelines is to produce useful recommendations by identifying the most relevant scientific information that should be adapted and applied (with caution) in individual patients. This is particularly true in COPD, a highly complex, heterogeneous disorder. The objective of this study was to evaluate how the questionnaires used in symptom evaluation and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD assessment tool can affect COPD classification.

This was a cross-sectional study conducted at the Outpatient Pulmonary Clinic of the *Hospital da Senhora da Oliveira*, in the city of Guimarães, Portugal. We included consecutive patients over 40 years of age who had been diagnosed with COPD according to the GOLD criteria[1] and in whom the disease was stable. The study was approved by the Research Ethics Committees of the *Hospital da Senhora da Oliveira* and of Minho University, in the city of Braga, Portugal, as well as by the Portuguese Data Protection Authority. All participating patients gave written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[2]

We applied a questionnaire designed to collect demographic and clinical data. Symptoms were evaluated with the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) scale (for dyspnea). The number of episodes of acute exacerbation of COPD (AECOPD) in the last year was evaluated. We defined AECOPD in accordance with the GOLD criteria: as an acute worsening of respiratory symptoms that results in the need for additional treatment, as well as prompting an unplanned medical visit. All participants underwent pulmonary function tests in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society,[3,4] and the results were referenced by using the Global Lung Function Initiative predictive equations.[5] Statistical analyses were then performed.

We studied a total of 303 outpatients with COPD. The main demographic, clinical, and functional characteristics of the patients are shown in Table 1. Only 207 patients (68.3%) completed the CAT and mMRC questionnaires. Applying the proposed GOLD cut-off points for degree of dyspnea (mMRC grade) or level of symptom severity that requires regular treatment (CAT score), we found discordance between the two measures in 47 (22.7%) of the 207 patients: 32 (15.5%) were categorized as group A and B; and 15 (7.2%) were categorized as group C and D. In 38 of those patients, the CAT score was ≥ 10 and the mMRC grade was < 2, whereas the other 9 patients presented an mMRC grade ≥ 2 and a CAT score < 10. The distribution of patients and the mean FEV_1 (% of predicted) in each GOLD group, for the two different (2016 and 2017) versions of the GOLD guidelines are also presented in Table 1. When we applied the 2017 GOLD criteria, 74 patients (24.4%) were moved from a higher severity group to a lower severity group.

In the present study, there was significant discordance between the CAT scores and mMRC grades, showing that the impact of COPD goes beyond just dyspnea. Therefore, in the 96 patients who did not complete the CAT, the symptomatic impact might have been undervalued and the proposed treatment might have been significantly different than what they really needed. These observations are consistent with those of other studies.[2] In a study conducted in Spain, the 2011 revision of the GOLD guidelines, which leaves the choice of method for determining the symptomatic impact (mMRC scale or CAT) up to the physician, was evaluated in terms of the comparison between the two measures.[6] The authors found that the classification of COPD patients varied depending on the measure employed, more than 25% of patients being classified in different "horizontal" categories, with different proposed treatments.

The GOLD ABCD assessment tool is currently used in order to guide pharmacological treatment. We observed discordance between the 2016 and 2017 revisions of the GOLD guidelines in 24.4% of the patients in our sample. Many of them, previously classified as belonging in group C or D, were reclassified as belonging in group A or B, for which the proposed pharmacological treatment is significantly different. Our data are corroborated by those of previous studies. One recent study compared the 2011 and 2017 revisions of the GOLD ABCD assessment tool in a sample of 1,532 patients with COPD.[7] The authors found that approximately 47% of the 1,070 patients who were classified in the higher-severity groups when the 2011

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Table 1. Demographic, clinical, and functional characteristics of patients with COPD, together with a comparison between the 2016 and 2017 Global Initiative for Chronic Obstructive Lung Disease criteria in terms of the distribution of patients and mean FEV_1.[a]

Characteristic	(N = 303)
Male gender	241 (79.5)
Age, years	67.5 ± 10.2
Age ≥ 65 years	186 (61.4)
≤ 3 years of schooling	89 (29.4)
Monthly income < €530	197 (65.7)
Smoking history, pack-years	49.3 ± 32.4
mMRC scale grade ≥ 2	185 (61.1)
CAT score ≥ 10	152 (72.4)
≥ 2 episodes of AECOPD in the last year	115 (38.0)
Post-bronchodilator FEV_1, % of predicted	53.2 ± 19.7
GOLD 2016	
Group	
A	51 (16.8)
B	66 (21.8)
C	23 (6.6)
D	163 (53.8)
FEV_1, % of predicted, by group	
A	76.17 ± 14.20
B	65.76 ± 12.81
C	47.01 ± 14.98
D	41.78 ± 19.68
GOLD 2017	
Group	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)
FEV_1, % of predicted, by group	
A	66.67 ± 20.07
B	53.61 ± 17.45
C	59.20 ± 21.75
D	43.40 ± 16.02

[a]Values expressed as mean ± SD or as n (%). mMRC: modified Medical Research Council; CAT: COPD Assessment Test; AECOPD: acute exacerbation of COPD; and GOLD: Global Initiative for Chronic Obstructive Lung Disease.

revision was used were reclassified into lower-severity groups, leading to treatment de-escalation, when the 2017 revision was used. Tudoric et al.[8] compared the 2016 and 2017 GOLD criteria, demonstrating two "vertical" shifts in the distribution of patients with COPD, more than one third of the patients being reclassified from group D to group B when the 2017 criteria were applied.

Medical decisions and pharmacological treatment can be significantly different when distinct validated tools, such as standardized questionnaires and clinical guidelines, are used. The undervaluation of symptoms can result in a greater need for rescue medication, lower quality of life, or lower exercise capacity. Nevertheless, the transition from the 2016 to the 2017 revision of the GOLD ABCD assessment tool would be expected to have a significant effect on therapeutic strategies. The worsening of the prognosis in groups A and B, due to the higher mean airflow limitation, is likely to make any acute exacerbation more serious. For example, the discontinuation of inhaled corticosteroids can be harmful in some of these patients.

Standardized questionnaires, such as the CAT and mMRC, should be used in concert, and the results should be integrated into a detailed clinical history. The changes in the classification of COPD severity in the 2017 revision of the GOLD ABCD assessment tool must be applied with caution to avoid undertreatment.

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Discordância de critérios novos e antigos de classificação de pacientes com DPOC

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AO EDITOR,

As decisões médicas devem se basear em avaliações precisas dos pacientes e em informações científicas robustas. O objetivo das diretrizes clínicas é fornecer recomendações úteis por meio da identificação das informações científicas mais relevantes, que devem ser adaptadas e aplicadas (com cautela) em cada paciente. Isso é particularmente verdadeiro no caso da DPOC, uma doença heterogênea e altamente complexa. O objetivo deste estudo foi avaliar como os questionários usados na avaliação dos sintomas e a ferramenta de avaliação ABCD da *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) podem afetar a classificação da DPOC.

Trata-se de um estudo transversal realizado no Ambulatório de Pneumologia do Hospital da Senhora da Oliveira, na cidade de Guimarães, em Portugal. Foram incluídos pacientes consecutivos com mais de 40 anos de idade, diagnóstico de DPOC de acordo com os critérios da GOLD[1] e doença estável. O estudo foi aprovado pelos Comitês de Ética em Pesquisa do Hospital da Senhora da Oliveira e da Universidade do Minho, na cidade de Braga, em Portugal, bem como pela Comissão Nacional de Proteção de Dados. Todos os pacientes participantes assinaram um termo de consentimento livre e esclarecido. Seguimos as diretrizes *Strengthening the Reporting of Observational Studies in Epidemiology*,[2] cujo objetivo é aprimorar a apresentação de resultados de estudos observacionais.

Aplicamos um questionário criado para coletar dados demográficos e clínicos. Os sintomas foram avaliados por meio do *COPD Assessment Test* (CAT, Teste de Avaliação da DPOC) e da escala modificada do *Medical Research Council* (mMRC) para dispneia. Foram também avaliados os episódios de exacerbação aguda da DPOC (EADPOC) no ano anterior. Definimos EADPOC de acordo com os critérios da GOLD, isto é, piora aguda de sintomas respiratórios e, consequentemente, necessidade de tratamento adicional e consulta médica não planejada. Todos os participantes foram submetidos a testes de função pulmonar realizados de acordo com as recomendações da *American Thoracic Society* e da *European Respiratory Society*,[3,4] e os resultados foram comparados com os valores de referência obtidos por meio das equações preditivas da *Global Lung Function Initiative*.[5] Foi então realizada a análise estatística.

Estudamos 303 pacientes ambulatoriais com DPOC. A Tabela 1 descreve as principais características demográficas, clínicas e funcionais dos pacientes. Apenas 207 pacientes (68,3%) completaram os questionários do CAT e da mMRC. Ao aplicarmos os pontos de corte propostos pela GOLD para a gravidade da dispneia (a pontuação na mMRC) ou dos sintomas com necessidade de tratamento regular (a pontuação no CAT), observamos discordância entre as duas medidas em 47 (22,7%) dos 207 pacientes: 32 (15,5%) foram classificados em grau A e B; e 15 (7,2%) foram classificados em grau C e D. Em 38 desses pacientes, a pontuação no CAT foi ≥ 10 e a pontuação na mMRC foi < 2, ao passo que os outros 9 pacientes apresentaram pontuação ≥ 2 na mMRC e < 10 no CAT. A Tabela 1 mostra a distribuição dos pacientes e a média do VEF_1 (em % do previsto) em cada grupo conforme as duas versões diferentes (de 2016 e 2017) das diretrizes da GOLD. Quando aplicamos os critérios de 2017 da GOLD, 74 pacientes (24,4%) foram transferidos de um grupo de maior gravidade para um grupo de menor gravidade.

No presente estudo, houve discordância significativa entre a pontuação do CAT e a da mMRC, o que mostra que o impacto da DPOC vai além da dispneia. Portanto, nos 96 pacientes que não completaram o CAT, é possível que o impacto sintomático tenha sido subestimado e o tratamento proposto tenha sido significativamente diferente do que eles realmente precisavam. Essas observações são consistentes com as de outros estudos.[2] Em um estudo realizado na Espanha, a versão de 2011 das diretrizes da GOLD, que permite que o médico escolha o método de determinação do impacto sintomático (mMRC ou CAT), foi avaliada por meio da comparação das duas medidas.[6] Os autores observaram que a classificação dos pacientes com DPOC variou de acordo com a medida empregada; mais de 25% dos pacientes foram classificados em diferentes categorias "horizontais", com diferentes propostas de tratamento.

A ferramenta de avaliação ABCD da GOLD é atualmente usada para orientar o tratamento farmacológico. Observamos uma discordância entre as versões de 2016 e 2017 das diretrizes da GOLD em 24,4% dos pacientes que compuseram nossa amostra. Muitos deles, previamente classificados como pertencentes ao grupo C ou D, foram reclassificados como pertencentes ao grupo

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Tabela 1. Características demográficas, clínicas e funcionais de pacientes com DPOC, além de uma comparação entre os critérios de 2016 e 2017 da *Global Initiative for Chronic Obstructive Lung Disease* quanto à distribuição dos pacientes e à média do VEF_1.[a]

Característica	(N = 303)
Sexo masculino	241 (79,5)
Idade, anos	67,5 ± 10,2
Idade ≥ 65 anos	186 (61,4)
Escolaridade ≤ 3 anos	89 (29,4)
Renda mensal < 530 €	197 (65,7)
Carga tabágica, anos-maço	49,3 ± 32,4
Pontuação ≥ 2 na mMRC	185 (61,1)
Pontuação ≥ 10 no CAT	152 (72,4)
≥ 2 episódios de EADPOC no ano anterior	115 (38,0)
VEF_1 pós-broncodilatador, % do previsto	53,2 ± 19,7
GOLD 2016	
Grupo	
A	51 (16,8)
B	66 (21,8)
C	23 (6,6)
D	163 (53,8)
VEF_1, % do previsto, por grupo	
A	76,17 ± 14,20
B	65,76 ± 12,81
C	47,01 ± 14,98
D	41,78 ± 19,68
GOLD 2017	
Grupo	
A	70 (23,1)
B	120 (39,6)
C	7 (2,3)
D	106 (35,0)
VEF_1, % do previsto, por grupo	
A	66,67 ± 20,07
B	53,61 ± 17,45
C	59,20 ± 21,75
D	43,40 ± 16,02

[a]Valores expressos em forma de média ± dp ou n (%). mMRC: escala modificada do *Medical Research Council*; CAT: *COPD Assessment Test* (Teste de Avaliação da DPOC); EADPOC: exacerbação aguda da DPOC; e GOLD: *Global Initiative for Chronic Obstructive Lung Disease*.

A ou B, para os quais o tratamento farmacológico proposto é significativamente diferente. Nossos dados são corroborados pelos de estudos anteriores. Um estudo recente comparou as versões de 2011 e 2017 da ferramenta de avaliação ABCD da GOLD em uma amostra composta por 1.532 pacientes com DPOC.[7] Os autores observaram que aproximadamente 47% dos 1.070 pacientes que foram classificados nos grupos de maior gravidade quando foi usada a versão de 2011 foram reclassificados em grupos de menor gravidade quando foi usada a versão de 2017, o que resultou em diminuição da intensidade do tratamento. Tudoric et al.[8] compararam os critérios de 2016 e 2017 da GOLD e demonstraram duas mudanças "verticais" na distribuição de pacientes com DPOC; mais de um terço dos pacientes foram reclassificados, do grupo D para o grupo B, quando foram aplicados os critérios de 2017.

As decisões médicas e o tratamento farmacológico podem mudar significativamente quando se usam instrumentos validados distintos, tais como questionários padronizados e diretrizes clínicas. A subestimação dos sintomas pode resultar em maior necessidade de medicação de resgate, menor qualidade de vida ou menor capacidade de exercício. Contudo, a transição da versão de 2016 para a versão de 2017 da ferramenta de avaliação ABCD da GOLD deverá ter um efeito significativo nas estratégias terapêuticas. A piora do prognóstico nos grupos A e B em virtude da maior média de limitação do fluxo aéreo provavelmente tornará mais grave qualquer exacerbação aguda. Por exemplo, a suspensão de corticosteroides inalatórios pode ser prejudicial em alguns desses pacientes.

Questionários padronizados, tais como o CAT e a mMRC, devem ser usados em conjunto, e os resultados devem complementar uma história clínica minuciosa.

As mudanças na classificação da gravidade da DPOC na versão de 2017 da ferramenta de avaliação ABCD da GOLD devem ser aplicadas com cautela a fim de evitar o subtratamento.

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Is an early diagnosis of COPD clinically useful?

To the Editor,

An early diagnosis of a disease among people who feel well, reducing future morbidity and mortality, is important in many chronic diseases, especially in malignancy. An early diagnosis should benefit patients. However, even in such disorders, an early diagnosis can turn indolent pathologies into illness and screening can result in an excess of diagnoses.[1] This is over-diagnosis, a growing problem in high-income countries. It can be considered when the treatment of the diagnosed conditions, sometimes indolent situations that would never cause patients harm, cannot improve patients' outcomes, exposing them to unnecessary risks and therefore being potentially harmful.[2,3] Chronic Obstructive Pulmonary Disease (COPD) represents one of the most significant health problems at international level. It is the only leading cause of death with rising mortality and morbidity. COPD is considered to be an underdiagnosed and undertreated disorder, especially in its mild and moderate degrees. Although the need for an early detection makes sense, when can an early diagnosis become an over-diagnosis?

Over-diagnosis and misdiagnosis represent two different concepts.[4] Over-diagnosis means identifying problems that were never going to cause harm.[3] It has two major causes: 'over-detection' and 'over-definition'. Misdiagnosis consists in giving a wrong diagnosis to a person who is really ill.[3] In primary health care, many COPD diagnoses are made without a spirometry confirmation, using inadequate algorithms and with difficulties establishing the correct differential diagnoses.[5]

Spirometry has an important role in the early diagnosis of COPD. In the early stages of the disease the clinical manifestations are inconstant, usually minor and not valued by patients. Symptoms are frequently accepted as normal or expected, attributed to smoking, and patients do not seek medical attention until the disease is more advanced and their symptoms are already compromising daily activities. Although we acknowledge that the early pathological changes in COPD are not captured by spirometry,[6] we do not currently have any marker to detect early onset of the airway disease, though, the use of spirometry, depending on the values of reference used, may be a cause of over-diagnosis, especially in the elderly.[7]

Some authors argue that pharmacological interventions in the early stages of COPD, when a faster disease progression is known to occur,[8,9] are of significant importance as they could delay its progression, like in many other chronic disorders. However, there is a wide range in FEV_1 decline in patients with COPD, and there is no tool to identify patients who would benefit from treatment to prevent the deterioration of respiratory function. Moreover, no markers of the disease are known to predict which patients with a recent onset of the disease will progress to a greater severity.[10] Until now, the presence of symptoms in mild COPD – a significantly different concept than early COPD - is the best predictor of acceleration in FEV_1 decline. Asymptomatic patients with mild airflow limitation do not present a faster decline in FEV_1 neither have worse quality of life than

healthy individuals.[11] However, they frequently present mild unreported exacerbations that impact patients' health status, and can be related to a small excess of FEV_1 decline.

