UNIVERSIDADE DA BEIRA INTERIOR
Ciências da Saúde

INHALER TECHNIQUE PERFORMANCE IN ELDERLY PATIENTS WITH ASTHMA AND COPD

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Tese para obtenção do Grau de Doutor em
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Abstract

Chronic Obstructive Pulmonary Disease (COPD) and Asthma affect up to 400 million people worldwide, and almost half of these patients have poor disease control. The elderly are more vulnerable to exacerbations, and that is due to the presence of comorbidities and frequent inhaler misuse. Educational programmes may reduce exacerbation risk, but its real impact on clinical outcomes is still unknown, as well as the main factors associated with individual risk. This thesis aims to evaluate the impact of inhaler technique performance on major outcomes in elderly patients and to identify their principal potential predictors.

Several methods were performed: A systematic review with meta-analysis focusing on interventional studies with inhaler education and clinical outcomes was carried out; through its results, a cost-effectiveness analysis was performed, estimating potential cost-savings and available budget for educational interventions; In addition, a cross-sectional study was performed, aiming to identify major predictors of inhaler performance and clinical risk. Several variables were collected as predictors, as well as the main clinical outcomes; finally, we designed a protocol for a randomised, single-blinded clinical trial, aiming to test the impact of a teach-to-goal placebo device education programme on clinical outcomes, in a one-year follow-up, versus "usual care".

The systematic review with meta-analysis collected data from eight interventional studies and a significant reduction in exacerbation risk of 29% (95% CI=14-41) was observed in the clinical trials. From the cost-effectiveness perspective, the affordable budget for educational interventions was estimated to be up to 1800 euros per patient per year, and the estimated average savings is 311.88 euros per patient per year, which may represent up to 131 million euros for the whole National Health Service. The cross-sectional study was performed with 130 elderly patients, with a mean age of 74.4 (± 6.4) years. The prevalence of errors in the inhaler technique was 71.6% (95% CI: 64-78.5) and that of critical errors was 31.1% (95% CI: 24-38.8). Major predictors of inhaler performance were: cognitive performance, adherence index, male gender, having previous education with placebo device performed by a physician, the existence of allergies or comorbidities with respiratory impact, active smoking and depression. The main predictors of symptoms control were: having previous teaching of inhaler technique delivered by a physician, smoking load, anti-influenza vaccination, depression, respiratory comorbidities, and educational level. Lung function was associated with smoking load, as well as presence of errors in drug activation and absence of end pause.

Our results suggest that interventions with inhaler technique education can significantly reduce the risk of exacerbations in elderly patients with Asthma or COPD, and are cost-effective. Moreover, it is possible to identify patients who are at greater risk of misusing their devices, and also have an increased risk of poor outcomes. However, causal studies with longitudinal designs and well-designed clinical trials should be carried out to clarify the major predictors for individual risk, as well as the real impact of inhaler performance education programmes.

Keywords

Asthma; Chronic Obstructive Pulmonary Disease; Elder; Inhaler Technique

Resumo

A Doença Pulmonar Obstrutiva Crônica (DPOC) e a Asma afetam até 400 milhões de pessoas em todo o mundo, e cerca de metade dos doentes têm a doença mal controlada. Os idosos são mais vulneráveis a exacerbações, e isso deve-se à presença de comorbilidades e frequentes erros no uso dos inaladores. Os programas educacionais podem reduzir o risco de exacerbação, mas o seu real impacto nos resultados clínicos ainda é desconhecido, assim como os principais fatores associados ao risco individual dos doentes. Esta tese tem como objetivo avaliar o impacto da performance da técnica inalatória nos principais parâmetros clínicos em doentes idosos e identificar seus principais preditores.

Vários métodos foram usados: Realizou-se uma revisão sistemática com meta-análise sobre estudos intervencionais com ensino da técnica inalatória nos parâmetros clínicos. Através dos seus resultados, foi realizada uma análise de custo-efetividade, estimando potenciais poupanças de custos e de orçamentação disponível para intervenções educativas. Além disso, foi realizado um estudo transversal, com o objetivo de identificar os principais preditores da performance da técnica inalatória e do risco clínico. Diversas variáveis foram recolhidas como preditores, assim como os principais parâmetros clínicos. Finalmente, desenhou-se um protocolo para um ensaio clínico aleatorizado, de ocultação simples, com o objetivo de testar o impacto de um programa de ensino por treino com dispositivos placebo nos parâmetros clínicos, ao longo de um ano, comparando com "ambiente real" (*usual care*).

Na revisão sistemática com metanálise recolheram-se dados de oito estudos intervencionais, e nos ensaios clínicos observou-se uma redução significativa no risco de exacerbações de 29% (IC95% = 14-41). Na perspetiva da relação custo-efectividade, o orçamento disponível para intervenções educacionais foi estimado em 1800 euros por doente por ano, e a poupança média estimada é de 311,88 euros por doente por ano, o que pode representar 131 milhões de euros para todo o Serviço Nacional de Saúde. O estudo transversal foi realizado com 130 idosos, com média de 74,4 (± 6.4) anos. A prevalência de erros na técnica inalatória foi de 71,6% (IC95%: 64-78,5) e de erros críticos foi de 31,1% (IC95%: 24-38,8). Os principais preditores de desempenho do inalador foram: desempenho cognitivo, índice de adesão, sexo masculino, ensino prévio com dispositivo placebo realizada por um médico, a existência de alergias ou comorbilidades com impacto respiratório, tabagismo ativo e depressão. Os principais preditores do controle dos sintomas foram: receber ensino prévio de técnica inalatória de um médico, carga tabágica, vacinação antigripal, depressão, comorbilidades respiratórias e escolaridade. A função pulmonar foi associada à carga tabágica, assim como à presença de erros na ativação do fármaco e à ausência de apneia final.