An early diagnosis of COPD in people who feel well requires a significant amount of time, effort and costs. The US preventive Services Task Force (USPSTF) did not find evidence that screening for COPD using spirometry in asymptomatic people improves health outcomes (health-related quality of life, morbidity or mortality), and four of five trials assessing the effects of screening in smoking cessation did not report significant differences in abstinence rates. Therefore, the USPSTF concludes with moderate certainty that screening for COPD in asymptomatic people has no net benefit.[12] Many other published guidelines also recommended against screening for COPD in asymptomatic patients. The major goals in the treatment of COPD are the reduction of symptoms and exacerbations, and improvement of exercise tolerance and health status. However, the evidence achieved by most of the published RCTs related to pharmacological therapy can be applied only to patients with a severe or a very severe disease, because they do not use asymptomatic participants. Moreover, adherence to inhaled medications in COPD patients is strongly related to symptoms and to the functional severity of the disease.[13] A good adherence profile is then not expectable in patients with early disease, or with mild COPD.

Lung cancer screening with low-dose computed tomography can be useful to improve early-stage detection, increasing resectability and survival. COPD and cigarette smoking are two known independent risk factors for lung cancer. Because of that, some authors argued that the early diagnosis of COPD in smokers can help to select candidates for lung cancer screening.[14] It is infrequent to see a normal spirometry in patients with lung cancer.[15] Calabrò et al demonstrated that even a small reduction in FEV_1% is a significant predictor of increased risk for lung cancer. Airflow obstruction can be understood as a surrogate marker for carcinogenic damage of the airways,[16] and screening for lung cancer can be done using a decrease in FEV_1%. These could be an important argument to support the importance of an early diagnosis of COPD.

We need an early diagnosis with demonstrated benefits to the patients but, without an accurate knowledge on markers of the disease activity, mainly in the early stages of COPD, guiding therapy and helping to understand the different accelerated declines in lung function, an early diagnosis can turn out to be an over-diagnosis.

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Primeira página:

Medical decision in COPD: The evidence-based history

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Duarte-de-Araújo conceived and developed the study, carried out selection of bibliography, wrote the first draft and collaborated in the final writing. Miguel Guimarães carried out the selection of bibliography, collaborate in the first draft and in the final writing. Pedro Teixeira collaborated in the first draft and reviewed the final draft. Venceslau Hespanhol reviewed the final draft. Jaime Correia-de-Sousa reviewed all the drafts and collaborated in the final writing. All the authors approved the final manuscript.

Segunda página:

Medical decision in COPD: The evidence-based history

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Terceira página:

Tipologia do artigo: "Opinião e debate"

Medical decision in COPD: The evidence-based history

Abstract

Randomised controlled trials together with systematic reviews and meta-analysis have been the cornerstone of clinical research. Some studies, because of the size of the sample, the use of randomisation and well-defined measurements, the participation of multiple institutions or long-term follow-up, are powered to give a significant level of evidence. We chronologically described and comment a group of trials on COPD that have significantly influenced the scientific and medical community in the understanding and management of the disease in the first years of the XXI century. They are embodied in the different versions of the GOLD strategy.

Key words: COPD; Evidence; Randomized controlled trials; Treatment; Outcomes.

Como alguns ensaios clínicos randomizados influenciaram a decisão médica na DPOC

Resumo

Os ensaios clínicos randomizados, juntamente com as revisões sistemáticas e meta-análises, tem sido o suporte da evidência em medicina. Alguns estudos, devido ao tamanho da amostra, ao uso de randomização, à participação de várias instituições ou a longos follow-ups, são capazes de fornecer um nível considerável de evidência. Descrevemos e comentamos cronologicamente um grupo de trabalhos no âmbito da doença pulmonar obstrutiva crónica (DPOC) que influenciaram significativamente tanto a comunidade científica como a comunidade médica na compreensão e tratamento da doença, nos primeiros anos do século XXI, e que por essa razão foram incorporados nas diferentes versões da estratégia GOLD.

Palavras-chave: DPOC; Evidência; Ensaios clínicos randomizados; Tratamento; Resultados.

Medical decision in COPD: The evidence-based history

The role of medicine is mainly to help patients. Medical decision and the choice of treatment must be based in the best scientific information currently available. Randomised controlled trials (RCTs) together with systematic reviews and meta-analysis have been the cornerstone of clinical research.[1] The objective of clinical guidelines is to produce useful recommendations for clinicians, by searching, analysing and assessing the more relevant available scientific information. Some studies, because of the size of the sample, the use of randomisation and well-defined measurements, the participation of multiple institutions or long-term follow-up, are powered to give a significant level of evidence.[2] We chronologically described and comment a group of trials on COPD that have significantly influenced the scientific and medical community in the understanding and management of the disease in the first years of the 21st century.

In Europe, by the end of the 20th century, both FEV_1 and FEV_1 decline were a central issue in the understanding of the disease. Extensive evidence showed that patients can benefit from treatment, beyond smoking cessation, and oxygen for hypoxemic patients.[3] Inhaled corticosteroids (ICS) were used to treat patients with COPD, and this empirical use seemed to be justified by the episodically increase in FEV_1 and the reported decrease of FEV_1 decline after treatment with oral corticosteroids. The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial was published in 2000, and for the first time health status was proven to decline over time, in patients with moderate to severe COPD.[4] In such patients, fluticasone propionate in high doses (500 µg twice daily) demonstrated to significantly reduce acute exacerbations and the rate of decline of health status, even if there was no benefit on the rate of FEV_1 decline. A previous study, the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP),[5] published in 1999, had shown that the overall effect of three years of treatment with budesonide on FEV_1 of smoking patients with mild COPD was small, and did not affect its long-term decline. Nonetheless, the ISOLDE study significantly encouraged the use of high doses of ICS in moderate to severe COPD patients in clinical practice.

At the beginning of the 21st century there was a significant evidence that long-acting β2 agonists (LABA) improved lung function, symptoms and health status. There was also some evidence that fluticasone delayed the deterioration of health status and reduced the rate of exacerbations. However, the effect of the combination of the two drugs was not known, and was tested for the first time in the TRISTAN study.[6] It showed that, in patients with moderate to severe COPD, the combination therapy (ICS + LABA) was associated with a better control of symptoms, reduction of exacerbations and a modest effect on FEV_1. The

influence of this two trials established, at that time, the paradigm of the association of high doses of ICS together with a LABA in the treatment of moderate to severe COPD, which would last in clinical practice long after opposing evidence. After a nihilistic approach in the treatment of COPD,[4] an aggressively optimistic approach was adopted.

Brantigan et al,[7] in 1959, first reported lung volume reduction surgery (LVRS), a palliative treatment for severe emphysema. It was reintroduced in 1995 by Cooper et al. This authors described, in 1996, the effects of 150 consecutive bilateral lung volume reductions in patients with severe emphysema.[8] However, there was a significant lack of criteria for patient selection. The National Emphysema Treatment Trial (NETT) identified high risk patients that should be excluded from surgical procedure, and demonstrated a better survival, compared to medical therapy, in patients with both predominantly upper-lobe emphysema and low base-line exercise capacity, after pulmonary rehabilitation.[9] This study, published in 2003, established the criteria currently used for selection of COPD patients to lung volume reduction surgery. Their effects were proved to be durable, with improvement of exercise capacity and symptoms, respectively throughout a 3- and 4-year period. Interventional therapy has naturally evolved to video-assisted thoracoscopy and to bronchoscopic interventions. Currently, some patients may have a better quality of life after LVRS, acting as a bridge to transplantation or even without needing a transplant.[10]

In the first years of the last decade COPD was already understood as a complex and heterogeneous disorder. It was known that FEV_1 does not capture the entire complexity of the disease. It does not fully correlate with other COPD outcomes, as the degree of dyspnoea or the systemic manifestations, and both dyspnoea and health-status seemed to more accurately predict risk of death. Different authors have investigated other predictive factors related to COPD mortality, like age, hypoxemia, co-morbidities and exercise tolerance. Acute exacerbations of COPD (ECOPD) were recognized to have a relevant role in the natural history of the disease, but little was known about their direct influence on patients' mortality. In 2004 Celli et al proposed the BODE index (the Body-Mass, Airflow Obstruction, Dyspnoea, and Exercise Capacity Index) to predict the risk of death, the more definitive outcome in COPD[11]. That was the first described multicomponent tool, and promised to be an important instrument in the careful assessment of patients.[12] Multidimensional indices were a significantly step forward to best describe the complexity of the disease.

In a prospective study of COPD patients followed for 5 years, Soler-Cataluna et al demonstrated the importance of severe acute exacerbations of COPD on patients' mortality.[13] It became evident that mortality increases with the frequency of exacerbations, controlling for other prognostic factors, as FEV_1, age, BMI, co-morbidity or respiratory failure. Smoking cessation in all patients, oxygen therapy

for hypoxemic patients and lung volume reduction surgery in selected patients, were the only therapeutic procedures proven to improve survival in COPD patients. Therefore, this study opened a new perspective in patients suffering from COPD, because medical treatments have proven to reduce the frequency of ECOPD. The importance given to ECOPD lead to the choice of exacerbations as a primary end-point in the evaluation of different pharmacological therapies in many clinical trials.

A reduction in mortality rate in patients treated with fluticasone was seen in a post hoc analysis of the ISOLDE study. It provided the rationale for a new study in which, for the first time, all-cause mortality in COPD patients was the primary outcome. There was a need to alter the progressive course of COPD. The TORCH (Towards a Revolution in COPD Health) was published in 2007.[14] It clarified, in part, the role of pharmacotherapy for COPD.[15,16] Until then, the overall utility of ICS in the treatment of COPD patients, although widely used in clinical practice, remained controversial in the scientific community.[17] The clinical implications of the trial were that monotherapy with ICS should not be advocated, monotherapy with LABA was safe and useful, and the combination therapy decreased exacerbations, improved health status, offers protection against a decline in lung function, but did not affected all-cause mortality.

Tiotropium was the first drug specifically designed for COPD patients. It was the first long-acting muscarinic antagonist (LAMA) to be commercialised, providing 24-hour improvements in FEV_1 and hyperinflation. The UPLIFT (Understanding Potential Long-Term Impacts on Function) trial was published in 2008,[18] and was designed to test the hypothesis that the regular use of tiotropium could decrease the rate of FEV_1 decline. The primary end-point was not met - the addiction of tiotropium to other classes of respiratory medications did not result in changes in the rate of FEV_1 decline - but it was associated with positive effects on health-related quality of life, and a reduced risk of exacerbations and hospitalisations. The clinical implication of the trial is that tiotropium should be used to treat symptoms but not to alter the natural history of the disease.[19]

As tiotropium, salmeterol, fluticasone and the association between the last two drugs have been shown to prevent ECOPD, a trial was designed to compare the efficacy of the combination therapy (ICS+LABA) versus tiotropium alone in preventing exacerbations, in severe and very severe COPD. The INSPIRE study, [20] also published in 2008, found no difference in the overall rate of exacerbations between the two treatment groups.

An epidemiological study on COPD,[21] the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), published in 2010, confirmed the previous evidence that exacerbations became more frequent as the severity of COPD increases. It was also clear, for the first time, that the most reliable

predictor of ECOPD, in an individual patient, was a previous story of exacerbations. The ECLIPSE study also established the paradigm of the frequent-exacerbator phenotype: independent of disease severity, stable over time and easily identified on the basis of previous history of exacerbations. Some COPD patients will be more prone to exacerbate not due to their functional severity but rather to an intrinsic personal susceptibility. This knowledge had important implications on the management of the disease. Agusti et al, analysing data collected at recruitment of the ECLIPSE study, also accomplished relevant observations reflecting the heterogeneity of the disease[22]. They conclude against the importance given to common COPD classification based upon the degree of airflow limitation, because it was a poor predictor of other features of the disease.

By the year 2011 there was sufficient evidence to recommend the use of long-acting bronchodilators to treat symptoms and reduce the risk of exacerbations in patients with moderate, severe and very severe COPD. However, there was no evidence regarding whether a long-acting β_2-agonist or a long-acting anticholinergic drug should be selected. In the POET-COPD study, patients with moderate to very-severe COPD and a history of exacerbations were evaluated. Tiotropium was found more effective than salmeterol, significantly increasing the time to the first moderate or severe exacerbation, and significantly decreasing the annual rate of ECOPD. Although a considerable number of patients received concomitant therapy with ICS and the inhalation devices used to deliver salmeterol (a pMDI) or tiotropium (the HandiHaler) were significantly different, this was the first study to demonstrate the superiority of a LAMA over a LABA in the prevention of exacerbations. The main clinical implication is that a LAMA should be the first bronchodilator to be selected in symptomatic patients with a history of recent exacerbations.[23]

The SPARK study was the first to report on the efficacy of a dual long-acting bronchodilator therapy in patients with severe and very severe COPD and a high risk of exacerbations.[24] At the time the trial was published, according to GOLD 2013 strategy, the assessment of risk for COPD exacerbations was based both in history of previous exacerbations and airflow limitation, and dual bronchodilator therapy was only the second choice recommendation, for both C and D categories. A dual bronchodilator therapy superiority (LABA + LAMA) was proven in preventing moderate to severe exacerbations, compared to a single long-acting antimuscarinic therapy. The message for clinical practice was clear, and the strength was enough to suggest a revision in the treatment strategy for GOLD C and D groups. However, the ICS/LABA association was the other first choice therapeutic recommendation for the same GOLD categories, and it was never compared with dual bronchodilator therapy, until the publication of the FLAME study in 2016.[25]

There was significant evidence to recommend the association of an ICS and a LABA to treat patients in risk of frequent exacerbations. Nonetheless, with the evidence on the superiority of the dual bronchodilator therapy over only one bronchodilator in preventing COPD exacerbations, the benefit of inhaled glucocorticoids, in addiction to two bronchodilators, was not significantly explored. The Withdrawal of Inhaled steroids During Optimized Bronchodilator Management (WISDOM) study was the first trial with sufficient power to prove the hypothesis of therapeutic de-escalation in COPD.[26] All patients were treated with tiotropium plus salmeterol. A stepwise reduction in fluticasone in one arm of the study did not increase the risk of moderate or severe exacerbations. The message for clinical practice was clear: the continuation of using ICS, in patients taking long-acting bronchodilators, can only be justified if a symptomatic improvement may be attributable to the ICS.

For many years, since the seminal research by Fletcher and Peto,[27] the natural course of the disease was understood as an acceleration of the natural age-related decline in lung function, assessed by FEV_1, in susceptible persons to tobacco smoke or other noxious particles or gases. Using material from three large studies, the Framingham Offspring Cohort, the Copenhagen City Heart Study and the Lovelace Smokers Cohort, Lange et al found that the lung-function reached at early adulthood was related to the diagnosis of COPD later in life.[28] In some COPD patients there was a rapid decline in FEV_1 from a normal level of lung function, but others do not have accelerated rates of decline, however they started from a low initial value of FEV_1. A wide range of individual trajectories, related to FEV_1 decline was also found. Furthermore, periods of rapid decline and others with normal decline can co-exist in the same person. This study, published in 2015, emphasised the need for an early diagnosis of COPD, and drew attention to other risk-factors, as maternal smoking and asthma or respiratory infections in childhood.

The FLAME study was published in 2016, and compared an ICS-LABA with a LAMA-LABA for the prevention of ECOPD of all severities. The rational of the study reports to previous studies, namely the POET, the SPARK and the WISDOM, and to the importance given to COPD exacerbations, a key feature in the natural history of the disease. The superiority of a LAMA-LABA combination versus an ICS-LABA combination was proved for the first time. The LAMA-LABA association was found to better improve lung function, quality of life and prevent exacerbations, no matter the base-line blood eosinophil count (2% or higher). This conclusion conflicts with other trials, showing increased rates of ECOPD among patients with a blood eosinophil count ≥ 4% or 300 cell/μL.[29]

In the same year, the Study to Understand Mortality and Morbidity in COPD (SUMMIT) found that fluticasone plus vilanterol therapy was safe and did not affect cardiovascular outcomes. It reduced exacerbations and the FEV_1 decline,

but did not affect the overall mortality in patients with both moderate COPD and heightened cardiovascular risk.[30]

The role of ICS in the treatment of COPD continues to be object of debate, and their role in step-up from dual (LAMA + LABA) to triple therapy has been weak. The IMPACT study, published in 2018, aimed to fill this gap, by comparing a once-daily triple therapy with dual therapy.[31] Not surprisingly, triple therapy resulted in a lower rate of moderate or severe COPD exacerbations, a lower rate of hospitalisations, better lung function and better related quality of life. The study also showed that combination therapy (ICS+LABA) was superior to double bronchodilator therapy, in preventing COPD exacerbations. This finding contrasts to the FLAME results. The inclusion of patients with a past history of asthma, and the withdrawal of ICS at randomisation, in patients to whom they were recommended, could justify the different findings between the two studies. This can also suggest that only a subset of patients could in fact benefit from triple therapy[32] . Meanwhile, when adding an ICS to a double bronchodilator therapy, clinicians may expect a lower rate of ECOPD but a higher risk of pneumonia. What can be more acceptable is a matter to be decided in an individual basis.

Evidence related to the treatment of patients with COPD is reflected in the GOLD strategy.[33] Smoking cessation is mandatory in all patients. Long-term oxygen therapy improves survival in chronic hypoxemic patients. Pulmonary rehabilitation improves dyspnoea, health status and exercise tolerance. In selected patients with upper lobe emphysema refractory to medical care, surgical or bronchoscopic treatments have to be considered. Pharmacologic therapy reduces symptoms, reduces the frequency and severity of exacerbations, and improves health status and exercise tolerance. There is no conclusive evidence supporting long-term decline in FEV_1 with current medications. Long-acting bronchodilators are central medication in this disease. In COPD patients without a previous history of asthma or features of asthma, ICS can be used in case of severe loss of lung function or frequent exacerbations, after optimisation of bronchodilator treatment.

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Educational intervention and improvement of inhaler technique in COPD patients

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Abstract:

Objectives: To evaluate if the application of an educational intervention in COPD outpatients, regarding the correct use of the IDs, can improve inhalation technique in a sustained way, and to assess the inhalers and patient-related characteristics that are associated with some improvement of inhalation technique.

Methods: Stable COPD outpatients diagnosed according to GOLD criteria were evaluated in two different medical visits. They were invited to demonstrate the use of their IDs, and inhaler technique was accessed by using check-lists that include correct steps and critical errors. Posteriorly a correct teaching and training were given to all participants. After 10 to 12 months patients were invited for a second medical visit, and re-evaluation of inhaler technique was done.

Results: We evaluated 170 participants performing 266 inhalation manoeuvers. There was an improvement on critical errors in all types of IDs with statistical significance in the IDs with an easy feed-back to the patient that a significant amount of medication has been inhaled. Improvement was significantly related to CAT score and in the subset of patients who improved their inhalation technique, males had an average BMQ Necessity score higher than females.

Conclusions: Significantly improvement of inhalation technique was found in the group of IDs that provided an easy feed-back to patient that a significant amount of medication has been inhaled. More symptomatic patients learn better a correct inhaler technique than the less symptomatic ones. The beliefs about the need of medication are associated to inhaler technique improvement in male COPD patients.

Key-words: COPD; Inhalation technique; Educational intervention; Sustained improvement.

Aprendizagem da técnica inalatória em doentes com DPOC

Resumo:

Objetivos: Avaliar se o ensino correto da técnica inalatória em doentes com DPOC a pode melhorar de uma forma sustentada e quais as caraterísticas dos inaladores e dos doentes que lhe estão associados.

Métodos: Doentes com DPOC estável ≥ 40 anos, diagnosticados de acordo com os critérios do GOLD foram avaliados em duas consultas médicas com um intervalo de dez a doze meses entre elas. Inicialmente foi aplicado um questionário demográfico, clínico

e o Questionário de Crenças sobre Medicamentos. Na avaliação da técnica inalatória foi usada uma tabela de passos necessários e erros críticos. Posteriormente, a todos os participantes foi feito ensino e permitido treino com inaladores contendo placebo, até ao seu uso correto. Na segunda consulta foi feita uma reavaliação da técnica inalatória.

Resultados: Avaliamos 170 participantes realizando 266 manobras inalatórias com 10 diferentes inaladores. Registou-se uma melhoria no número de erros críticos em todos os tipos de inaladores, com significado estatístico naqueles que mais facilmente informavam o doente de que a inalação fora correta. A melhoria da técnica inalatória relacionou-se significativamente com o score do CAT. No subgrupo de doentes que melhoraram sua técnica inalatória, os homens tiveram uma média do score de necessidade do BMQ significativamente maior do que as mulheres.

Conclusões: Uma significativa melhoria da técnica inalatória foi observada nos inaladores que mais facilmente informam o doente sobre a correção da técnica inalatória. Os doentes mais sintomáticos mantiveram uma correta técnica inalatória de forma mais sustentada. As crenças sobre a necessidade do uso de inaladores estão associadas a uma melhor aprendizagem da técnica inalatória nos homens com DPOC.

Palavras-chave: DPOC; Técnica Inalatória; Ensino; Aprendizagem.

Background and objectives

Chronic Obstructive Pulmonary Disease (COPD) currently represents one of the most significant health problems at international level, and its economic and social impact is still constantly increasing.[1] COPD is a chronic and incurable disease, but symptoms significantly improve with therapy. Inhalers are the way used for an effective administration of medication, and it is of paramount importance that patients use them correctly, to ensure that a full dose is received. However, inhalers misuse remains unacceptably high.[2] A large proportion of patients refer lack of effective training from their health care professionals (HCPs) and few are systematically checked in their medical visits, regarding the inhaler technique.[3] Face-to-face inhalers' demonstration of the correct inhalation technique, verbal instructions, training the correct use and patients' teach-back are probably the most effective methods of teaching the correct inhalation technique (IT). As it can deteriorate over time, periodic evaluation and re-training is recommended.[4,5] It is not yet determined if improvement, after a single education intervention, is sustained over time.[6] The primary objective of this study was to evaluate if the application of an educational intervention in COPD outpatients, regarding the correct use of inhaler devices (IDs), can improve inhalation technique in a sustained way. The secondary objective was to assess the inhalers and patient-related characteristics that are associated with a sustained improvement in IT. The variables under study, evaluated for potential association to IT improvement, were type of ID, age, gender, education level, income, Graffar Social Classification score, the Beliefs about Medicines Questionnaire (BMQ) Necessity score, smoking status, mMRC degree, CAT

score, FEV_1% and the number of COPD acute exacerbations (ECOPD) in the previous year.

Materials and methods

This is an interventional study conducted in the outpatient respiratory care of Guimarães hospital. Stable COPD patients over 40 years, diagnosed according to GOLD criteria and using inhaler devices were evaluated in two different medical visits, with a ten to twelve-months interval between visits. They were recruited consecutively and evaluated on a first medical visit between March 2016 and May 2017. No participants were enrolled in another different study, and all gave their written informed consent. The study was approved by the Guimarães Hospital Ethics Committee, the Research Ethics Committee of Minho' University and by the Portuguese Data Protection Agency. Refusal to participate and inability to understand and respond to simple questionnaires were the exclusion criteria. In the first visit, a survey of demographic and clinical data, the Graffar Social Classification questionnaire, validated for use in Portuguese population,[7] and the Portuguese version of BMQ were applied.[8] The BMQ is an eleven-item questionnaire with a five-item Necessity scale and six-item Concern scale, assessing respectively the beliefs about the medication' necessity and concerns related to side-effects, dependence and toxicity of medication. Evaluation of symptoms was done using the Portuguese versions of the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). The number of ECOPD referred in the last year was recorded. We defined ECOPD according to GOLD as an acute worsening of respiratory symptoms that results in additional therapy,[9] but also requiring an unplanned medical visit. All participants performed at least one spirometry according to ERS/ATS criteria and referenced according to the Global Lung Function Initiative prediction equations (GLI 2012).[10,11] Participants were invited to demonstrate the use of their prescribed ID, and demonstrations were done using inhalers containing placebo medications. Inhaler technique was accessed by using previous defined checklists of 5 steps for each ID (Table 1).

[Please insert Table 1 here]

They were developed according to the instructions provided by the manufactures and to previous literature,[12] and include essential steps and critical errors. Errors considered critical are related to priming/loading or the inhalation maneuver, and could substantially affect drug delivery to the lungs. These included lack of inhalation through the mouthpiece for all devices, slow and not forceful inhalation for dry powder inhalers (DPI) and rapid or forceful inhalation for pressurized metered-dose inhalers (pMDI) or soft-mist inhalers (SMI). Critical errors device-dependent are listed in Table 2.

[Please insert Table 2 here]

After this assessment, face-to-face demonstration and training with placebo inhalers were given to all participants, until a correct use was achieved. Ten to twelve months later, participants were invited by mail for a second medical visit,

and re-evaluation of inhalers' technique was done by the same HCP using the same check-lists. Patients using different IDs were excluded. The difference in the number of critical errors between the two visits and the difference in total number of critical errors, because many patients used two or more inhalers, were defined as outcomes. Both outcomes were expressed as qualitative (equal number of critical errors, more errors - worsening of IT, less errors - improvement of IT).

Statistical analysis was performed with SPSS Statistics for Windows software, version 23.0. Armonk, NY: IBM Corporation. For null hypothesis testing Chi-Square test and Analysis of Variance with Covariant (ANCOVA) was performed. The level of statistical significance was set at $p < 0.05$.

Results

Sample characteristics

288 out 319 patients were invited for the second medical visit, but only 201 agree to participate. From then, 31 were excluded because they were using different IDs. We evaluated 170 participants (mean age = 66.8 years, 78.2% males) performing 266 inhalation manoeuvers. Ten different IDs were examined (Aeroliser®, Breezhaler®, Diskus®, Ellipta®, Genuair®, Handihaler®, pMDI, Respimat®, Spiromax® and Turbuhaler®) in a total of 31 (11.7%) pMDI, 63 (23.7%) single-dose inhalers (sDPI) 136 (51.1%) multiple dose inhalers (mDPI) and 37 (13.9%) SMI-Respimat®. The main demographic, clinical and functional characteristics of patients are described in Table 3.

[Please insert Table 3 here]

Tobacco smoking was the most common exposure identified. The mean tobacco exposure was 48.75 pack-years, and 15.4% of subjects were current smokers. The distribution of patients according to GOLD 2017 stage and classification were 10.6%, 38.8%, 37.6% and 12.9% GOLD 1 to 4, and 18.8%, 40.6%, 1.8% and 36.8% GOLD A to D.

Results by IDs

In the second visit, a technique free from any errors was observed in 145 (54.5%) demonstrations, only 2.2% more than in the first evaluation. Errors were related to priming/loading (9.8%), lack of exhalation before inhalation (12.8%), inhalation manoeuvre (11.3%), lack of holding the breath after inhalation (27.1%) and incorrect finalisation (13.9%). After teaching the correct inhaler technique, critical errors were more often related to inhalation manoeuvres than to priming/loading. Holding the breath after inhalation was the step more difficult to be learned. Misuse related to priming/loading and misuse related to inhalation manoeuvre were respectively higher in mDPI group (13.3%) and in pMDI (38.7%, $p<0.001$) group. Forgetting to hold the breath after inhalation was higher in sDPI group (38.1%, $p=0.031$). Table 4 presents the difference on errors related to the 5 steps for a correct inhaler technique in different types of inhaler devices.

[Please insert Table 4 here]

Data are presented as the difference between the percentage of errors in visit 2 and visit 1. An improvement in number of critical errors was observed in 50 (18.8%) and a worsening in 21 (7.9%) demonstrations. There was an observed improvement on critical errors in all types of IDs, with statistical significance in sDPI group. We found also a statistically significant improvement in number of critical errors In the group of IDs (Aeroliser + Breezhaler + Handihaler + Genuair) with an easy feed-back to the patient that a significant amount of medication has been inhaled (Table 5). Although some improvement in inhalation technique was observed in pMDI group, its misuse related to inhalation manoeuvre remains the more common reason for any inhaler misuse.

[Please insert Table 5 here]

Results by patients' characteristics

A worsening in the total number of critical errors was observed in 20 (8.8%) patients, and an improvement in 47 (25.9%). Worsening or improvement were not significantly related to demographic characteristics as age (p=.262), gender (p=0.331), education level (p=.379), monthly income (p=0.965) or Graffar Social Classification score (p=0.144). They were also not related to airflow limitation (p=0.694). Improvement was significantly related to CAT score (CAT<10: 22.2% worsened and 22.2% improved inhalation technique; CAT≥10: 6% worsened and 25% improved inhalation technique, p=0.037), but not to mMRC grade (p=0.474), smoking history (p=0.752) or COPD acute exacerbations (p=0.472). Some change in inhaler technique after an education intervention was not significantly related to BMQ Necessity score (p=0.719). However, in the subset of patients who improved their inhalation technique, male patients had an average BMQ Necessity score significantly higher than females (mean BMQ Necessity score were respectively 21.97 and 17.88, p=0.017 – figure 1).

[Please insert Figure 1 here]

Discussion

Some improvement in inhalation technique was achieved after a single education intervention in all types of IDs, with statistical significance in the group of inhalers with an easy feed-back to the patient that a significant amount of medication has been inhaled. It appears that some devices' attributes, by improving patients' confidence on their use, improve the maintenance of a correct inhaler technique. A previous study referred that the same devices' attributes leads to patients' confidence and improves treatment adherence in COPD patients.[3] A significant number of papers explore the effects of educational intervention on frequency of inhaler errors. They vary in the duration of interventions, in the tools used to assess inhalers' errors and in HCP involved in the studies, but a significant improvement in inhalation technique is usually reported. In a recent systematic review on critical inhaler errors, 11 out of 21 studies exploring the relationship

between previous inhaler instructions and frequency of inhaler errors, found a positive association between previous instructions and a better inhaler technique.[13] In the present study, after teaching the inhaler technique, the misuse related to inhalation manoeuvre in the pMDI group remains the more common reason for any inhaler misuse. This is consistent with a previous study on seven different devices, where the worse technique was found in the pMDI group, with only 79% of patients using them correctly after education and training.[14]

In our study, a significant rate of patients improved their inhalation technique; however, a worsening was also observed. The difference between technique improvement and worsening are related to the role played by the education intervention, the maintenance of training by the daily use and the over-time deterioration of inhalation technique. In COPD patients, mMRC and ECOPD are often examined outcomes related to inhaler technique. In a small experimental study, the number of ECOPD was significantly related to inhaler technique and to an education intervention, after a 3 months follow-up.[15] In a small cross-sectional study carried out in Portuguese asthma and COPD patients, previous education on inhalation technique was associated with lower number of inhalers' errors, however without impact on COPD stability.[16] In another small study published by the same Portuguese group, an education intervention regarding the inhalation technique was not related to clinical improvement in COPD patients, reevaluated 6 to 8 months later.[17] In our study we failed to demonstrate any significant association between improvement of inhaler technique and many demographic, clinical or functional characteristics of COPD patients. Nonetheless, this lack of statistical significance gives clinical relevance to the need of teaching the inhalation technique to all patients equally. In this sample the only significant association was the positive association between symptoms and improvement of the inhaler technique. This can be a sample characteristic; however more symptomatic patients can be more motivated to learn how to use inhalers properly. We found that male patients who improve their inhalation technique seems to be more believers in the need of medication than women. We can thus assume that men, but not women, have to believe in the need for medication to learn better and improve inhalation technique. This information is new and need to be confirmed by other studies.

To the best of our knowledge, this is the largest study carried out in Portuguese population of COPD patients, concerning the sustained improvement of the inhalation technique after a single educational intervention. However, this study was conducted in a single institution, with patients being treated by pulmonologists, and other possible education interventions, conducted by others HCPs, were uncontrolled. This may limit the generalisation of results to other populations.[18] We compared the number of critical errors before and after an education intervention. The definition of critical errors when using inhalers is of great importance, because they are likely to significantly decrease delivery of medication to the lungs, and thus impair health-related outcomes. However, there is currently a lack of consensus on their definition.[13] Though it is based on previous medical literature, our definition of critical errors deserves discussion. Nonetheless, re-evaluation of inhalers' technique was done using the same

check-list of steps and errors of the previous visit, and re-evaluation was done by the same HTP, to avoid inter-observer variability. Some of this data can be useful in clinical practice in planning educations interventions related to inhaler devices.

Conclusions

A correct teaching of inhaler technique improves patients' mastery to use inhalers in a sustained way. This data corroborates the observations of other authors, and draws attention to the effectiveness of educational interventions. An easy feedback that a significant amount of medication has been inhaled, presented by some inhaler devices, improve the maintenance of a correct inhaler technique. More symptomatic patients learn better a correct inhaler technique than the less symptomatic ones. The beliefs about the need of medication are associated with the maintenance of a correct mastery in male COPD patients. Clinicians must recognise that the inhaler device is as important as the drug itself, and this means not only prescribing the right device for a particular patient, but also training the patients in their correct use.

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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, contributed to the section on methods and results, and collaborated in the final writing. Venceslau Hespanhol reviewed the final draft. Jaime Correia-de-Sousa reviewed all the drafts and collaborated in the final writing. All the authors approved the final manuscript.

Disclosure

The authors have no conflicts of interest to declare.

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Table 1: Check-list of 5 steps and errors for each ID

1- Correct priming or loading
(Incorrect priming or loading were considered a critical error)
2- Exhalation before inhalation
(No-exhalation before inhalation was not considered critical)
3- Correct inhalation
(Incorrect inhalation was considered a critical error)
4- Holding the breath a few seconds after inhalation (not required when using a spacer)
(Not holding the breath or exhalation through the mouthpiece was not considered critical)
5- Finalization (cleaning the mouth-piece, removing the used capsule after verifying that no powder remains, checking color changing in control window, closing ID and washing the mouth if necessary)

Table 2: Critical errors in different IDs

1- Aeroliser®, Breezhaler®, and Handihaler®: failure to insert the capsule, failure to press and release buttons, powder remaining in the capsule after inhalation.
2- Diskus®: failure to open the cover, to slide the lever until it clicks, or not keeping inhaler horizontally
3- Ellipta®: failure to slide cover down until a click is heard or block air vent with fingers.
4- Genuair®: failure to remove the cap, to press and release the button until the control window has changed to green, not holding inhaler horizontally, and not changing control window to red after inhalation
5- pMDI: failure to remove cap, not shaking the inhaler (suspensions only), not holding the inhaler in the upright position, poorly synchronized hand actuation and inhalation, inhalation through the nose, actuation against teeth, lips or tongue.
6- Respimat®: lack of cartridge in the device, failure to open the cap, twisting the base or pressing the dose-release button, poorly synchronized hand actuation and inhalation.
7- Spiromax®: failure to hold the inhaler in upright position, failure to open mouthpiece cover until a click is heard or blocking air vent with fingers.
8- Turbuhaler®: failure to remove cover, to hold the inhaler upright when twisting the grip (tolerance $\pm$ 45°) until a click is heard.

Table 3- Demographic, clinical and functional characteristics of COPD patients

Characteristics	n = 170
Mean age (years)	66.8
Age ≥ 65 years	102 (60.0)
Male gender	133 (78.2)
Education level ≤ 3 school years	49 (28.8)
Education level ≤ 6 school years	152 (89.4)
Very low monthly income (< 530 Euros)	119 (70.0)
Graffar social classification 4 + 5	105 (62.5)
mMRC grade ≥ 2	107 (62.9)
CAT score ≥ 10	100 (78.7)
ECOPD ≥ 2 (last year)	70 (41.2)
Post-bronchodilator mean FEV_1%	52.8
GOLD 2017 stage and classification (n; %):	
I - 18 (10.6); II - 66 (38.8); III - 64 (37.6); IV - 22 (12.9)	
A - 32 (18.8); B - 69 (40.6); C - 3 (1.8); D - 66 (38.8)	

Note: Data shown as mean or n (%).
Abbreviations: mMRC, modified Research Council Dyspnea Questionnaire; CAT, COPD Assessment Test; ECOPD, chronic obstructive pulmonary disease acute exacerbations; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 4: Errors variation in visit 2 related to visit 1, by groups of inhaler devices.