Estes resultados sugerem que as intervenções com ensino da técnica inalatória podem reduzir significativamente o risco de exacerbações em doentes idosos com Asma ou DPOC e são custo-efetivas. Além disso, é possível identificar pacientes com maior risco para o uso indevido dos dispositivos, bem como para um maior risco de desfechos clínicos adversos. No entanto, devem ser realizados mais estudos longitudinais de causalidade e ensaios clínicos bem desenhados, de modo a esclarecer os principais preditores do risco individual, bem como o real impacto de programas de ensino sobre técnica inalatória.

Palavras-chave

Asma; Doença Pulmonar Obstructiva Crónica; Idosos; Técnica Inalatória

Resumo Alargado

A Doença Pulmonar Obstrutiva Crónica (DPOC) e a Asma são as principais doenças respiratórias crónicas e afetam cerca de 400 milhões de pessoas em todo o mundo. Aproximadamente metade destes doentes apresenta a sua doença mal controlada, estando com sintomas persistentes, o que lhes confere um risco acrescido de exacerbações e eventos adversos, que muitas vezes colocam a vida em risco. O tratamento da Asma e da DPOC assenta essencialmente na terapia inalatória, que dirige os fármacos diretamente para as vias aéreas. No entanto, a maioria dos doentes não usa corretamente os seus inaladores, comprometendo a eficácia terapêutica e o controlo clínico. Muitos estudos têm sugerido que o bom uso dos dispositivos inalatórios está associado a menor risco de exacerbações e menores custos de saúde.

Os idosos apresentam maior vulnerabilidade para os eventos adversos associados a Asma e DPOC, e isso deve-se a presença de comorbilidades frequentemente associadas, mas também a maior prevalência de erros na técnica inalatória. O correto uso dos dispositivos pode ser ensinado aos doentes através de diversas ferramentas, como folhetos, vídeos ou treino prático por dispositivos placebo, mas o seu real impacto nos resultados clínicos ainda é desconhecido. Por outro lado, é ainda difícil em ambiente real identificar os doentes de maior risco e que devem ser alvo de intervenções personalizadas e prioritárias, quer no que diz respeito ao risco de má técnica inalatória quer no que concerne ao risco de pior controlo da doença e consequentes exacerbações.

Esta tese tem como objetivos gerais avaliar o impacto da técnica inalatória e do seu ensino personalizado, em idosos com Asma ou DPOC, bem como identificar os principais preditores de má performance da técnica inalatória e de acrescido risco clínico.

Para o alcance dos objetivos propostos foram realizadas tarefas em 3 principais fases, através dos seguintes métodos:

- Numa primeira fase realizou-se uma revisão sistemática com meta-análise, abordando estudos com intervenções de ensino da técnica inalatória aos idosos com Asma ou DPOC, e medindo o seu impacto em resultados clínicos. Para tal realizou-se uma pesquisa bibliográfica abrangente, selecionando estudos intervencionais aleatorizados e não aleatorizados, independentemente do método de ensino da técnica inalatória usado, e definindo como resultados principais o controlo clínico de sintomas, a qualidade de vida, a função pulmonar e a taxa de exacerbações. Utilizaram-se as recomendações PRISMA para a avaliação dos resultados obtidos. Através dos

resultados da revisão sistemática sobre o impacto no risco de exacerbações, nomeadamente na redução do risco relativo, realizou-se uma análise de custo-efectividade na perspectiva do prestador de cuidados. Para tal, usou-se um modelo de árvore de decisão, com uma adaptação ao cenário Português, nomeadamente nos custos associados à hipotética intervenção e aos resultados medidos. Elaborou-se um modelo de intervenção baseado em consulta médica e de enfermagem, de frequência anual e que inclui ensino da técnica inalatória bem como avaliação clínica e funcional dos doentes. Avaliou-se o seu potencial impacto económico em termos de poupanças estimadas e de orçamentação disponível para a intervenção. Realizou-se ainda uma análise de sensibilidade para definir limiares de confiança para o melhor e pior cenário, em função dos intervalos de confiança de todos os dados e estimativas usadas.

- Numa segunda fase, realizou-se um trabalho de investigação original e transversal, com idosos com Asma ou DPOC e acompanhados em Cuidados de Saúde Primários. Os principais objetivos foram identificar os preditores de performance da técnica inalatória e de risco clínico. Para tal estimou-se uma amostragem necessária de 130 participantes, com representatividade estatística suficiente para garantir a robustez e os pressupostos necessários à modelação multivariada. Como preditores possíveis identificaram-se e recolheram-se diversas características base de natureza sociodemográfica, clínica e pessoal, bem como dos principais indicadores de performance da técnica inalatória, avaliada por listas de verificação validadas. Como potenciais resultados de medida, identificaram-se os principais indicadores de controlo clínico, qualidade de vida, controlo funcional respiratório e a história de exacerbações prévias.
- Finalmente, e em face dos principais resultados e conclusões previamente recolhidas, desenhou-se um protocolo de ensaio clínico aleatorizado e com ocultação simples. Este estudo terá como objetivo testar um programa de ensino da técnica inalatória, recorrendo a treino prático com dispositivos placebo, ao longo de um ano de acompanhamento, com intervenção realizada aos 0, 3 e 6 meses. O braço de intervenção será comparado com o braço de "ambiente real" (*usual care*), de modo a avaliar o seu impacto no controlo de sintomas, na qualidade de vida, na função pulmonar e no risco anual de exacerbações. Para este estudo estimou-se uma amostragem de 146 participantes (73 em cada braço), que permitirá detetar uma redução de forma estatisticamente significativa de 50% na taxa de exacerbações anuais. O estudo terá ocultação simples dos participantes e contará com diversas medidas de controlo de viés e contaminação, nomeadamente através da duplicação da equipa de investigadores, ocultando a recolha de dados, bem como através da minimização do efeito Hawthorn e através de análises interinas.