	Errors related to: priming/loading	no-exhalation	inhalation	holding the breath	finalization
mDPI	-3%	-5.9%	-8.1%	+1.5%	+0.8%
pMDI	-12.9%	-22.4%	-9.7%	-19.9%	-19.4%
sDPI	-12.7%	-11.2%	-7.9%	+6.4%	+1.8%
Soft-mist Inhaler	-8.1%	-5.4%	-13.5%	-8.1%	-8.1%

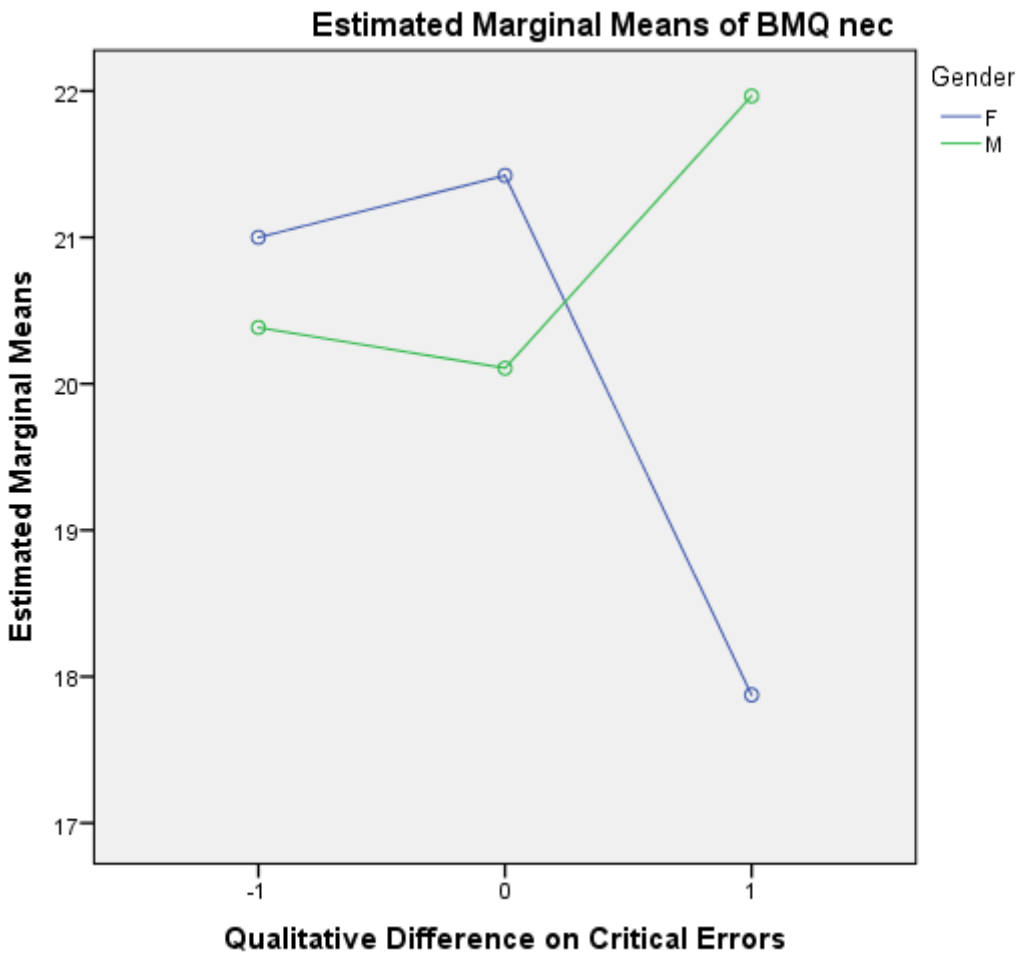
Abbreviations: mDPI, multiple-dose dry-powder inhalers; pMDI, pressurized inhalers; sDPI, single-dose dry-powder inhalers.

Table 5: Variation on critical errors in the different groups of inhaler devices.

			Errors M1				McNemar test
		No Error	Error	Total	Worsened	Improved	P -value
mDPI	No error	92	20	112	8.1%	14.7%	
Error M2	Error	11	13	24			0.150
	Total	103	33	136			
pMDI	No error	12	7	19	3.2%	22,6%	
Error M2	Error	1	11	12			0.070
	Total	13	18	31			
sDPI	No error	48	10	58	1.6%	16.1%	
Error M2	Error	1	3	4			0.012
	Total	49	13	62			
Softm	No error	23	8	31	8.1%	21,6%	
Error M2	Error	3	3	6			0.227
	Total	26	11	37			
sDPI + Genuair	No error	76	14	90	1.04%	14.6%	0.001
Error M2	Error	1	5	6			
	Total	77	19	96			

Note and abbreviations: Errors M1, Moment 1: first assessment; Errors M2, Moment 2: 2nd assessment; mDPI, multiple-dose dry-powder inhalers; pMDI, pressurized inhalers; sDPI, single-dose dry-powder inhalers; Softm, soft-mist inhalers; errors shown as number of demonstrations; Worsened/Improved described as % of demonstrations.

Figure 1: Necessity score by gender and difference in critical errors between the two visits.



Published abstracts related to thesis

Abstracts published in Eur Respir J. 2017;50: Suppl 61.

Misuse of inhalers devices in clinical practice

Duarte-de-Araújo A, Teixeira P. Figueiredo M, Hespanhol V, Correia-de-Sousa J

In COPD, therapeutic success depends on a correct inhalation technique, and the choice of inhaler devices (ID) can be as determinant as the drug itself.

We present the preliminary results of an ongoing prospective cross-sectional study aimed to assess the patient's inhaler technique in COPD patients, diagnosed according to GOLD guidelines. We defined a check-list with five steps for each ID, for a correct inhalation technique, as well as essential steps and critical errors, and patient were asked to demonstrate their inhaler technique. A statistics analysis was then performed.

We studied 203 COPD outpatients over 40 years-old (median 67.16 years), performing a total of 336 inhalations (30,4% incorrect). Ten types of IDs were examined, and misuse access according to priming/loading and inhalation procedures. Critical mistakes ranged from 27.6% for soft-mist inhaler to 50.0% for pMDI, and in DPIs group from 0% for Aeroliser® to 48.3% for Handihaler®. Preference reasons for an inhaler were the ease of use (39.8%), their characteristics (25.7%) and seem more practical to use (25.2%). No significant relationship was found between correct use and patient preference (p=.236). There was also no significant relationship between the correct use and the number of inhalers used per patient (p=.531).

Despite technological advances, inhalers mishandling remains an important clinical issue. A good inhalation technique depends on the type of ID. Poor coordination and inhalation failure remain cause of pMDI misuse. Soft-mist inhaler had the low rates of incorrect use. Misuse was not associated with multiple inhalers use nor to patient' preference.

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Abstract published in Eur Respir J. 2018;52: Suppl 62.

COPD: Are beliefs about inhaled medication associated with patients' inhaler technique?

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Key-words: COPD, Inhalation Technique, Beliefs about medication

Objectives: To evaluate if patients' beliefs about inhaled medication are associated with inhaler technique.

Methods: COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. A survey of demographic and clinical data and the cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese was applied. Participants were invited to demonstrate the use of their inhaler devices (ID), and inhalation technique was accessed by using checklists of correct steps. Errors considered critical were likely to make therapy useless. Ability to use inhalers was defined as the quotient between the number of inhalers without critical errors and the total number of inhalers used. Statistical analysis was performed with linear regression modelling.

Results: The study included 250 participants (mean age = 66.64 years, 76.4% males) using 10 different IDs. Misuse due to critical errors were observed in 47.4% of the women and 33.5% of men, in a total of 92 patients. In this group there was a statistical significant correlation between the BMQ Necessity score and number of critical errors (r= -.289) or the ability to use IDs (r=.310). The patients' beliefs about the necessity to use IDs were respectively significant direct and inverse predictors of ability to use inhalers (β= .310; p=.003; r^2=.096) and misuse due to critical errors (β= -.289; p=.005; r^2=.084). In this group of patients the beliefs about inhalers' need accounts for 9.6% of the observed variance in the ability to use IDs.

Conclusions: Physicians should focus their attention on patients who inadequately use inhalers and take in account their beliefs about the need of inhaled medication.

Efficacy of an Educational Intervention in the Sustained Improvement of Inhalation Technique

Duarte-de-Araújo A[1,2,3], Teixeira P [1,2], Figueiredo M [3], Hespanhol V [4,5], Correia-de-Sousa J [1,2,6]

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Key-words: COPD, Inhalation Technique, Educational Intervention

Introduction and objectives: The misuse of inhaler devices (ID) in COPD patients remains a topic of outstanding relevance. Even after learning a correct inhalation technique, it can deteriorate over time. If, after a single education intervention, improvements are sustained over time, is not yet determined. This is the aim of this study.

Methods: COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. In a previous visit, participants were invited to demonstrate the use of their prescribed ID. For each inhaler device we defined a checklist of steps for a correct inhalation technique, and critical errors, which are likely to make therapy useless. After this evaluation, demonstrations and training with placebo inhalers were given to all participants, until a correct use was achieved. In a second medical visit, 10 to 12 months after the first, a re-evaluation was done by the same healthcare professional using the same check-list. Patients using different ID were excluded. A statistics analysis was then performed.

Results: We revaluated 136 subjects (mean age = 66.78 years, 79.4% males) performing 214 inhalation manoeuvers. Ten types of IDs were examined (28 pMDI, 27 soft-mist inhaler, 50 sDPI and 109 mDPI). More participants (53.3%/55.6%) demonstrate a faultless inhalation technique in the second visit and misuse due to critical errors was less common (29.4%/17.8%), but not statistically significant. An improvement in inhalation technique was observed in all types of IDs, with statistical significance in the sDPI group (p=.007). Although some improvement in inhalation technique was observed in pMDI group, its misuse related to inhalation manoeuvre remains the single more common reason for any inhaler misuse.

Conclusions: Although some sustained improvement was achieved after a single education intervention, inhalers mishandling remains an important clinical concern. The inhalation manoeuver is a challenging issue when using a pMDI.

Characterization of adherence to inhaled medication in COPD patients

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Key words: COPD; Adherence; Inhaled Medication

Objectives: Adherence to inhaled medication in COPD patients is a challenging issue, but relatively understudied. The aim of this study is its characterisation, focused on patient-related determinants.

Methods: COPD out-patients from a respiratory unit ≥ 40 years diagnosed according to GOLD criteria were included consecutively. The Measure of Treatment Adherence, the Beliefs about Medicines Questionnaire, and a demographic, clinical and COPD questionnaires were used. After applying these questionnaires, semi-structured interviews were carried out, participants were encouraged to justify their opinions and behaviours. Field-notes were made during and after the interviews, and each interview was analysed before the next one. A quantitative and qualitative analysis of the variables was then performed.

Results: Of the 319 participants (mean age=67.7 years, 78.1% males) 300 completed the MTA questionnaire. 31.3% were considered poorly-adherent, and 16.7% non-adherent to inhaled therapy. Association with statistical significance was found between non-adherence and current smoking status (p = .044), and between adherence and GOLD stage, being higher from GOLD 1 to 4 (p=.001). A statistical significant negative association was found between FEV_1 and adherence to medication (p= .000). The mean BMQ Necessity score was higher in adherent patients (p=.000), being the mean Concern score similar (p=.877). We found 9 patterns of poor-adherence, 6 reasons given for poor-adherence behaviours, 5 reasons for good-adherence behaviours and 3 patient-related domains on adherence to medication.

Conclusions: 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 behaviours, which are based on three major groups of patient related-determinants: health-related experiences, health-related behaviours and health-related beliefs.

Misuse of inhalers devices in clinical practice

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Keywords: COPD; inhalation technique.

Introduction: The type of inhaler device is an important determinant of a correct inhalation technique, and in COPD the therapeutic success depends on a correct inhalation technique.

Objectives: to evaluate if the type of ID, the patient's preference or the number of DI used by patient can predict a correct inhalation technique.

Methods: COPD out-patients over 40 years old diagnosed according to GOLD criteria were recruited consecutively. We defined for each ID five steps for a correct inhalation technique and two essential steps/critical errors, which are likely to make therapy useless. A demographic and clinical survey was applied, and patients were asked to demonstrate the use of their prescribed inhalation devices.

Results: We studied 295 subjects (mean age= 67.7 years, 76.9% males), performing a total of 510 inhalation maneuvers. Ten types of IDs were examined, and 47.5% of inhalations had at least one step incorrectly performed. In 149 (29.2%) demonstrations critical errors were observed: 52.9% with pMDIs, 23.3% with sDPIs, 26.2% with mDPIs and 27.5% with the soft-mist inhaler. In mDPI group, critical errors ranged from 16.1% with Ellipta® to 35.1% with Turbohaler®. Misuse was related to priming/loading in 6.9%, to inhalation in 13.1% and to both in 9.2%. Preference reasons for an inhaler were the ease of use (65.4%), ID characteristics (25%) and be accustomed (2.9%). No significant relationship was found between correct performance of key maneuvers and patient preference (26.8% of preferred and 27.1% of non-preferred IDs had incorrect use, p=948), nor with number of inhalers used per patient (one ID, incorrect use=31%, 2 IDs=27.9%, 3 or 4 IDs=33.3%; p=.519).

Conclusions: Older devices are more prone to critical errors, but despite significant developments in device engineering in the last years, inhalers mishandling remains an important clinical issue.

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Misuse of inhaler devices in chronic obstructive pulmonary disease: patient-related determinants

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Keywords: COPD; inhalation technique.

Introduction: in COPD patients, the correct use of inhalers is one of the most important issues for therapeutic success.

Objectives: to evaluate if demographic, clinical or functional characteristics can predict a correct inhalation technique.

Methods: COPD out-patients over 40 years old diagnosed according to GOLD criteria were recruited consecutively. We defined for each ID five steps for a correct inhalation technique and two essential steps/critical errors, which are likely to make therapy useless. A demographic and clinical survey was applied, and patients were asked to demonstrate the use of their prescribed inhalation devices.

Results: We studied 295 subjects (mean age= 67.7 years, 76.9% males) performing a total of 510 inhalation maneuvers. Ten types of IDs were evaluated, and 47.5% of inhalations had at least one step incorrectly performed. In 149 (29.2%) demonstrations critical errors were observed: 52.9% with pMDIs, 23.3% with sDPIs, 26.2% with mDPIs and 27.5% with the soft-mist inhaler. Misuse was related to priming/loading in 6.9%, to inhalation in 13.1% and both in 9.2%. No significant relationship was found between total number of correct steps or correct performance of key maneuvers and income, typology of residence, FEV_1, CAT score, mMRC grade and GOLD 2017 stage and classification. We found a significant relationship between total number of correct steps and age (p=.032), gender (p=.005), education level (p=.002) and Graffar score (p=.030). We found also a significant relationship between correct performance of key maneuvers and age (p=.023) or gender (p=.000). Younger patients, men, those with more education lever or better socioeconomic status demonstrated a better inhalation technique.

Conclusions: Despite significant developments in device engineering in the last years, inhalers mishandling remains an important clinical issue. Teaching and inhalation technique follow-up should be reinforced in women, in elderly patients and in those with lower education level or lower socioeconomic status.

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COPD: Efficacy of a Single Educational Intervention in Improvement of Inhalation Technique

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Key-words: COPD, Inhalation Technique, Educational Intervention

Objectives: In COPD patients, inhalers mishandling remains an important clinical issue. The objective is to evaluate if inhalation technique may improve after a single intervention education.

Methods: COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. In a previous visit, participants were invited to demonstrate the use of their prescribed inhaler devices (ID). For each ID we defined a checklist of steps for a correct inhalation technique and critical errors which are likely to make therapy useless. After this evaluation, demonstrations and training with placebo inhalers were given to all participants, until a correct use is achieved. After 10 to 12 months a re-evaluation was done by the same healthcare professional using the same check-list. Patients using different ID were excluded. A statistical analysis was performed using SPSS Statistics for Windows.

Results: The study involved 170 subjects (mean age = 66.81 years, 78.2% males) performing 266 inhalation manoeuvers with 10 different IDs. An improvement in number of critical errors was observed in 18.8% and a worsening in 7.9% of demonstrations. There was an observed improvement in all types of IDs, however only sDPI inhalers group presented statistical significance (p=.012). An improvement in number of critical errors was not significantly related to demographic or clinical characteristics as age (p=.121), gender (p=.331), education level (p=.379), income (p=.965), smoking history (p=.752), level of dyspnoea (p=.474), acute exacerbations (p=.472) and airflow limitation (p=.694).

Conclusions: Some improvement of inhalation technique was achieved after a single education intervention in all types of IDs. Statistical significance was obtained regarding the type of inhaler device but not for patients' demographic or clinical characteristics.

Association between the beliefs about Inhaled medication and inhalers mishandling in COPD out-patients

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Key-words: COPD, Inhalation Technique, Beliefs about medication

Objectives: In COPD patients, inhalers misuse is a common problem in real life. The objective is to evaluate if the patients' beliefs about inhaled medication are associated with inhaler technique.

Methods: COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. A survey of demographic and clinical data and the cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese was applied. Participants were invited to demonstrate the use of their inhaler devices (ID), and inhalation technique was accessed by using previous defined checklists of steps for a correct inhalation technique. Errors considered critical were likely to make therapy useless. Ability to use inhalers was defined as the quotient between the number of inhalers without critical errors and the total number of inhalers used. A statistical analysis was then performed with linear regression modelling.

Results: The study included 250 subjects (mean age = 66.64 years, 76.4% males) using 10 different IDs. Misuse due to critical errors were observed in 47.4% of the women and 33.5% of men, in a total of 92 patients. In this group there was a statistical significant correlation between the BMQ Necessity score and number of critical errors ($r = -.289$) or the ability to use IDs ($r = .310$). The patients' beliefs about the necessity to use IDs were respectively significant direct and inverse predictors of ability to use inhalers ($\beta = .310$; $p = .003$; $r^2 = .096$) and misuse due to critical errors ($\beta = -.289$; $p = .005$; $r^2 = .084$). In this group of patients the beliefs about inhalers' need account for 9.6% of the observed variance in the ability to use their IDs.

Conclusions: Physicians should focus their attention on patients who inadequately use inhalers and take in account their beliefs about the need of inhaled medication.

Relationship between symptoms instability and COPD severity

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Keywords: COPD; symptoms; instability.

Introduction: COPD is a complex and heterogeneous disease. The definition of groups of patients with their own distinctive characteristics may facilitate the choice of the best therapeutic approach.

Objectives: We present the preliminary results of an ongoing cross-sectional study aimed to define large and easy to distinguish groups of patients that share some characteristics whose knowledge can influence therapeutic options.

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were included. A survey of demographic and clinical data were applied, and assessment of symptoms were done using COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC).

Results: We studied 203 subjects (155 males, mean age= 67.6 years, SD=10.91). The distribution of patients, according to GOLD 2017 stage and classification were 9.4%, 42.9%, 34% and 13.8% stage 1 to 4, and 23.2%, 39.9%, 2% and 35% groups A to D. We found no significant difference between gender, related to age and number of exacerbations. CAT total score and mMRC grade were higher in women (p=.024 and p=.038, respectively). Patients with a smoking history are mainly men and have a significantly lower mean age. We found no association between age and disease severity, nor between smoking history and airflow limitation, risk of exacerbations or symptoms. Patients with mMRC grade ≥2 (p=.000) and a CAT total score ≥10 (p=.000) and those with a poor respiratory function, according to GOLD stage (p=.001) are at increased risk of acute exacerbation. We found a strong association between airflow limitation, according to GOLD classification, and the mMRC grade (p=.000) and CAT total score (p=.011). Many patients (40.9%), beyond exercise persistent dyspnea, report worsening of symptoms in winter and/or with change in weather. We found a significant association between symptoms variation or instability and a history of frequent (≥2) treated exacerbations (p=.001).

Conclusions: There is a clear relationship between risk of acute exacerbation and airflow limitation, between symptoms and airflow limitation, and between symptoms and exacerbations. There is also a clear relationship between symptoms instability and COPD exacerbations. Symptoms variation or instability seems to be a predictor of disease severity.

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Misuse of inhalers devices in clinical practice

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Keywords: COPD; inhalation technique.

Introduction: In COPD, therapeutic success depends on a correct inhalation technique, and the choice of inhaler devices (ID) can be as determinant as the drug itself.

Objectives: We present the preliminary results of an ongoing cross-sectional study aimed to access the patient's inhaler technique.

Methods: COPD out-patients over 40 years old were recruited consecutively. We defined for each ID five steps for a correct inhalation technique and two essential steps and critical errors, which are likely to make therapy useless. Patients were asked to demonstrate the use of their prescribed inhalation devices, just as he or she does it at home. A statistics analysis was performed, using IBM SPSS Statistics for Windows, Version 22.0.

Results: We studied 282 subjects performing a total of 467 inhalation maneuvers. Ten types of IDs were examined, and 48% of inhalations had at least one step incorrectly performed. In 138 (29.6%) demonstrations critical errors were observed: 53.6% with pMDIs, 25.2% with sDPIs, 26.4% with mDPIs and 27.5% with the soft-mist inhaler. In mDPI group, critical errors ranged from 18.5% with Ellipta® to 33.3% with turbohaler®. Misuse was related to priming/loading in 7.1%, to inhalation in 13.5% and both in 9%. Preference reasons for an inhaler were the ease of use (64.6%), ID characteristics (25.4%) and be accustomed (3%). No significant relationship was found between correct performance of key maneuvers and patient preference (25.9% of preferred and 35.1% of non-preferred IDs had incorrect use, p=.308), or number of inhalers used per patient (one ID, incorrect use=30%, 2 IDs=28.2%, 3 or 4 IDs=32.3%; p=.521).

Conclusions: Inhalers mishandling remains an important clinical issue, as in other populations studied. However, in our survey misuse was not associated to multiple inhalers use nor to patient' preference. A good inhalation technique depends on the type of ID, and failure of inhalation maneuver, although the most subjective step, is the main cause of ID misuse.

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COPD: frailty factors and risk of exacerbation

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Keywords: COPD; Symptoms; Exacerbations

Introduction: Susceptibility to infections plays a role in exacerbation of COPD (ECOPD). Patients with COPD often fulfil criteria of frailty, because of age, low income, low socioeconomic status, cigarette smoking and multimorbidity, having increased risk of acute respiratory infections.

Objectives: We present the preliminary results of an ongoing cross-sectional study aimed to evaluate some frailty factors as risk factors of exacerbation (ACOPD).

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were included. A survey of demographic, socioeconomic and clinical data were applied.

Results: We studied 282 subjects (78% males, mean age=67.8 years, SD=10.4), 46.8%, 14.5% and 38.7% referring no, one and two or more treated exacerbations in the last year. The distribution of patients according to GOLD 2017 stage and classification were 9.6%, 44.3%, 33.3% and 12.8% GOLD 1 to 4, and 22.7%, 39.4%, 2.1% and 35.8% GOLD A to D. We found significant association between risk of exacerbations and both education level (p=.024) and income (p=.042). Binary logistic regression indicates an odds ratio of two times more risk of ECOPD for lower education level (<4 years of school) and 1.58 more risk of exacerbations for lower income, when controlling for age and gender. Age and gender are not related with increased risk of ECOPD. Comorbidities as chronic heart diseases, diabetes, obesity, chronic bronchitis or referred asthma in childhood are also not significantly related with increased risk of exacerbation. Although, sample data suggests a relationship between comorbidities and risk of exacerbations, however without statistics significance.

Conclusions: Many COPD patients fulfil criteria of frailty, but only low income and low education level are related to increased risk of ECOPD.

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The influence of the social representations of COPD on adherence to inhaled medication

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Keywords: COPD; adherence; social representations.

Background and objectives: There are few studies that investigate the social representations of COPD, and how they influences adherence to inhaled medication. This is the aim of this study.
Methods: We present the preliminary results of an ongoing cross-sectional study on COPD patients. The Measure of Treatment Adherence, the Beliefs about Medicines Questionnaire, and a demographic, socioeconomic, clinical and an easy-to-answer survey on COPD were applied. After the application of these questionnaires, semi-structured interviews were carried out. Participants were encouraged to justify their opinions and behaviors, according to Grounded Theory qualitative methodology. The objective was to obtain new information from patients' themselves. Field-notes were made during the interview, and each interview was analyzed before the next one. A quantitative and qualitative analysis of the variables was then performed.
Results: Of the 174 participants (mean age=67.8 years, SD=10.79), 78.2% males, 85.1% living in predominantly urban spaces, 85% referred low education level (≤ 4 years of school) and 66.1% low income (≤ 530 €). Poor adherent behaviors was referred by 30.6%, but only 15.3% were considered non-adherent. The mean BMQ Necessity score was higher in adherent patients (p=.000), being the mean Concern score similar (p=.841). Adherence is related to GOLD 2016 stage and classification, being higher from GOLD I to IV (p=.039) and from A to D (p=.025). We found 3 patterns of unintentional non-adherence, 7 patterns of intentional non-adherence, 5 reasons and 4 domains for intentional non-adherence. We found also 9 different reasons and 3 domains for good adherence behaviors. The majority of patients recognized COPD as a chronic disease (89.3%), and a serious illness (79.1%), since it is symptomatic and limiting.
Conclusions: Adherence is related to the perception of necessity, and to the clinical and functional severity of the disease. New information obtained was related to the patterns and reasons for non-adherence, and to behavior actions that reinforce compliance. The more important practical differences between patients and doctors cultural perception about the treatment lies in its usefulness in prevention of exacerbations and disease progression.

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Chronic Obstructive Lung Disease: A non-adherent phenotype?

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Keywords: COPD; adherence; inhaled medication

Background and objectives: Poor adherence to medication is currently considered a major health problem. The adherence to inhaled therapy prescribed in COPD is unknown in our country, and its characterization is the aim of this study.

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were included. A survey of demographic and clinical data were applied, and assessment of symptoms were done using COPD Assessment Test (CAT) and the Medical Research Council Dyspnoea Questionnaire (mMRC). The Measure of Treatment Adherence (MTA) and the Beliefs about Medicines Questionnaire (BMQ) were also applied. A statistics analysis was then performed, using IBM SPSS Statistics for Windows, Version 22.0.

Results: Of the 314 participants (mean age=67.7 years, 78% males), 79.6% live in predominantly urban spaces, 88.1% referred low education level (≤ 6 years of school) and 65.3% low income (≤ 530 €). Were considered non-adherent to inhaled therapy 16.3% of patients. Age, gender, education level, income and Graffar social classification were not statistically related to adherence. There was also no association between adherence and number of reported exacerbations. We found a statistical significant association between airflow limitation (FEV_1%) and adherence to medication (the higher airflow limitation, the higher adherence, p= .000). Adherence is also related to GOLD stage, being higher from GOLD 1 to 4 (p=.001). The association between adherence and ABCD groups, GOLD 2017, was under statistical significance. However, an association with statistical significance was found between adherence and current smoking status (25% of smokers and 14.6 % of ex-smokers or never-smokers were non-adherents, p = .040). Binary logistic regression indicates an odds-ratio of 2.4 times more risk of non-adherence for current smokers, when controlling for age, gender, education level, mMRC and FEV_1. The mean BMQ Necessity score was higher in adherent patients (20.59/15.58, p=.000), being the mean Concern score similar (10.80/10.63, p=.825).

Conclusions: Adherence is related to the perception of the necessity and to the functional severity of the disease. The non-adherent patient is usually a current smoker with lower degree of airflow limitation and lower perception of medication' necessity.

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MISUSE OF INHALER DEVICES IN COPD: PATIENT--RELATED DETERMINANTS

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Key-words: COPD; inhalation technique

Introduction: In COPD patients, the correct use of inhalers is one of the most important issues for therapeutic success. Gender, age, education level and severity of the disease are patient-related determinants of a correct technique.

Objectives: To evaluate if demographic, clinical or functional characteristics can predict a correct inhalation technique.

Methods: COPD out-patients over 40 years old diagnosed according to GOLD criteria were recruited consecutively.We defined for each IDfive steps for a correct inhalation technique and twoessential steps and critical errors, which are likely to make therapy useless. A demographic and clinical survey was applied. Patients were asked to demonstrate the use of their prescribed inhalationdevices, just as he or she does it at home. A statistics analysis was performed, using IBM SPSS Statistics for Windows, Version 22.0.

Results: We studied 295 subjects (mean age= 67.7 years, SD=10.33, 76.9% males) performing a total of 510inhalation maneuvers. Ten types of IDs wereevaluated, and 47.5% of inhalations had at least one step incorrectly performed. In 149 (29.2%) demonstrations critical errors were observed: 52.9% with pMDIs, 23.3% with sDPIs, 26.2% with mDPIsand 27.5% with the soft-mist inhaler. In mDPI group, critical errors ranged from 16.1% with Ellipta® to 35.1% with Turbohaler®. Misuse was related to priming/loading in 6.9%, to inhalation in 13.1% and both in 9.2%. No significant relationship was found between total number of correct steps or correct performance of key maneuvers and income, typology of area of residence (TIPAU 2014), FEV_1, CAT score, mMRC grade and GOLD 2017 stage and classification. However, we found a significant relationship between total number of correct steps and age (p=.032), gender (p=.005), education level (p=.002) and Graffar score (p=.030). We found also a significant relationship between correct performance of key maneuvers and age (p=.023) or gender (p=.000). Younger patients, males, those with more education lever or better socioeconomic status demonstrated a better inhalation technique.

Conclusions: Despite significant developments in device engineering in the last years, inhalers mishandling remains an important clinical issue. Teaching and inhalation technique' follow-up should be reinforced in women, in elderly patients and in those with lower education level or lower socioeconomic status.

Risk factors for respiratory tract infections and exacerbation of COPD

A Duarte-de-Araújo*, P Teixeira**, M Figueiredo***, V Hespanhol****, J Correia-de-Sousa*****

Keywords: COPD; Symptoms; Exacerbations

Introduction: Susceptibility to infections plays a role in acute exacerbation of COPD (ECOPD). Individual risk factors associated with respiratory tract infections include increasing age, low socioeconomic status, cigarette smoking, heart disease, bronchiectasis, chronic bronchitis or multimorbidity, and are often presented by patients with COPD.

Objective: to evaluate if some risk factors for respiratory infections can predict an increased risk of ECOPD.

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were included. A survey of demographic, socioeconomic and clinical data were applied. We defined acute exacerbation as a worsening of one or more major respiratory symptoms, requiring an unplanned medical appointment that led to some treatment or modification of previous treatment. A statistics analysis was performed using IBM SPSS Statistics for Windows, Version 22.0.

Results: We studied 314 subjects (78% males, mean age=67.7 years), 79.6% living in urban areas, 203 referring low income and 29.3% very low education level (≤3 years). Clinically, 48.1%, 14% and 37.9% referred no, one and two or more treated exacerbations in the last year. The distribution of patients according to GOLD 2017 stage and classification were 10.5%, 43.3%, 34.1% and 12.1% GOLD 1 to 4, and 23%, 39.8%, 2.2% and 35% GOLD A to D.

We found significant association between risk of exacerbations and both education level (p=.023) and income (p=.031). Binary logistic regression indicates an odds ratio of 1.5 times more risk of ECOPD for lower education level (≤3 years of school) and 1.9 more risk of exacerbations for lower income, when controlling for age and gender. Female gender (p=.018) were related with increased risk of ECOPD. Age, asthma in childhood (X^2=.964; p=.617), diabetes (X^2=998; p=.607), obesity (X^2=.126; p=.941), bronchiectasis (X^2=7.660; p=.467) and depression or anxiety (X^2=1.798; p=.407) were not significantly related with increased risk of exacerbation. Ischemic heart disease (X^2=7.186; p=.028) and chronic bronchitis (X^2=13.516; p=.009) were related with increased risk of acute exacerbations.

Conclusions: COPD patients have many risk factors for respiratory tract infections, others than COPD itself, but only low income, low education level, and comorbid conditions as chronic bronchitis and ischemic heart disease are related to increased risk of ECOPD.

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Symptoms irregularity can predict an increased risk of acute exacerbation of COPD

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Keywords: COPD; symptoms; variability; irregularity.

Introduction: In medicine, added-value means intervention in order to improve patient' health status. COPD is a complex and heterogeneous disease, and acute exacerbations are the main cause of mortality. The recognition of broad patient's characteristics may facilitate the choice of the best initial therapeutic approach.

Objectives: To evaluate whether some clinical or functional characteristics can predict an increased risk of acute exacerbations of COPD.

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were included. A survey of demographic and clinical data was applied, and assessment of symptoms was done using COPD Assessment Test (CAT) and the Medical Research Council Dyspnea Questionnaire (mMRC). Acute exacerbation of COPD was defined as a worsening of one or more major respiratory symptoms, requiring an unplanned medical visit that led to any treatment or modification of previous treatment. A statistics analysis was performed, using IBM SPSS Statistics for Windows, Version 22.0.

Results: We studied 314 subjects (78% males, mean age= 67.7 years).The distribution of patients, according to GOLD 2017 stage and classification were 10.5%, 43.3%, 34.1% and 12.1% stage 1 to 4, and 23%, 39.8%, 2.2% and 35% groups A to D. Age was not related with increased risk of exacerbation. Female gender (p=.018) was related with increased risk of exacerbation. CAT total score and mMRC grade were higher in women (p=.002 and p=.011, respectively). Patients with a smoking history are mainly men and have a significantly lower mean age. We found no association between age and disease severity, nor between smoking history and airflow limitation, risk of exacerbations or symptoms. Poor respiratory function, according to GOLD stage (p=.000) are at increased risk of acute exacerbation. We found a strong association between increased airflow limitation, according to GOLD classification, and the mMRC grade (p=.000) and CAT total score (p=.011). Patients with mMRC grade ≥2 (p=.000) or a CAT total score ≥10 (p=.000) are at increased risk of acute exacerbation. Many patients (74.8%), beyond exercise persistent dyspnea, report worsening of symptoms in winter and/or with change in weather. We found a significant association between this symptoms variability or irregularity and a history of frequent (≥2) treated exacerbations (p=.007), when controlling for gender, history of asthma and FEV_1%.

Conclusions: Women are more symptomatic and have more risk of acute exacerbations. There is a clear relationship between risk of acute exacerbation and airflow limitation, between symptoms and airflow limitation, and between symptoms and exacerbations. There is also a clear relationship between symptoms variability and COPD exacerbations. Symptoms irregularity can predict an increased risk of exacerbation.

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COPD: Clinical relevance of the definition of air-flow limitation

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Key-words: COPD; Air-flow limitation; Criteria for diagnosis.