A revisão sistemática com meta-análise recolheu dados de quatro ensaios clínicos aleatorizados e quatro estudos intervencionais de desenho pré-pós, envolvendo mais de 1800 participantes. Em todos os estudos foi realizada intervenção com ensino da técnica inalatória, sendo o mais frequente método usado o treino prático por dispositivos placebo. Em praticamente todos os estudos foram incluídos outros aspetos para além do ensino da técnica inalatória isolado, como o ensino de autogestão da doença e a evicção de fatores desencadeantes das exacerbações. Dos ensaios clínicos (estudos aleatorizados) obteve-se uma redução significativa no risco de exacerbações anual de 29% (risco relativo estimado=0.71, IC95%=0.59-0.86; p<.001), mas não na melhoria do controlo sintomático, da qualidade de vida ou da função pulmonar. Esta redução do risco relativo de exacerbações, quando extrapolada para uma análise de custo-efectividade, revelou ser custo-efetiva. No melhor cenário, estimou-se uma orçamentação disponível para intervenção educativa até 1800 euros por doente por ano, de acordo com os custos reportados em Portugal. Em termos globais, será possível aplicar para intervenções educativas até 22% dos custos das exacerbações, e isto é aplicável em qualquer país. A poupança média estimada com o modelo de intervenção desenhado é de 311.88 euros por doente por ano, o que pode representar até 131 milhões de euros no serviço nacional de saúde português. O rácio incremental de custo-efectividade em Portugal varia entre 93.73 e 437.43 euros, por cada exacerbação evitada.

O estudo de investigação exploratório transversal foi realizado com 130 participantes idosos com Asma ou DPOC, com uma média de idades de 74.4 (±6.4) anos. A prevalência de erros na técnica inalatória foi de 71.6% (IC95%: 64-78.5) e de erros críticos foi 31.1% (IC95%: 24-38.8). Os dispositivos pressurizados de dose calibrada (pMDI) foram os que mais erros críticos revelaram. 82.3% dos participantes apresentavam comorbilidades e mais de metade tinham doença em estadio moderado a severo, de acordo com as classificações internacionalmente consensuais. Na modelação estatística multivariada, os principais preditores de performance da técnica inalatória identificados foram: a performance cognitiva, o índice de adesão à terapêutica, o género masculino, a existência de ensino prévio através de treino prático com dispositivos placebo realizada por médico, a existência de alergias ou comorbilidades com impacto respiratório, o tabagismo ativo e a depressão. Os principais preditores do controlo clínico de sintomas foram: a existência de ensino prévio da técnica inalatória por médico, a carga tabágica em unidades/maço/ano, a vacinação antigripal, a existência de depressão, de comorbilidades respiratórias e o nível de educação e escolaridade. A função pulmonar associou-se de forma significativa à carga tabágica, bem como à existência de erros na ativação da dose do inalador e à ausência da apneia final após a inalação.

Já em relação ao ensaio clínico proposto, este procurará esclarecer o verdadeiro impacto que o ensino da técnica inalatória, por dispositivos placebo, terá na redução de

exacerbações e na melhoria do controlo clínico dos doentes idosos com Asma e DPOC. Espera-se com estes resultados confirmar o benefício deste método de ensino, tornando possível aprimorar as recomendações de prática clínica, dirigindo estratégias educacionais mais eficazes a estes doentes.

Os resultados dos trabalhos desenvolvidos nesta tese revelam que as intervenções que incluem ensino de técnica inalatória aos doentes são eficazes, podendo reduzir significativamente o risco de exacerbações nos idosos com Asma e DPOC. Apesar disto, é recomendável que as mesmas incluam outras dimensões de educação e capacitação dos doentes, uma vez que faltam estudos que avaliem o verdadeiro impacto do ensino da técnica inalatória como intervenção isolada. Por outro lado, estas intervenções são custo-efectivas, havendo confiança para a sua implementação em terreno real e de forma sistemática, através de consultas regulares com médicos e/ou enfermeiros, uma vez que permitem gerar poupanças significativas. Para além disso, é possível identificar os doentes que estão em maior risco para o mau uso dos dispositivos e para piores resultados clínicos, devendo ser alvo de intervenções personalizadas. Assim, são de destacar os doentes idosos que têm função cognitiva comprometida, baixa escolaridade, alergias ou comorbilidades com impacto respiratório, que nunca tenham recebido ensino prévio da técnica inalatória, que tenham antecedentes tabágicos e que demonstrem erros críticos. Apesar disto, os fatores determinantes para classificar o risco individual destes doentes deverão ser explorados em estudos de causalidade com desenhos longitudinais, uma vez que diversos fatores de confundimento podem estar envolvidos. Também, o verdadeiro impacto das intervenções educativas com ensino da técnica inalatória de forma isolada ainda está por determinar, tal como a diferença de eficácia entre diferentes métodos de ensino. Estes aspetos são particularmente importantes em doentes idosos, pelo seu acrescido risco, e devem ser alvo de testes em ensaios clínicos bem desenhados com minimização de potenciais vieses.

Palavras-chave

Asma; Doença Pulmonar Obstructiva Crónica; Idosos; Técnica Inalatória

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List of Abbreviations

ACO	Asthma-COPD Overlap
ACSS	Portuguese Central Administration of Health System
ACT	Asthma Control Test
ADMIT	Aerosol Drug Management Improvement Team
AQLQ	Asthma Quality of Life Questionnaire
AUC	Area Under the Curve
BAI	Breath-Actuated Inhaler
CARAT	Control of Allergic Rhinitis and Asthma Test
CAT	Asthma Quality of Life Questionnaire
CCQ	Clinical COPD Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
DALYs	Disability Adjusted Life Years
DPI	Dry Powder Inhaler
ER	Emergency Room
FEV1	Forced Expiratory Volume in First Second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICER	Incremental Cost Effectiveness Ratio
ICS	Inhaled Corticosteroid
LABA	Long-Acting B2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
MEF25-75	Maximum Expiratory Flows of 25-75% of FVC
mMRC	modified Medical Research Council
MoCA	Montreal Cognitive Assessment
NNT	Number Needed to Treat
OECD	Organisation for Economic Co-Operation and Development
PEF	Peak Expiratory Flow
pMDI	Pressurized Metered-Dose Inhaler
pMDI+S	Pressurized Metered-Dose Inhaler Plus Spacer
QALY	Quality Adjusted Life Years
RCT	Randomised Control Trials
SMD	Standardised Mean Difference
SMI	Soft Mist Inhaler
TSA	Trial Sequential Analysis
UBI	Universidade da Beira Interior
WHO	World Health Organization