Introduction: A persistent airflow limitation, defined as a low ratio of FEV1/FVC, is required for the diagnosis of COPD. According to GOLD, a post-bronchodilator FEV1/FVC <0.70 confirms the presence of airflow limitation. However, there is currently no consensus on the best criteria to be used for the diagnosis of a low FEV1/FVC, and many authors argued that the use of LLN would reduce over diagnosis in elderly people.

Objectives: To compare the characteristics of COPD patients that meet both criteria defining airflow limitation, FEV1/FVC <0.70 and < LLN, with those who do not meet the LLN criteria.

Methods: COPD out-patients over 40 years and diagnosed according to GOLD criteria were recruited consecutively. Assessment of symptoms was done using the CAT and mMRC questionnaires. Spirometries were performed according to ERS/ATS criteria and referenced according to the Global Lung Function Initiative prediction equations (GLI 2012). The variables under study were age, gender, smoking status, FEV_1, symptoms, number of reported acute exacerbations, history of asthma and current heart disease. A statistical analysis was performed, using IBM SPSS Statistics for Windows, Version 22.0.

Results: A total of 303 individuals were included. 46 patients had FEV1/FVC > LLN, were significantly older (p=.001, 76.1% ≥ 65 years), less actual smokers (p=.047), and less frequent exacerbators (p=.023). The mean FEV_1% was significantly higher (p=.000) in this group, and patients were less symptomatic, with lower mMRC grade (p=.007) and CAT scores (p=.004). Although they were older, prevalence of current cardiac conditions was similar (p=.258), but a diagnosis of asthma before 40 years was less referred (p=.029).

Conclusions: This symptomatic group of patients with exposure to relevant risk factors but not meeting the LLN criteria were usually less symptomatic, with less risk to exacerbate and less airflow limitation. They are more likely to have a milder form of COPD.

Teaching the inhalation technique: Can we predict a sustained improvement in COPD patients?

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Key-words: COPD, Inhalation Technique, Educational Intervention

Objectives: In COPD patients, inhalers mishandling remains an important clinical issue. Even after learning a correct inhalation technique, it can deteriorate over time. The aim of this study is to evaluate the inhalers and patient-related characteristics that can predict a sustained improvement of inhalation technique, after a single intervention education.

Methods: COPD out-patients diagnosed according to GOLD criteria, were recruited consecutively. In a previous visit, participants were invited to demonstrate the use of their prescribed inhaler devices (ID). For each ID we defined a checklist of steps for a correct inhalation technique and critical errors which are likely to make therapy useless. After this evaluation, demonstrations and training with placebo inhalers were given to all participants, until a correct use is achieved. In a second medical visit, 10 to 12 months after the first, a re-evaluation was done by the same healthcare professional using the same check-list. Patients using different ID were excluded. A statistics analysis was then performed.

Results: We re-valuated 136 out of 319 subjects performing 214 inhalation manoeuvers with 10 different IDs. Misuse due to critical errors were less common in the second visit (29.4%/17.8%). An improvement in the total number of critical errors was observed in 27.9% and a worsening in 9.6% of participants. An association between patients' demographic or clinical characteristics and a decrease of critical errors was not statistically significant. An improvement of inhalation technique was observed in all types of IDs, with statistical' significance in sDPI group (p=.007). Although some improvement in inhalation technique was observed in pMDI group, its misuse related to inhalation manoeuvre remains the more common reason for any inhaler misuse.

Conclusions: An improvement in the efficient use of IDs after a single educational intervention was related to the type of inhaler device but not to patients' demographic or clinical characteristics.

Association between the patients' beliefs and improvement of inhalation technique

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Key-words: COPD, Inhalation Technique, Educational Intervention, Patients' Beliefs

Objectives: To evaluate if patients' beliefs about inhaled medication are associated with a sustained improvement in inhaler technique.

Methods: Stable COPD patients over 40 years, diagnosed according to GOLD criteria, and using inhaler devices were evaluated in two different medical visits, with a ten to twelve-months interval between visits. In the first visit, a survey of demographic and clinical data, and the cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese were applied. Participants were then invited to demonstrate the use of their prescribed inhaler devices (ID). For each ID we defined a checklist of steps for a correct inhalation technique, and critical errors which are likely to make therapy useless. After this evaluation, demonstrations and training with placebo inhalers were given to all participants, until a correct use is achieved. In the second medical visit, 10 to 12 months after the first, a re-evaluation was done by the same healthcare professional using the same check-list of the first visit. Patients using different ID were excluded. A statistical analysis was performed with linear regression modelling.

Results: We evaluated 170 participants performing 266 inhalation manoeuvers with 10 different IDs. There was an improvement on critical errors in all types of IDs with statistical significance in the IDs with an easy feed-back to the patient that a significant amount of medication has been inhaled. Some change of the inhaler technique after an education intervention was not significantly related to BMQ Necessity score (p=0.719). However, in the subset of patients who improved their inhalation technique, male patients had an average BMQ Necessity score significantly higher than females (mean BMQ Necessity score were respectively 21.97 and 17.88, p=.017).

Conclusions: A correct teaching of inhalers' technique improve patients' mastery to use inhalers in a sustained way. The beliefs about the need of medication are associated with the learning and maintenance of a correct inhaler technique in male COPD patients.

Factors Related to Poor Clinical Outcomes in Chronic Obstructive Pulmonary Disease

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Key-words: COPD, Inhalation Technique, Adherence, Prescriber Disagreement; Clinical outcomes.

Objectives: To evaluate factors that can be related to poor clinical outcomes in COPD focused on prescriber disagreement to therapeutic standards, poor adherence to inhaled medication and inhalers mishandling.

Methods: A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães. Patients ≥ 40 years diagnosed according to GOLD criteria were recruited consecutively. A survey of demographic and clinical data was applied. Adherence was assessed using the Measure of Treatment Adherence (MTA) questionnaire. Evaluation of current medication was self-reported by patients and by using the hospital data base and the health data platform, and then compared to therapeutic standards as proposed by GOLD 2017 for the same ABCD groups. Participants were also invited to demonstrate the use of their inhaler devices (ID), and inhalation technique was accessed by using checklists of correct steps. Errors considered critical were likely to make therapy useless. Total number of critical errors was defined as the quotient between the sum of the number of critical errors done with all the IDs and the total number of possible critical errors. A statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results: We studied 303 participants (79.5% males, mean age = 67.46 years). A total of 285 completed the MTA questionnaire. Poor-adherence was referred by 88 patients (30.9%) and 47 (16.5%) were considered non-adherent to inhaled medications. We found deviations from the international therapeutic standards in 136 (45.3%) patients. The most frequent deviations are related to overuse of inhaled corticosteroids (98 patients), overuse of bronchodilators (34 patients), under-medication (11 patients) and doubling the medication (8 patients). 285 patients performed 501 inhalations maneuvers with 10 different IDs. Inhalers' misuse due to critical errors was observed in a total of 113 (39.6%) patients.

Conclusions: In the present analysis prescriber disagreement from international guidelines was more frequent than poor-adherence or inhalers misuse. Because the more often deviations are related to overuse of IC, it is yet not clear whether this leads to adverse outcomes.

Patients' beliefs about inhaled medication are associated with a better inhaler technique

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Key-words: COPD, Inhalation Technique, Beliefs about medication

Objectives: To evaluate if patients' beliefs about inhaled medication are associated with inhaler technique.

Methods: A cross-sectional study on COPD was conducted in the ambulatory pulmonary clinic of Hospital de Guimarães. Patients ≥ 40 years diagnosed according to GOLD criteria were recruited consecutively. A survey of demographic and clinical data and the cross-cultural adaptation of the Beliefs about Medicines Questionnaire (BMQ-specific) into Portuguese was applied. Participants were invited to demonstrate the use of their inhaler devices (ID), and inhalation technique was accessed by using checklists of correct steps. Errors considered critical were likely to make therapy useless. Total number of critical errors (TCE) was defined as the quotient between the sum of the number of critical errors done with all the IDs and the total number of possible critical errors. Patient's ability to use inhalers (ABL) was defined as the quotient between the number of inhaler devices without any critical errors and the total number of IDs used. A statistical analysis was performed with linear regression modelling.

Results: We studied 300 participants performing 521 inhalation manoeuvres with 10 different IDs. Misuse due to critical errors was observed in a total of 118 (39.3%) patients. 250 (83.3%) participants responded to the BMQ, and misuse due to critical errors was observed in 92 (36.8%) of them. In this sub-group of patients there was a statistical significant correlation between the BMQ Necessity score and total number of critical errors (TCE, r = -0.289) or the ability to use IDs (ABL, r =0.310). The patients' beliefs about the necessity to use IDs were respectively significant direct and inverse predictors of ability to use inhalers ($\beta = 0.310$; $p = 0.003$; $r2 = 0.096$) and misuse due to critical errors ($\beta = -0.289$; $p = 0.005$; $r2 = 0.084$). In this group of patients the beliefs about inhalers' need account for 9.6% of the observed variance in the ability to use them.

Conclusions: When teaching a correct inhaler technique, physicians should take in account and reinforce the patients' beliefs about the need of inhaled medication.

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A Duarte-de-Araújo[1,2,3], P Teixeira [1,2], C Durães[3], M Figueiredo[3], V Hespanhol [4,5], J Correia-de-Sousa [1,2,6]

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Key words: COPD, Tools, Medical decision

Discordances in the diagnosis and treatment of patients with COPD when using different tools

Objectives: To evaluate how the criteria defining airflow limitation, the questionnaires used in symptoms evaluation and the GOLD ABCD assessment tool version can influence medical decision in COPD patients.

Methods: We conducted a post-hoc analysis of a cross-sectional study on COPD patients diagnosed according to GOLD criteria and recruited consecutively in the ambulatory pulmonary clinic of Hospital de Guimarães, between March 2016 and May 2017. Evaluation of symptoms was done using the COPD Assessment Test (CAT) and the Medical Research Council Dyspnea (mMRC) questionnaires. The number of acute exacerbations (ECOPD) referred in the previous year was evaluated. Spirometries were performed according to ERS/ATS criteria, and referenced according to the Global Lung Function Initiative prediction equations (GLI 2012). A statistical analysis was then performed with IBM SPSS Statistics for Windows.

Results: 46 (15.2%) out 303 patients had FEV_1/FVC > lower limit of normal (LLN 5%, Z-score -1.64). They were significantly less symptomatic, less frequent exacerbators and the mean FEV_1% was significantly higher. According to GOLD guideline they have a milder form of COPD, but when using the LLN criteria to define airflow limitation, COPD wold be ruled out, and pharmacologic treatment could be significantly different.

207 patients (68.3%) responded to both CAT and mMRC questionnaires. In this sub-group of patients, and using the GOLD proposed cut-points to consider more breathlessness or more symptomatic impact that needs regular treatment, discordance was found in 47 (22.7%) patients, 15.5% in low-risk A and B categories and 7.2% in C and D high-risk categories. Using different validated questionnaires, some patients moves between groups, deserving different pharmacologic therapy.

During the period of patients' recruitment, a refinement of the ABCD assessment tool was proposed in the 2017 GOLD Report, and the distribution of patients was 23.1%, 39.6%, 2.3% and 35% from A to D groups. However, using the previous GOLD version, the distribution of patients was 16.8%, 21.8%, 7.6% and 53.8% from A to D. Discordance was obtained in 24.4% of patients, with significant differences in the proposed pharmacologic treatment algorithm and management strategies.

Conclusions: Medical decision and pharmacologic treatment can be significantly different when using different validated tools, as are standardised questionnaires or clinical guidelines.

Abstract published in Chest. 2019; 155(4) Suppl, 225 A.

COPD: analysing factors associated with a successful treatment

To evaluate if non-adherence to inhaled medications, inhalers mishandling or the prescribers' non-adherence to GOLD strategy are associated with mMRC grade, CAT score, COPD acute exacerbations or FEV_1%.

A cross-sectional study on COPD was conducted on ambulatory COPD patients ≥ 40 years, diagnosed according to GOLD criteria. A survey of demographic and clinical data was applied. Adherence was assessed by using the Measure of Treatment Adherence (MTA) questionnaire. Inhalation technique was evaluated by using checklists of steps and inhalers' misuse was defined when one or more critical errors were done. To evaluate prescribers' non-adherence to GOLD strategy, patients' current medication was compared to therapeutic standards proposed by the GOLD 2017 for the same ABCD groups.

We studied 303 participants, 79.5% males, mean age = 67.5 years. A total of 285 completed the MTA questionnaire. Non-adherence was referred by 16.5% of patients. A significant negative association was found between adherence and CAT score and FEV_1%. 285 patients performed 499 inhalations manoeuvres. Inhalers' misuse, observed in 113 (39.6%) patients, was not associated with CAT score, mMRC grade, ECOPD or FEV_1%. We found deviations from the GOLD in 133 (44.3%) patients, which were negatively related to CAT score, mMRC grade and ECOPD.

Symptoms and airflow limitation were associated with a better adherence to medication. We failed to prove an association between inhalers' misuse and symptoms, exacerbations and airflow limitation. Previous ECOPD seems to improve prescribers' adherence to treatment guidelines.

To understand and correct common and modifiable factors related to poor clinical outcomes.

APPENDIXES

Guimarães, 27 de Novembro de 2015

A quem possa interessar da
Escola de Ciências da Saúde da UM

O Senhor Dr. António Manuel Duarte Araújo, Assistente Hospitalar Graduado de Pneumologia em funções no Serviço de Pneumologia do Hospital Senhora da Oliveira e com quem tenho trabalhado regularmente desde 1994, tem desempenhado as suas funções com competência e dedicação manifestando também possuir as características intelectuais, de trabalho e de persistência indispensáveis para ter sucesso num projeto desta natureza..

Exprimo a minha opinião por solicitação do Sr. Dr. Duarte Araujo e para ser apresentada conjuntamente com outros documentos para a candidatura de um programa doutoral da Escola das Ciências da Saúde da Universidade do Minho.

Com os melhores cumprimentos

Mª Manuel Figueiredo

Assistente Hospitalar Senior de Pneumologia

Diretora do Serviço de Pneumologia do H. Senhora da Oliveira

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Universidade do Minho
Escola de Ciências da Saúde

Declaração

Declaro a aceitação da responsabilidade, como orientador, pelo acompanhamento das actividades de investigação do Licenciado Duarte Araújo com o projecto com o título "Estudo de Fatores Condicionantes de Sucesso Terapêutico na Doença Pulmonar Obstrutiva Crónica", no âmbito do 3º Ciclo de Estudos do Programa Doutoral em medicina da Escola de Ciências da Saúde da Universidade do Minho. Este projecto terá como co-orientador o Professor Venceslau Hespanhol, Professor Agregado da Faculdade de Medicina da Universidade do Porto.

Braga, 1 de Novembro de 2015

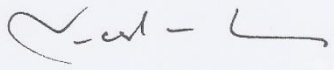
Jaime Correia de Sousa, MD, PhD

DECLARAÇÃO

António Duarte Araújo é um pneumologista experiente, cuja formação se iniciou no S. de Pneumologia do H. S. João, onde teve oportunidade de desenvolver as suas capacidades técnico-científicas. Realizou e colaborou em várias investigações, envolvendo as áreas da ciência básica e da clínica, o que constituiu a base científica que lhe permitiu, ao longo da sua carreira, evoluir em diferentes contextos. Aceitou o desafio de integrar a equipa de pneumologia no H. Sª da Oliveira em Guimarães e colaborou na criação e no desenvolvimento do Serviço de Pneumologia desse Hospital. Na posse de uma relevante experiência pneumológica, mormente, em doenças obstrutivas pulmonares, tem como objetivo ir mais longe. Associando a metodologia cientifica ao conhecimento clínico, pretende melhorar a eficiência diagnóstica, terapêutica e o prognóstico dos doentes com Doença Pulmonar Obstrutiva Crónica (DPOC).

Desenhou um projeto de investigação doutoral, da qual serei co-orientador, onde se propõe estudar doentes com DPOC, fundamentalmente focado nos aspetos do diagnóstico e tratamento da doença cujos resultados irão, por certo, contribuir para um melhor conhecimento da DPOC e para um benefício efetivo dos cuidados de saúde destes doentes.

Porto, 28 Novembro, 2015



Venceslau Pinto Hespanhol
(Prof. Associado Convidado, com Agregação
Faculdade Medicina Porto)

Termo de Consentimento Informado para Estudo de Investigação

Estudo de Fatores Condicionantes de Sucesso Terapêutico na Doença Pulmonar Obstrutiva Crónica

Eu, abaixo-assinado, _____ fui informado de que o Estudo de Investigação acima mencionado se destina a trabalho de doutoramento em medicina. Sei que neste estudo está prevista a realização apenas de inquéritos, tendo-me sido explicado em que consistem. Foi-me garantido que todos os dados relativos à identificação dos participantes neste estudo são confidenciais e que será mantido o anonimato. Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto. Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo _____.

Data	Assinatura
___/___/_____	_____

Investigador Responsável: Dr. Duarte de Araújo

Data	Assinatura
___/___/_____	_____

GOVERNO DE PORTUGAL

CHAA

Comunicação Interna nº 49/CES

Data 11/11/2015

Para Centro Académico

Assunto: Pedido de emissão de parecer para estudo de Investigação

Nos termos da reunião desta Comissão de Ética, dá-se conhecimento a V. Exas do parecer emitido em reunião do passado dia 11 de Novembro de 2015:

> "Apreciado o pedido de realização de um estudo de investigação subordinado ao tema "Estudo de factores condicionantes de sucesso terapêutico na Doença Pulmonar Obstrutiva Crónica", a realizar no Serviço de Pneumologia, tendo como médico investigador principal o Assistente Hospitalar de Pneumologia, Dr. *António Manuel Silva Duarte Araújo*, A Comissão de Ética em face das informações constantes do processo entendeu nada a opor ao estudo proposto, desde que na sua execução sejam cumpridos rigorosamente os princípios aplicáveis da deliberação nº 227 da CNPD, seja preservada a confidencialidade dos dados e o anonimato dos doentes e se comprometa a entregar a esta Comissão de Ética fotocópias assinadas dos formulários de informação e consentimento esclarecido do doente ou do seu representante legal."