CHAPTER ONE

General Introduction

General Introduction

"…the most expensive inhaler is the one that is not used correctly"

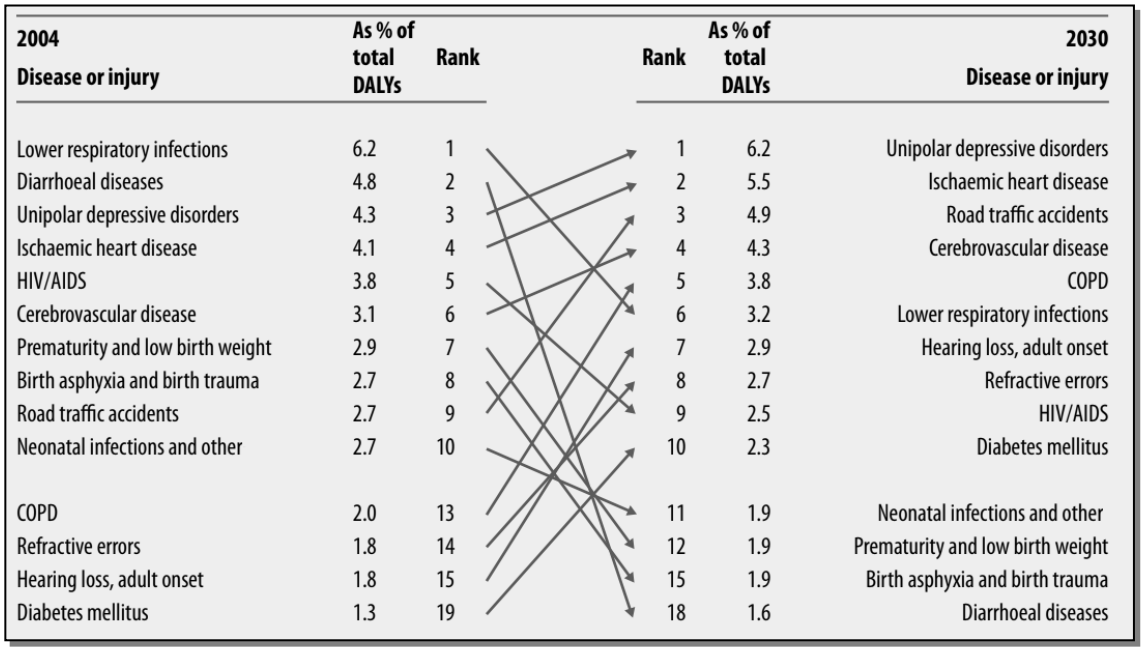
- The Aerosol Drug Management Improvement Team

1.1 The burden of Asthma and COPD

Human health has experienced major shifts in the last hundred years, in a tremendous epidemiological revolution (1). Chronic conditions took their place among the main health priorities, overcoming infectious diseases as the main causes of death. This was mostly due to better lifestyle conditions, better sanitation, better health care resources, and also, to the ageing of population in most countries.

Respiratory diseases currently account for one of the most important causes of death worldwide. Most of that phenomenon is due to lower respiratory infections, but also to the increasing prevalence and incidence of chronic conditions, such as Asthma and Chronic Obstructive Pulmonary Disease (COPD). The last report of the World Health Organization (WHO) on the global burden of diseases pointed out that near 7% of all deaths are due to respiratory diseases, and COPD leads this subset right after infectious diseases (2). Asthma and COPD together affect more than 300 million people worldwide and near 40 million in Europe, and those numbers kept arising in the last few years. Asthma and COPD are both within the ten main causes of years of life lost, and 13% of those patients have moderate or severe disability, which has significant impact on people's quality of life and also on health services' burden. A recent report from the Institute for Health Metrics and Evaluation reaffirms such findings (3).

Figure 1.1.1 present the main leading causes of burden of diseases in terms of Disability Adjusted Life Years (DALYs), with a perspective from 2014 and an estimation to 2030. COPD currently represents the thirteenth leading cause of burden of diseases, with 2% of total DALYs, but it should be highlighted that it is estimated to rise up to nearly 4%, right to the top five, in the next few decades. Nevertheless, lower respiratory infections will drop from the leading cause of disability to the sixth position, with a decrease of 3% on its quota. These changes highlight the epidemiological shift that will happen in the next few years, and other diseases are following the same pattern, such as mood disorders, cardiovascular and cerebrovascular diseases, diabetes and also some sensorial diseases, such as hearing loss and refractive errors.



2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases

Figure 1.1.1 - Ten leading causes of burden of disease, worldwide, at 2004 and 2030. Adapted from The Global Burden of Disease – WHO (2).

The burden of Asthma and COPD embraces several dimensions of disability and complications. According to a recent report from the Organisation for Economic Co-operation and Development (OECD) (4), in 2015 Asthma and COPD were responsible for almost 240 hospital admissions/100.000 inhabitants. Although Portugal has a lower rate of 74 admissions/100,000 inhabitants, in some countries those numbers rise to nearly 430 (Figure 1.1.2).

Asthma and COPD are associated with significant risk of adverse outcomes and death. In Portugal, in 2009, respiratory diseases were responsible for more than 83.000 hospitalisations, which represent 14% of total admissions and for about 10% of all deaths (5, 6). Asthma, COPD and rhinitis altogether affect up to 40% of the population. The standardised death rate for COPD in Portugal is nearly 18/100,000 inhabitants, slightly below the OECD mean, and has been diminishing in the last few years (7). However, it is still responsible for 20% of all deaths from respiratory causes. The mean age of COPD patients increased 2 years in the past decade, and that is mainly due to the ageing population in Portugal (6). These patients are frequently undiagnosed in Primary Health Care, and only 10% of those diagnosed have a confirmatory spirometry. In Asthma, the hospital admissions rate is nearly 26.8/100,000 inhabitants (8), but it causes only 1% of all deaths from respiratory causes. Regarding the elderly, Portugal has the second highest mortality rate from respiratory diseases, with more than 500 deaths per 100,000 habitants (5), which represent up to 130 years of life lost per 100,000 inhabitants. Hospital admissions carry a significant economic burden, with a total net expenditure of €213 million every year in Portugal. Treatment of respiratory diseases

accounts for 7% of the total public budget of the National Health Service, and most of it is due to acute care (5). It is estimated that Asthma and COPD represent a total cost up to €4 billion in Europe (9, 10), and COPD only may account for 50% of all respiratory treatment costs (11). In Portugal, regular treatment of a patient with COPD costs up to €1500 every year (7) and with an Asthma patient a mean of €1200 (12). Asthma alone leads to a total expenditure of almost €400 million in Portugal, and one third of it is due to acute care (13).

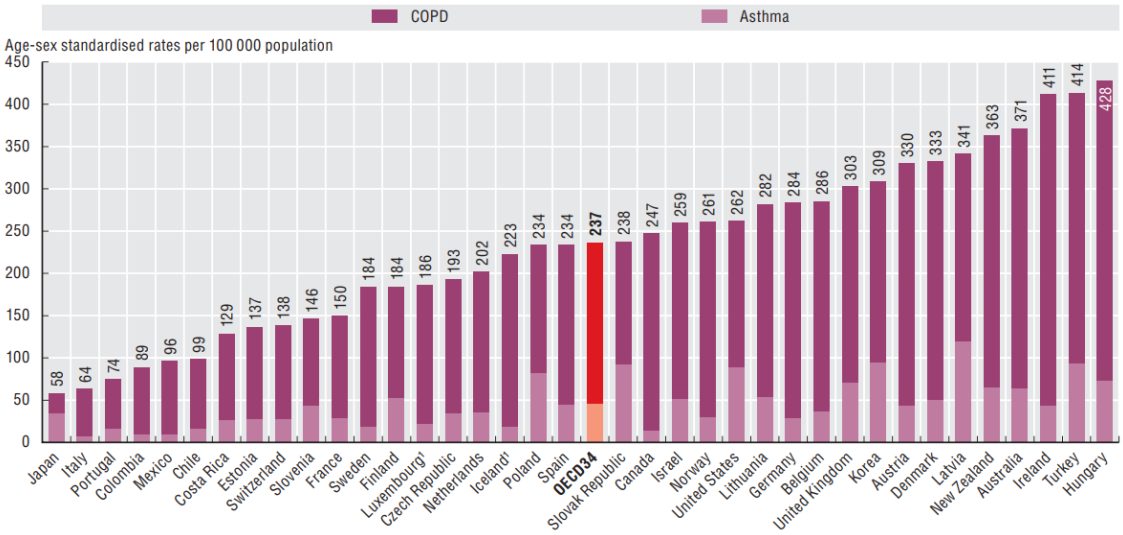


Figure 1.1.2 - Asthma and COPD hospital admissions in adults, 2015 (or nearest year). Adapted from Health at a Glance – OECD (4).

The definition of Asthma and COPD, as well as their clinical staging, has been under several reviews over time, under the light of new evidence on its pathogenesis, endotypic and phenotypic features. Both rest on the same basis, an inflammatory component with varying features but involving subsequent airway obstruction. However, Asthma and COPD differ in clinical presentation, although such difference may be less apparent in elderly patients.

According to the Global Initiative for Asthma (GINA) 2018 Report (14), Asthma is an "*heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation*". It can manifest itself in several clinical phenotypes, but such classification has not reached a full consensus so far since different parameters have been used for definition of clinical/functional phenotypes, and other definitions of phenotypes on the basis of the presence or absence of atopy, features of inflammation, types of triggers, age of onset or other have also been put forward. Clearly, future studies will further address the issue of classifying patients into multiple phenotypic clusters, which may be helpful to adequately

tailor treatments. The worldwide prevalence of Asthma is nearly 10%, but it may reach 18% in some countries (14). A recent national survey in Portugal estimated a prevalence of 6.8% of Asthmatic patients, which represents nearly 700,000 people, but lifetime Asthma prevalence may reach 10% (15, 16), as reported worldwide. However, real data from Portugal, and according to clinical primary health care records in the Portuguese National Health Service, show that only 2% of the population is documented as having Asthma, which suggests widespread underdiagnosis (5).

COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (11), is 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*". COPD definition seems more accurate and objective than Asthma, giving a greater importance to persistent symptoms and airflow limitation, which may be intermittent in Asthma, as well as to a previous and chronic respiratory exposure, such as to smoke and heavy particles. COPD classification has been under recent review, and it now includes four different grades, according to three main aspects: symptomatic control, airflow limitation and previous history of exacerbations. However, airflow limitation has lost some importance to the other two. COPD affects more than 380 million people, with a global prevalence estimated in 11.7%; however, most reports show a prevalence of less than 6%, which also suggests clear underdiagnosis (11). The same phenomenon occurs in Portugal. A recent study estimated a prevalence up to 14.2% in patients above 40 years old (17); however underdiagnosis may reach up to 86% of patients, because only near 1% of the population is correctly identified (5).

Nevertheless, there are a few subsets of patients in whom the diagnosis is still difficult to establish, because they often present symptoms of both Asthma and COPD. Frequently this happens with smokers or older adults, or even with foreign Asthma patients that spent many years with their disease uncontrolled, due to smoking or exposure to noxious gases. This is called the Asthma-COPD Overlap (ACO) (18), and it is more than a simple disease itself. For this reason, GOLD and GINA have recently released a consensus report establishing its definition as being "*characterised by persistent airflow limitation with several features usually associated with Asthma and several features usually associated with COPD. ACO is therefore identical in clinical practice by the features that it shares with both Asthma and COPD"*. These patients usually need to be treated with approaches from both diseases, combining inhaled corticosteroids (more relevant in Asthma) and bronchodilators (more relevant in COPD). The underlying mechanisms of ACO are still largely unknown, but these patients present a higher clinical risk for exacerbations and adverse outcomes. The global prevalence of ACO is estimated to vary between 15% and 55%, according to different studies (18).