Com os melhores cumprimentos.

João Lima Reis
Presidente da CES

CES/mg

Universidade do Minho

SECVS

Subcomissão de Ética para as Ciências da Vida e da Saúde

Identificação do documento: SECVS 016/2016

Título do projeto:

: Estudo de Fatores Condicionantes de Sucesso Terapêutico na Doença Pulmonar Obstrutiva Crónica

Investigador(a) responsável: Dr.ª Maria Manuel Figueiredo; Serviço de Pneumologia, E.P.E. - Hospital Senhora da Oliveira; e António Manuel Duarte Araújo, Escola de Ciências da Saúde, Universidade do Minho, e Serviço de Pneumologia, E.P.E. - Hospital Senhora da Oliveira

Subunidade orgânica: Escola Ciências da Saúde, Universidade do Minho

Outras Unidades: Serviço de Pneumologia, E.P.E. - Hospital Senhora da Oliveira

PARECER

A Subcomissão de Ética para as Ciências da Vida e da Saúde (SECVS) analisou o processo relativo ao projeto em epígrafe. Os documentos apresentados revelam que o projeto obedece aos requisitos exigidos para as boas práticas na experimentação com humanos, em conformidade com o Guião para submissão de processos a apreciar pela Subcomissão de Ética para as Ciências da Vida e da Saúde. Face ao exposto, a SECVS nada tem a opor à realização do projeto.

O estudo deverá solicitar Parecer e/ou autorização e seguir as diretivas nacionais e/ou locais de cada lugar de recolha, como aplicável, particularmente das Unidades Hospitalares e/ou Unidades de Saúde onde será realizado e/ou onde serão recolhidas as amostras e/ou dados e/ou aplicados os questionários, se aplicável.

Salientam-se as seguintes considerações éticas:

A realização de projetos de investigação deverá em consideração as regras de conduta e diretivas de boas práticas no âmbito da investigação clínica com seres humanos. Deverá ser solicitado Parecer e/ou Autorização, incluindo notificação de tratamento de dados pessoais à Comissão Nacional de Proteção de Dados, e seguir as diretivas

nacionais e/ou locais, de cada lugar de recolha, como aplicável, incluindo de Unidades Hospitalares e/ou Unidades de Saúde onde será realizado o estudo, e/ou onde serão recolhidas as amostras e/ou dados e/ou aplicados os questionários, se aplicável.

Salienta-se o respeito pelas normas e as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996, Edimburgo 2000, Washington 2002, Tóquio 2004 e Seul 2008), da Directiva 95/46/EC do Parlamento Europeu e do Conselho, das Directrizes Sobre as Boas Práticas Clínicas da EMEA - Agência Europeia do Medicamento (Londres 2000), das Directrizes Éticas Internacionais para a Pesquisa Envolvendo Seres Humanos da Organização Mundial de Saúde (Genebra 2002), das Directrizes Éticas Internacionais para os Estudos Epidemiológicos do Conselho de Organizações Internacionais de Ciências Médicas (Genebra 2009) e da Resolução da Assembleia da República nº1/2001.

Quando aplicável o Consentimento Informado recomendam-se as normas e/ou documentos-guia da Direção Geral de Saúde e/ou da ARS Norte na elaboração do mesmo. A inclusão dos participantes em qualquer um dos âmbitos de investigação considerados num Projeto de Investigação está subjacente o seu consentimento escrito (Lei n.º 12/2005, de 26 de janeiro; Lei n.º 46/2007, de 24 de agosto). O preenchimento e assinatura do formulário de consentimento informado, livre e esclarecido, deverá ser feito em duplicado, garantindo a privacidade e confidencialidade dos dados pessoais e o direito a recusar/abandonar o estudo sem sofrer qualquer penalização.

Indica-se que recolha de produtos biológicos deverá ter em conta os princípios para obtenção e conservação de material biológico (Art. 18.º) da Lei n.º 12/2005, de 26 de janeiro. O tratamento das informações de saúde recolhidas terá em consideração os princípios aplicáveis aos tratamentos de dados pessoais efetuados no âmbito de Investigação Clínica, definidos pela Comissão Nacional de Proteção de Dados e decorrentes da Deliberação nº 1704/2015.

Informações pessoais tratadas não deverão ser identificáveis, mas sim irreversivelmente anonimizadas (Art. 3.º da LPDP), e todos os dados obtidos no âmbito de um Projeto de Investigação estão ao abrigo de medidas técnicas e organizativas adequadas que dão cumprimento ao disposto no Art. 14.º e Art. 15.º da LPDP. Aplica-se ainda o disposto no n.º1 do Art. 17º da LPDP relativamente ao sigilo profissional. Quando não for possível a anonimização dos dados, estes deverão codificados de acordo com uma chave específica, acessível apenas aos investigadores do estudo, e que dificulta a identificabilidade dos participantes, tal como especificado na Deliberação

nº 1704/2015 da CNPD. Os dados obtidos deverão ser conservados de forma a permitir a identificação dos seus titulares apenas durante o período necessário para a prossecução das finalidades da recolha ou do tratamento posterior, tal como definido no Art. 5.º, n.º 1, alínea e), da LPDP.

O Modelo de declaração de compromisso e confidencialidade utilizado pelo IR deverá ser seguido e assinado por outros investigadores ou colaboradores na investigação, conforme aplicável, destinado a documentar o seu envolvimento nas garantias de confidencialidade e boas práticas dadas pelo(a) IR Sempre que necessário, os membros da equipa de investigação deverão assinar uma Declaração de Interesses e Incompatibilidades de acordo com o Decreto-lei n.º 14/2014, de 22 de janeiro.

Neste contexto, assume-se que os investigadores que trabalham com amostras humanas, ou com a análise de dados, estão obrigados a manter sigilo profissional sobre os dados pessoais e sobre os resultados ou demais obtidos, segundo a ética profissional, nunca devendo, por isso, fazer uso dos mesmos a não ser para o fim a que se destinam. Esta obrigação mantém-se em efeito após término do projeto de investigação."

Braga, 29 de setembro de 2016.

A Presidente

MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO

Assinado de forma digital por MARIA CECÍLIA DE LEMOS PINTO ESTRELA LEÃO
Dados: 2016.09.30 11:24:24 +01'00'

(Maria Cecília de Lemos Pinto Estrela Leão)

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

AUTORIZAÇÃO N.º 5148 /2016

I. Pedido

António Manuel Silva Duarte de Araújo notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de elaborar um estudo de fatores condicionantes de sucesso terapêutico na doença pulmonar obstrutiva crónica.

Trata-se de um estudo observacional prospetivo que tem como objetivo a «identificação de fatores que pela sua correção se possam traduzir em melhoria dos cuidados de saúde prestados aos doentes com DPOC que frequentam a consulta de pneumologia do hospital da Senhora da Oliveira, Guimarães (HG)».

A população alvo do estudo serão pessoas, maiores de 40 anos, com diagnóstico de Doença Pulmonar Obstrutiva Crónica.

Os dados serão recolhidos num "caderno de recolha de dados" no qual não há identificação nominal do titular, apenas a primeira letra do primeiro nome, primeira letra do apelido, e números correspondentes a dia, ano e mês de nascimento. Na base de dados não entrará nenhuma desta informação, não havendo qualquer identificação do participante.

As categorias de dados pessoais tratados são as seguintes: n.º do participante no estudo, sexo, idade, sintomas e doenças respiratórias, medicamentos usados e adesão à medicação.

II. Apreciação

A CNPD já se pronunciou na sua Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da Lei 67/98, de 26 de outubro, com as alterações da Lei n.º 103/2015, de 24 de agosto (LPDP), bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde.

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No caso em apreço, a notificação enquadra-se no âmbito tipificado pela referida Deliberação.

A informação tratada é recolhida de forma lícita (art.º 5.º, n.º1, alínea a), da LPDP) para finalidades determinadas, explícitas e legítimas (cf. alínea b) do mesmo artigo) e a informação recolhida não é excessiva.

O fundamento de legitimidade é o consentimento expresso e escrito do titular (cf. artigo 7.º, n.º 2, da LPDP).

Os titulares dos dados, previamente ao consentimento (que deve ser informado, livre, expresso e específico), deverão ser informados sobre a natureza, o alcance, as consequências e os riscos do estudo, bem como o direito de se retirar do mesmo, sem quaisquer consequências (cf. alínea j) do artigo 2.º da Lei n.º 21/2014, de 16 de abril).

III. Decisão

Assim, tendo em atenção o disposto nas disposições combinadas dos artigos 28.º, n.º1, alínea a), e 30.º da LPDP, e as condições e limites fixados na referida Deliberação, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados pessoais nos seguintes termos:

Responsável pelo tratamento: António Manuel Silva Duarte de Araújo;

Finalidade: estudo de fatores condicionantes de sucesso terapêutico na doença pulmonar obstrutiva crónica;

Categoria de Dados pessoais tratados: n.º do participante no estudo, sexo, idade, sintomas e doenças respiratórias, medicamentos usados e adesão à medicação;

Entidades a quem podem ser comunicados: Não há;

Formas de exercício do direito de acesso e retificação: Junto do médico assistente;

Interconexões de tratamentos: Não há;

Transferência de dados para países terceiros: Não há;

Prazo de conservação: o código do titular deve ser destruído no prazo de 5 anos após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 1704/2015 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente,

COMISSÃO NACIONAL DE PROTECÇÃO DE DADOS

dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 14 de junho de 2016

Filipa Calvão (Presidente)

Graffar Social Classification (Classificação Social de Graffar, adaptada):

PROFISSÃO

1. Grandes industriais e comerciantes. Gestores de topo de empresas /administração pública. Profissões liberais. Professores, diretores de bancos, militares de alta patente.
2. Médios industriais / comerciantes / agricultores. Dirigentes intermédios e quadros técnicos de empresas / administração pública; peritos, técnicos.
3. Pequenos industriais / comerciantes; encarregados, operários qualificados.
4. Pequenos agricultores, operários semiqualificados com ensino obrigatório, escriturários, polícias sem formação superior, cozinheiros.
5. Mão-de-obra indiferenciada; jornaleiros, ajudantes de cozinha, trabalhadores da limpeza, operários não especializados e sem ensino obrigatório.

INSTRUÇÃO

1. Licenciatura ou superior.
2. Bacharelato, curso superior.
3. Ensino secundário completo; 9º ano mais curso laboral.
4. Escolaridade obrigatória segundo a idade.
5. Não completou a escolaridade obrigatória.

PRINCIPAL FONTE DE RENDIMENTO

1. Propriedade; fortuna herdada ou adquirida.
2. Altos vencimentos e honorários.
3. Vencimentos certos.
4. Remuneração incerta; por semana, por tarefa, por hora.
5. Assistência (excluindo pensões de desemprego / incapacidade laboral.

TIPO DE HABITAÇÃO

1. Luxuosa.
2. Espaçosa e confortável; ar condicionado/ aquecimento central.
3. Casas ou andares modestos mas bem conservados, cozinha e WC completo e dentro de casa; eletrodomésticos essenciais.
4. Habitação degradada, sem eletrodomésticos essenciais, cozinha ou WC fora de casa ou incompletos.
5. Imprópria.

LOCAL DE RESIDÊNCIA

1. Bairro residencial elegante.
2. Bom local; ruas largas, casas confortáveis e bem conservadas.
3. Zona antiga ou rural, ruas estreitas, casas pouco confortáveis ou mal conservadas.
4. Bairro operário ou social
5. Bairro de lata.

CLASSIFICAÇÂO SOCIAL

1. Classe I: famílias cuja soma varia entre 5 – 9 pontos
2. Classe II: 10- 13 pontos
3. Classe III: 14- 17 pontos
4. Classe IV: 18- 21 pontos
5. Classe V: 22- 25 pontos

Medida de Adesão aos Tratamentos (MAT)

1. Alguma vez se esqueceu de tomar os medicamentos para a sua doença?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
2. Alguma vez foi descuidado com as horas da toma dos medicamentos para a sua doença?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
3. Alguma vez deixou de tomar os medicamentos para a sua doença por se ter sentido melhor?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
4. Alguma vez deixou de tomar os medicamentos para a sua doença, por sua iniciativa, após se ter sentido pior?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
5. Alguma vez tomou mais um ou vários comprimidos para a sua doença, por sua iniciativa, após se ter sentido pior?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
6. Alguma vez interrompeu a terapêutica para a sua doença por ter deixado acabar os medicamentos?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6
7. Alguma vez deixou de tomar os medicamentos para a sua doença por alguma outra razão que não seja a indicação do médico?					
Sempre	quase sempre	com frequência	por vezes	Raramente	Nunca
1	2	3	4	5	6

Delgado A, Lima M. Contributo para a validação concorrente de uma medida de adesão aos tratamentos (contribution to concurrent validity of treatment adherence).Psicologia, Saúde e doenças. 2001; 2(2):81-100.

Estudo de Fatores Condicionantes de Sucesso Terapêutico na Doença Pulmonar Obstrutiva Crónica

Nome do doente-

Processo nº-

A- Inquérito demográfico

Nome_____

Processo nº_____

Contacto do dte_____

A-1ª consulta

B-Seguimento há_____anos no serviço de pneumologia.

Sexo 1-M___

2-F___

Idade_____

Estado civil:

C-Casado/união de facto

S-Solteiro

V-viúvo

D-divorciado

Residência: U- ambiente urbano

R- ambiente rural

M- moderadamente urbanizado

Concelho de _____

Com quem vive:

A- Família/marido/esposa____
B- Só___
C- Lar idosos___
D- Outras:_____

Profissão / ocupação_____

Situação laboral:

E- Empregado_____
D- Desempregado_____

B- Baixa médica prolongada_____

R- Reformado_____

O- Outro_____

Rendimento individual:

A- Inferior ao salário mínimo nacional (530 E)_____
B- Entre 1 e 2 SMN (530- 1060 E)_____
C- Entre 2 e 3 SMN (1060-1590 E)_____
D- Maior de 3 SMN (>1590 E)_____

Escolaridade:

A- Analfabeto ou não completou ensino primário (até 3ª classe)____
B- Ensino primário completo ("4ª classe")_____
C- Ensino básico (COMPLETOU 9º ANO)____
D- Ensino secundário (completou 12º ano)____
E- Frequência do ensino superior_____

Teste de GRAFFAR:

Classificação social: pontos_____classe(I-V)_____

O senhor(a) sofre de DPOC:

Sabe o que é a DPOC? Sim___Não_____

Sabe por outro nome? Qual_____

Não tem qualquer ideia?_____

O seu médico disse-lhe que sofria de DPOC? Sim___não____disse-lhe por outras palavras? Quais?_____

Com que palavras caraterizaria (descreveria) melhor a sua doença?_____
_____

Sabe que é uma doença crónica, para toda a vida?_____

Sabe se é uma doença grave? _____Porquê?_____

Procurou informação sobre a sua doença? Não____Sim_____

Junto do médico especialista?_____

Junto do médico de família?____Outro profissional?_____Outra pessoa?_____

Enfermeiro?_____Farmacêutico/tec de farmácia?_____Internet?_____ Outro?_____

Hábitos tabágicos:

A- Fumador
B- Ex-fumador (definido como tendo deixado de fumar há mais de 6 meses): deixou de fumar há_____anos.
Fuma/fumou: desde_____ até_____ Média de_____/dia

+

desde____ até _____média de_____/dia :

Total de anos_____UMA:_____

C- Não fumador
D- Fumador passivo
E- Fumador intermitente

Outras exposições relevantes para DPOC:

Exposição ocupacional: Profissão / Ocupação?_____ Tipo de exposição?_____nº anos_____

+

Exposição ocupacional: Profissão / Ocupação?_____ Tipo de exposição?_____nº anos_____

A- Sim
B- Não

(Só para o género feminino): exposição doméstica a gases, fumos ou vapores com origem na biomassa:

Tipo de exposição_____

Quando?_____

Na sua casa, em qualquer altura da sua vida e por mais de 6 meses, usaram fogão a carvão/lenha/madeira/petróleo para **cozinhar?**

A- Sim
B- Não

Por quantos anos esteve perto desse fogão para cozinhar? ____anos

E em média, quantas horas por dia ficava perto desse fogão? _____

Ainda usam esse tipo de fogões em sua casa? S____N____

Esse fogão tem ou tinha chaminé para o exterior? S___N___

Em sua casa, em toda a sua vida e por mais de 6 meses, usaram carvão/lenha/madeira **para aquecer a casa**?