Etiological factors and triggers

The onset of Asthma and COPD can be due to many different etiological factors (see figure 1.4.1 further), and some are closely related to primordial prevention features, such as outdoor and indoor dust exposure, air quality and smoking policies (6). In fact, in Portugal air quality is considered good, overall, but only 20% of the population is under an acceptable monitoring system, which makes them more vulnerable to such exposure. Smoking is also known to be a strong trigger of Asthma and COPD burden. In Portugal, smoking rate is about 20%, slightly below the European average, which, to some extent, may explain the lower disease prevalence. In addition, it should be considered that elderly people in Portugal, mainly those living in rural areas, were under significant exposure to fumes, due to the regular use of home fireplaces and firewood for heating and cooking purposes.

In Asthma, in particular, a significant role for gene-environment interactions on disease onset has been demonstrated, and most of those interactions may occur in early life or even in-utero (14). Some of the involved factors are related to nutrition, early allergen exposure, pollutants, microbes and psychosocial triggers. In addition, other factors may contribute to worsening of symptoms or exacerbations, such as smoking, low pulmonary function, obesity, economic difficulties, allergies and frequent previous exacerbations. Comorbidities may also play a role in this continuum, namely gastroesophageal reflux, depression and anxiety, rhinitis (mainly allergic rhinitis), sinusitis and nasal polyposis.

There are many aetiological factors that are both related to Asthma as to COPD, but in COPD some specific ones may be involved, such as alpha-1 antitrypsin deficiency and lung growth and development (11). In addition, several factors may worsen clinical control, such as smoking, occupational and environmental exposure to noxious gases, or even comorbidities, such as cardiovascular diseases (heart failure, ischaemic heart disease, arrhythmias, peripheral arterial disease and hypertension), skeletal muscle dysfunction, metabolic syndrome (such as diabetes), osteoporosis, anxiety, depression, gastroesophageal reflux, bronchiectasis, sleep apnoea syndrome and lung cancer.

1.2 Disease control and exacerbations

Many patients with Asthma or COPD present frequent symptoms, revealing poor clinical control (11, 14). However, defining good clinical control and disease severity is also difficult since these semiological concepts have been changing over time. GINA defines Asthma severity and clinical control based upon the prescribed treatment step in five major classes, and this is now considered the gold standard for use in clinical practice and in epidemiological studies (14). This is based on the assumption that patients are prescribed the best treatment option, and thus, a "*difficult-to-treat and severe*" (*or difficult-to-manage*) Asthma is the one that keeps revealing daily symptoms or regular exacerbations, despite optimal therapy with high doses of inhaler corticosteroid plus a long-acting bronchodilator and a proper management of comorbidities. These patients frequently experience exacerbations that could be life-threating, and according to GINA (14), these are "*episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing or chest tightness and progressive decrease in lung function (…) that is sufficient to require a change in treatment*". Exacerbations usually occur in response to an external trigger or agent, and usually assume different terminologies in clinical practice, such as "*flare-up*", "*episode*" or "*attack*".

The definition of clinical control in COPD is also difficult, but globally it is similar to Asthma, as a result of a comprehensive approach to chronic obstructive diseases as a whole. According to GOLD, clinical control of COPD should be based on several features, such as the presence of symptoms, the frequency of exacerbations and the grade of airway obstruction. COPD exacerbation is also life threating, and GOLD defines it as "*an acute worsening of respiratory symptoms that results in additional therapy*". Exacerbations can be classified as mild, moderate or severe, according to the intensity of the clinical manifestations, the type of therapeutic agents used and the need for hospitalisation (11). The main objective of treatment of these patients is to maintain good symptomatic relieve, good tolerance to exercise, and to prevent lung function decline, future exacerbations and death (14, 19).

According to a national survey in Portugal, almost half of the Asthmatic patients have their disease uncontrolled, but nearly 90% of them think the opposite (20). In 2010, exacerbation rates reached about 23% in secondary health care and 3% needed a hospital admission to be properly treated. More than one third of these patients had not had any medical appointment in the previous year, although it is highly recommended to keep a regular follow-up. The Portuguese National Directorate for Health recommends that patients with Asthma should have a follow-up appointment every 3 to 6 months, focusing on inhaler technique review, as well as on allergen and smoking avoidance (8). It also highlights the role of Primary Health Care and Family Doctors in such control. This is in accordance with international recommendations (11, 14). Regarding COPD, admission rates in Portugal are significantly below the OECD average (71.6 *versus* 198.4 admissions per 100,000 habitants), and have been

decreasing nearly 12% every year (7). Nevertheless, the mean hospital stay time is nine days, which may also be due to high prevalence of comorbidities (nearly 37%) and to the ageing population (78% of those patients are elderly). Exacerbations in Asthma and COPD lead to a significant economic burden on health services. Acute medical care with Asthma may reach €200 per patient (13), but in COPD this amount can vary from €50 up to €6,000 per patient (7, 21).

The *continuum* of exacerbations and lung function

Exacerbations in Asthma and COPD are very complex events, because many pathophysiological mechanisms lay underneath them. In fact, due to the different endotypic and phenotypic presentations of such patients, is has been difficult to clarify all the inflammatory pathways of exacerbations and disease progression. In Asthma (14), the main pattern lies on acute inflammatory mediators and though activation of cells such as T lymphocytes, eosinophils and/or neutrophils. These contribute towards airflow limitations and mucus hypersecretion. Differently from COPD, airway remodelling and fibrosis are usually absent in most cases of Asthma, and this is usually reversible with proper treatment, since the fibroelastic properties of airway's wall are maintained. However, a subset of these patients, mainly those who are non-allergic and smokers, tend to show fixed airflow limitation, and some even develop ACO. On other hand, in COPD (11, 22), chronic inflammatory mediators are usually present in a more complex setting. A complex protease-antiprotease imbalance, an increased oxidative stress, as well as the activation of dendritic cells, CD8 type T cells and fibroblasts, lead to a progressive airflow limitation and gas trapping, which ultimately leads to gas exchange abnormalities, pulmonary hypertension and emphysema.

Several factors may contribute to increased risk of exacerbations, as previously mentioned, but the role of smoking (23), poor adherence and poor inhaler technique (14), as well as educational and socioeconomic determinants, obesity and being child or elder (20) should be highlighted. Health literacy seems to be highly related to adverse outcomes, and some studies approaching its true impact start to suggest that this could be even more relevant than comorbidities (24). These findings are divergent somehow, because comorbidities also seem to worsen dyspnoea in these patients (25), and self-knowledge alone seems to be not enough to prevent the onset of new exacerbations in high-risk patients (26).

Lung function is a dynamic phenomenon, because it naturally changes over time with ageing, starting to decline at age 25, and this is more evident in smokers and former smokers (27) (Figure 1.2.1). By the older age the normal lung function is significantly compromised, which leads to worsening of respiratory symptoms (28). The average decline in Forced Expiratory Volume at first second (FEV1) in non-smoking healthy adults is about 15-20 mL/year, but this

could be increased in Asthma and COPD (14). In Asthma, this decline is not as marked as in COPD, but it could be irreversible in high-risk and uncontrolled patients. In COPD, lung function keeps declining even with optimal treatment, and it may be worsened by comorbidities (11, 29). Frequent exacerbations lead to progressive and irreversible changes in lung structure and lung function, but that is not all, because other systemic complications may occur with frequent events. For instance, there is evidence that exacerbations worsen cognitive function in elderly patients (30, 31).

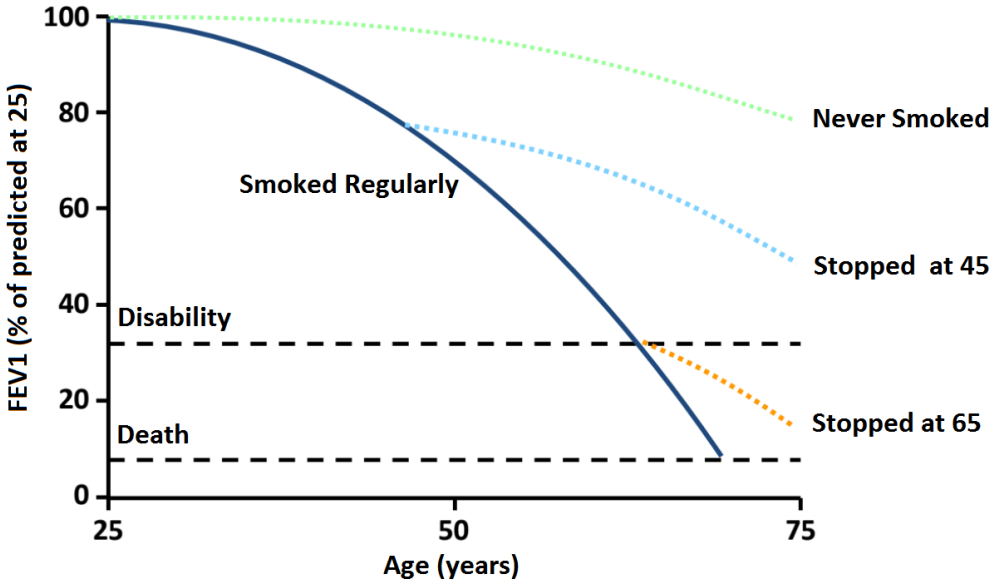


Figure 1.2.1 - The decline in lung function with age, smoking, and smoking cessation. FEV1 – Forced Expiratory Volume in first second. Adapted from Fletcher et al (27).

1.3 Inhaler technique performance

The best way to treat Asthma and COPD is by delivering the drug directly into the lungs via inhaler devices. The development of inhaler therapy started many centuries ago, but it was near the 19th century that it started to be addressed as a medical device therapy (32, 33). Since then, inhaler therapy has evolved significantly, and currently, inhaler devices allow the ability to deliver the drug into the lower and upper airways, in accordance with the desired effect and location, and by adjusting different particle sizes and kinetics. Today, several types of inhalers are available in the market, differing slightly among countries. In Portugal (34), the main type of devices may be subdivided according to the physical state of the drug and its release form, into (Figure 1.3.1): dry powder inhaler (DPI), soft mist inhaler (SMI), breath-actuated inhaler (BAI) and pressurized metered-dose inhaler (pMDI). The last type can also be coupled to a spacer (pMDI+S).

Different aspects should be considered when choosing an inhaler, because all the main inhaler technique steps should suit the patient's profile (35, 36). The main common steps of inhaler technique are: drug activation, previous expiration, drug inhalation and finally an end pause. The first problem starts with drug activation, because each inhaler has some specific features of drug activation previous to inhalation itself. Although manufacturers usually develop instructions for their inhalers, those occasionally differ from the main guidelines, thus hampering proper learning by patients (37). This is particularly relevant with DPI, due to the recent increase in different available inhalers, and with pMDI, because these need to be shaken previously and also because drug release (activation) should be done right after the beginning of inhalation (hand-breath coordination). Except when using a pMDI+S, the inhalation in all devices should be done after a previous expiration, in order to "create available space" in lower airways, and followed by an end pause, in order to allow proper sedimentation of drug particles. Nevertheless, each one of these categories has some specific features to be considered during inhalation itself. For instance, DPI need a deep and strong inhalation, so that bigger particles can disaggregate into smaller ones, during device exit, to reach enough speed to carry them through the airways. With the remaining devices (pMDI, pMDI+S, SMI and BAI) the inhalation flow should be steady and soft enough to allow disaggregation of drug particles from propellant. This will also create a laminar flow as particles travel through the airways, thereby minimizing deposition on oropharynx.