A- Sim
B- Não

Por quantos anos usaram carvão/lenha/madeira para aquecer a casa? ____anos

E em média quantos dias por ano ficava perto desse aquecimento? ____dias

E esse aquecimento tinha chaminé para o exterior? _____

B- Dados clínicos

Nº de agudizações no último ano: 0 - 0

1 - 1

2 - ≥ 2 ou ≥ 1 internamento

Nº de internamentos no último ano por agudização de DPOC: 0- 0

1- 1

2- ≥ 2

Nº internamentos cuidados intensivos_____

Nº de recorrências SU/ consultas médicas não de rotina por agudização da DPOC_____

Sintomatologia HABITUAL, não a que tem hoje, mas a que sente na maior parte dos dias; se **OCASIONAL**, referir:

A-tosse ____

B-expetoração (escarro no peito)_____

C-hemoptises/expetoração hemoptoica (expetoração com sangue)_____

D-pieira (chiadeira no peito)_____

E-dispneia (falta de ar, cansaço a respirar)_____

F-opressão (aperto) tórax_____

Sintoma mais importante/predominante_____

Sintoma mais preocupante_____

Predominância da sintomatologia (dispneia, expetoração, tosse, pieira):

A- Exercícios/esforços físicos___

B- Alterações meteorológicas (“mudanças de tempo”)____

C- Sazonal inverno_____

D- diurna____

E- Noturna____

F- Início manhã_____

G- final da tarde/ anoitecer_____

H- Sasonal verão_____

I- Exercício + noturna + sazonal

J- Exercício + alterações meteorológicas

K- Exercício + alterações meteorológicas + início manhã

L- Exercício + alterações meteorológicas + sazonal

M- Exercício + inicio manhã

N- Exercício + sazonal

O- Exercício + noturna

P- Alterações meteorológicas + sazonal

Q- Exercício + alterações meteorológicas + inicio manhã

R- Exercício + final tarde

Comorbilidades (avaliadas por história clínica, informação familiares, medicação que faz, relatórios médicos/cartas de alta hospital, informação no processo hospitalar, informação do médico de família, plataforma de dados da saúde):

A-HTA___

B-Patologia cardiovascular:_____

doença cardíaca isquémica___

ICC___ Disritmia____outra_____

C- Diabetes mellitus _____

D- Doença de refluxo gastro esofágico_____

E- Depressão/ansiedade____

F- Neoplasia pulmonar____

G- SAOS____

H- Dislipidemia _____

I- Osteoporose _____

J-Asma atual _____

K- AVC/AIT

L- Outros_____

História de asma ou “bronquite” em criança/jovem/antes dos 40 anos_____

Obesidade (IMC >30)_____

História atual sugestiva de bronquite crónica (BC: tosse e /ou expetoração por mais de 3 meses consecutivos, 2 ou mais anos consecutivos - “passa todo o inverno com tosse e expetoração?”)_____

A- Sim

B- Não

RXt - descrição: _____
_____

TAC torax?_____data_____descrição _____
_____

Sequelas de TP?_____ nódulo(s) pulmonares?_____ massa(s)? _____
bronquiectasias?_____tipo?_____
localização? _____

Insuficiência respiratória crónica? _____

Valores da gasometria arterial? _____

OLD?_____VNI?_____ qual?_____

Caraterização da gravidade da DPOC:

Dispneia (Escala de Dispneia mMRC: Graus 0-4)

Assinale com uma cruz (X), o quadrado ☐ correspondente à afirmação que melhor descreve a sua sensação de falta de ar.

GRAU 0
Sem problemas de falta de ar exceto em caso de exercício intenso.
"Só sinto falta de ar em caso de exercício físico intenso". ☐

GRAU 1 Falta de fôlego em caso de pressa ou ao percorrer um piso ligeiramente inclinado.
"Fico com falta de ar ao apressar-me ou ao percorrer um piso ligeiramente inclinado". ☐

GRAU 2
Andar mais devagar que as pessoas da minha idade devido a falta de fôlego, ou necessidade de parar para respirar quando anda no seu passo normal.

"Eu ando mais devagar que as restantes pessoas devido à falta de ar, ou tenho de parar para respirar quando ando no meu passo normal". ☐

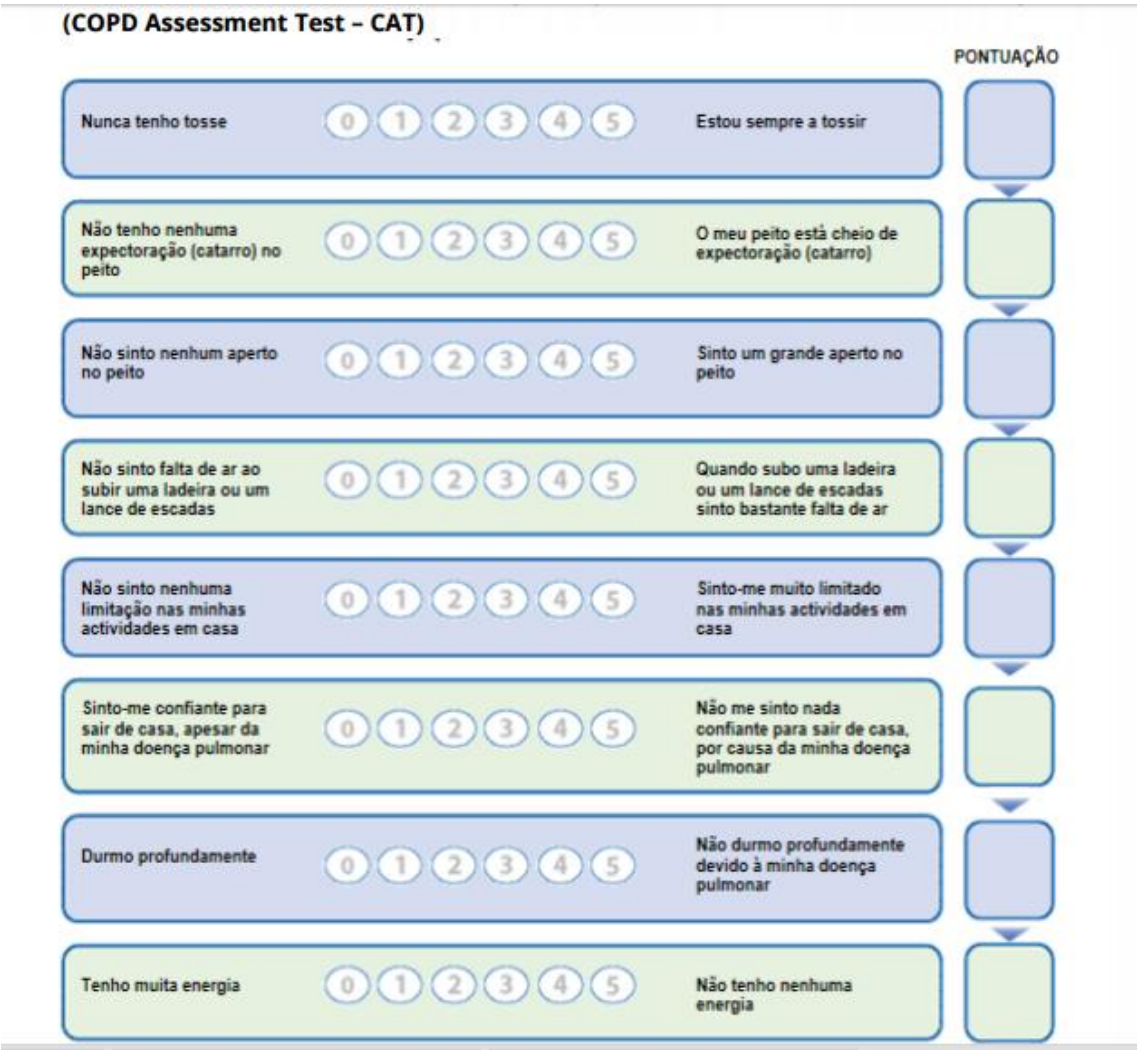
GRAU 3
Paragens para respirar de 100 em 100 metros ou após andar alguns minutos seguidos.

"Eu paro para respirar depois de andar 100 metros ou passados alguns minutos". ☐

GRAU 4 Demasiado cansado/a ou sem fôlego para sair de casa, vestir ou despir.
"Estou sem fôlego para sair de casa". ☐

Impacto no bem-estar - CAT (COPD Assessment Test): registo de pontuação

Pontuação CAT	Nível de impacte
<10	Reduzido
10–20	Médio
21–30	Alto
>30	Muito alto



Função respiratória: Anexar **espirometria.**

Pós broncodilatação	Pós broncodilatação
FEV_1 / FVC < 0.7	GOLD 1 – Ligeiro $FEV_1 \geq 80\%$
	GOLD 2 – Moderado $FEV_1 < 80\%$ e $\geq 50\%$
	GOLD 3 – Grave $FEV_1 < 50\%$ e $\geq 30\%$
	GOLD 4 – Muito Grave $FEV_1 < 30\%$

Caraterização da terapêutica prescrita:

Registo de todas as terapêuticas atuais para DPOC (nomes dos medicamentos):
_____
_____
_____

SABA, SAMA, LABA, LAMA, ICS, ICS+LABA, LABA+LAMA, teofilina, outros _____

Faz vacinação antigripal? S N

Fez prevenção doença pneumocócica? S N

Nebulizador: sim____ não_____ tipo de uso_____

Oxigenoterapia (OLD)_____

Oxigenoterapia de deambulação_____

Ventiloterapia? _____ descrição _____

Reabilitação respiratória?_____

Aconselhamento de evicção tabágica?_____

Aconselham/ exercício físico? _____

Aconselhamento nutricional? _____

Adesão à medicação inalatória:

Estas perguntas referem-se apenas à medicação inalatória (inaladores, "bombinhas") para a sua doença respiratória:

Medida de Adesão aos Tratamentos (MAT)

1. Alguma vez se esqueceu de tomar os medicamentos inalatórios para a sua doença respiratória?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

2. Alguma vez foi descuidado com as horas da toma dos medicamentos inalatórios para a sua doença respiratória?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

3. Alguma vez deixou de tomar os medicamentos inalatórios para a sua doença respiratória por se ter sentido melhor?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

4. Alguma vez deixou de tomar os medicamentos inalatórios para a sua doença respiratória após se ter sentido pior?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

5. Alguma vez fez a sua medicação inalatória mais vezes que o recomendado, por sua iniciativa, após se ter sentido pior?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

6. Alguma vez interrompeu a sua medicação inalatória por a ter deixado acabar?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

7. Alguma vez deixou de tomar a medicação inalatória para a sua doença respiratória por outra razão que não seja a indicação do médico?

sempre	quase sempre	com frequência	por vezes	raramente	nunca
1	2	3	4	5	6

BMQ:

Gostariamos de saber qual a opinião que tem acerca dos **medicamentos por via inalatória ("as bombinhas" ou inaladores**) que está a tomar para a sua **doença respiratória (para a sua "falta de ar" ou para a sua "bronquite")**. As frases que se seguem são opiniões que as pessoas têm acerca dos medicamentos que tomam. Por favor indique em que grau concorda ou discorda, escolhendo a resposta adequada.

(perguntas a serem feitas pelo entrevistador)

BMQ1- Neste momento a minha saúde depende de medicamentos.

N1	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

BMQ2- Ter que tomar medicamentos preocupa-me.

C1	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

3- A minha vida seria impossível sem medicamentos.

N2	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

4- Sem medicamentos eu estaria muito doente.

N3	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

5- Às vezes eu preocupo-me com os efeitos que os medicamentos me podem provocar se eu os tomar durante muito tempo.

C2	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

6- Os meus medicamentos são um mistério para mim.

C3	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

7- A minha saúde no futuro irá depender de medicamentos.

N4	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

8- Os meus medicamentos perturbam a minha vida.

C4	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

9- Às vezes preocupo-me com a possibilidade de ficar muito dependente dos meus medicamentos

C5	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

10- Os meus medicamentos impedem que eu fique pior.

N5	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

11- Estes medicamentos dão-me desagradáveis efeitos secundários.

C6	5-concordo totalmente	A
	4-concordo	A
	3-não tenho a certeza	B
	2-discordo	C
	1-discordo totalmente	C

Avaliação da técnica inalatória:

Nome:_____
Processo nº_____

Nº de DI em uso atualmente _____ DI preferido pelo doente_____

Motivo: A (+ fácil); B (+ prático); C (Habitual); D (características do inalador) E (requer menor esforço / sabor do medicamento) F (não sabe) G (outro)

DI(s) preteridos pelo doente, ainda que usados anteriormente (de todos os que usou): _____

Chek-list de demonstração de uso dos dispositivos inalatórios**:**

Inalador pressurizado: 

1- Retirar a tampa, agitar bem (suspensões), segurar corretamente (posição correta).

2- Expirar lentamente para fora antes de pressionar.

Expirou para dentro do inalador?

3**- Colocar na boca e inspirar lenta e profundamente ao mesmo tempo que pressiona para libertar o aerossol (sincronização),** continuar a respirar lentamente pela boca até encher os pulmões.

Verificar:

- **Atuação contra a língua, dentes ou lábios?**
- **Respirou pelo nariz?**
- **Atuação antes de iniciar inspiração ou no fim desta?**
- **Múltiplas atuações?**
- **Suspendeu a respiração após disparo?**

4- Retirar da boca e suspender respiração.

Expirou para dentro do inalador?

5- Limpar o bocal, colocar tampa e lavar a boca se necessário (corticoides isolados ou em associação).

Inalador pressurizado com câmara expansora: 

1- **Retirar a tampa do inalador, agitar bem (suspensões) e colocar o inalador na câmara expansora na posição vertical.**

2- Segurar corretamente e expirar lentamente, preferencialmente para fora da CE antes de pressionar.

3- **Colocar na boca e inspirar lenta e profundamente após pressionar o inalador.**

Verificar:

Múltiplas atuações?

Inspirou pelo nariz?

Não selou a boca no bocal?

4- Continuar a respirar (cerca 6 vezes ou 10 segundos) e remover a camara expansora da boca.

5- Retirar o inalador da câmara expansora, limpar o bocal, colocar a tampa e lavar a boca se necessário (CI). Ver higiene da câmara expansora.

 **Respimat®**

1- **Girar a base até se ouvir um estalido e abrir totalmente a tampa.**

Dispositivo sem o carregador?

2- Expirar totalmente para fora do inalador.

Expirou para dentro do inalador?

3- **Colocar na boca, apontar na horizontal e disparar ao mesmo tempo que inspira pela boca lenta e profundamente (sincronização)**.

4- Retirar o inalador da boca, suspender a respiração, depois expirar.

(Repetir de 1 a 4 no caso de 2 inalações)

5- Limpar o bocal e repor a tampa.



4 -**Breezhaler®;** **5 - Aeroliser®;** **6 -- Handihaler®**

1- Retirar/levantar tampa e abrir o inalador, retirar cápsula do blister, colocar na câmara e fechar o inalador, e segurando na vertical furar apenas uma ou 2 vezes; soltar botões.

2- Expirar totalmente para longe do inalador.

Expirou para dentro do DI depois de carregado?

3- **Colocar na boca e inspirar rapidamente e profundamente.**
Respirou lentamente?

Respirou pelo nariz?

4- Retirar o inalador da boca, suster a respiração e depois expirar.
Expirou para dentro do inalador ou de imediato?

5- Abrir o inalador, verificar se ficou pó dentro da cápsula, retirar cápsula, fechar o inalador, limpar o bocal, tapar e lavar a boca se necessário. Manobra 3 e 5 interpretadas conjuntamente.

7- Novoliser® / GENUAIR®

1- Retirar a tampa, segurar na horizontal e pressionar até ouvir um clique.

2- Expirar totalmente para fora do inalador.
Expirou para dentro do inalador?

3- Colocar na boca, inspirar rápida e profundamente até ouvir um clique e a cor da janela mudar de verde para vermelho.
Inspirou pelo nariz?

4- Retirar o inalador da boca e suspender a respiração.

Expirou para dentro do inalador?

4- Limpar o bocal, confirmar nº de doses restantes; colocar tampa e lavar boca se necessário (CI).

5-

Diskus® 

1- Abrir totalmente o disco até ouvir estalido; com o dispositivo colocado corretamente e o bocal voltado para o doente, **deslizar a alavanca até ouvir um estalido, sempre com o dispositivo na horizontal.**

2- Expirar totalmente para fora do inalador.

Expirou para dentro do inalador?

3- Colocar o bocal entre os lábios e inspirar rápida e profundamente

Inspiração lenta/superficial?

Inspirou pelo nariz?

4- Retirar da boca e suspender a respiração.

Expirou para dentro do inalador?

5- Limpar e fechar totalmente o inalador e lavar a boca se necessário.

Turbuhaler® 

1- Retirar a tampa, e com o inalador na vertical (ângulo < 45º), rodar a base totalmente para um lado e depois para o outro até ouvir um clique.

Inspirou com o inalador na posição incorreta ou continuou a rodar após clique?

2- Expirar totalmente para fora do inalador.

Expirou para dentro do inalador?

3- Colocar nos lábios e inspirar rápida e profundamente.

Inspirou pelo nariz?

Inspiração lenta ou superficial?

4- Retirar o inalador da boca e suspender respiração.

Expirou para dentro do DI?

6- Limpar o inalador e colocar tampa e lavar a boca se necessário.

Ellipta®

1- Abrir o inalador deslizando totalmente a tampa.

2- Expirar totalmente para fora do inalador.

3- Colocar o inalador nos lábios e inspirar profunda e rapidamente.

Tapou os orifícios de entrada do ar?

Inspirou pelo nariz?

4- Retirar da boca e suster a respiração.

Expirou para dentro do inalador?

5- Limpar e fechar o inalador e lavar a boca se necessário.

Spiromax

1- **Abrir o inalador na vertical e na posição correta, deslizando a tampa até ouvir um estalido.**

6- Expirar totalmente para fora

Expirou para dentro do inalador?

7- **Colocar o bocal do inalador nos lábios na posição vertical correta e inspirar profundamente e rapidamente.**

Inspirou pelo nariz?

Inspirou lenta ou superficialmente?

8- Retirar da boca e suster a respiração.

Expirou para dentro do inalador?

9- Limpar e fechar o inalador e lavar a boca se necessário.