Nevertheless, many patients use more than one single type of device, which makes it harder to teach them how to use the inhaler properly (38). In fact, using multiple devices is one of the main factors contributing to poor adherence, and that should be checked regularly, since many patients do not use their inhalers with the prescribed frequency (14, 39). Adherence is also closely related to poor inhaler technique, and teaching inhaler technique itself may significantly improve adherence (40). In addition, several studies have shown the impact of adherence on clinical control of Asthma and COPD (41), and this is particularly compromised

in respiratory diseases, when compared to other diseases (42). Besides, adherence is a key factor to exacerbation risk (19, 40, 43) and thus, to its respective economic burden (44). Several methods may be used to check inhaler adherence, and new electronic devices have arisen with reliable measures to help clinical practice (45).

Figure 1.3.1 – Available inhalers in Portugal in 2019. BAI – Breath-actuated inhaler. DPI – Dry powder inhaler. pMDI – Pressurized metered-dose inhaler. SMI – Soft mist inhaler. Adapted from Aguiar R, et al. (34).

The patient's perspective

Inhaler technique performance has been under research for a few decades, and quite early it became clear its close relation to adherence, to drug deposition in the lungs and, ultimately, to clinical control (46, 47). Most patients use their inhalers incorrectly, and the prevalence of inhaler errors varies significantly across several studies. According to recent systematic reviews, it may reach up to 90% in some particular patients and occurs in all different steps of inhaler performance (48, 49). Moreover, only 11% of patients receive regular inhaler review and 25% have never received proper education (49, 50). Besides the technological evolution in inhaler therapy and the emerging of new and more evolved devices, this problem still remains, and no improvements have been seen in inhaler performance, in the past few decades (51) (figure 1.3.2).

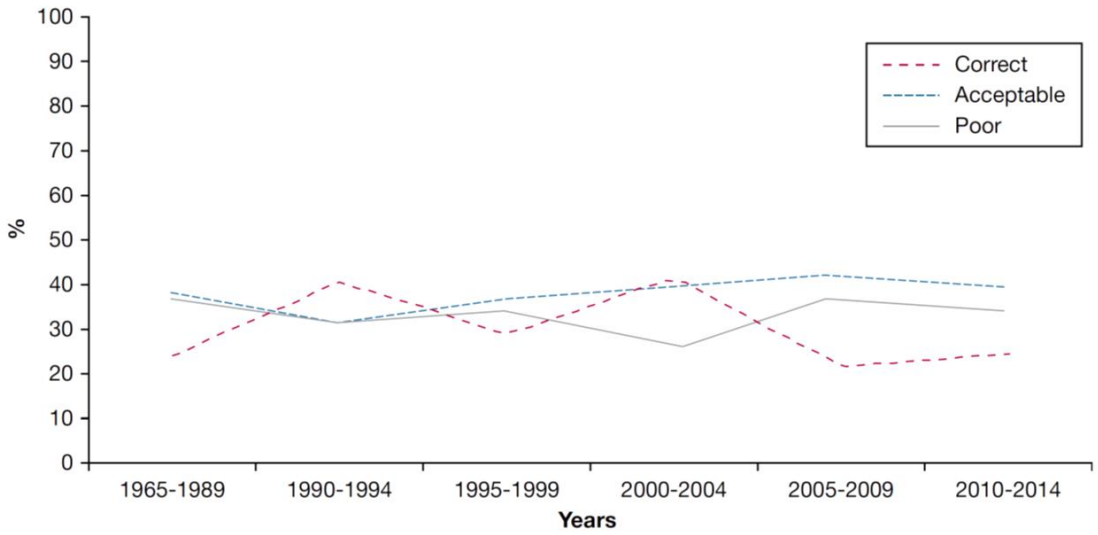


Figure 1.3.2 - Evolution of inhaler performance on reported studies over the last 40 years. Adapted from Sanchis J, et al. (51).

Inhaler errors contribute to a significant burden on Asthma and COPD management, not only in terms of mortality and morbidity, but also economically (52), estimating that it leads to almost €800 million spent in Europe annually (10). Inhaler errors, however, are not all the same, and some steps seem to be more determinant to reach therapeutic efficacy. These are called critical errors, and some studies started to analyse them, pointing out a prevalence up to 50% (48, 53). Even though it is not yet clear which errors are the most critical, since they also depend on patient's and disease's profile, some have been identified, namely the need for a proper hand-breath coordination with pMDI, a sufficient inhalation flow with DPI, and a previous expiration (53, 54).

Many years ago, studies started to compare different inhalers, trying to figure out which ones would be better in terms of performance (55, 56). However, growing evidence showed that inhaler errors are performed with all of them (57, 58). Some research suggested that DPI may be better than pMDI (48, 55, 59-62), but they are also more expensive (63), and pMDI could be better used with less critical errors when coupled to a spacer (58). Recent inhalers tried to overcome barriers in drug activation steps, making it simpler to perform, and some studies suggest they might be better than older ones (64-66).

It is well established that poor inhaler performance is significantly associated with adverse disease outcomes, mainly poor clinical control, lower quality of life and an increased risk of exacerbations (41, 67-71). Several studies have tried to identify the major predictors of inhaler performance, but the evidence is still scarce and occasionally contradictory. Patients' motivation and preferences may play an important role in that context (60, 72), but that is

not clear yet (73). Other potential determinants have been identified, such as: age (61, 74, 75), gender (76), educational and socioeconomic level (67, 74, 75, 77, 78), living alone (77), having comorbidities (77) and being prescribed multiple devices (79). In addition, patients who have received previous inhaler education also show better performance (61, 67, 74, 75, 78). Many of such determinants are both predictors of inhaler performance and of disease outcomes, as previously mentioned. This may be due to common causal pathways or confounding, and it raises tremendous doubts upon their true causal effect (see figure 1.4.1 further).

The health professional's perspective

Facing the growing evidence regarding poor inhaler use by patients, some studies started early on to focus on health professionals, since they are the main drive to provide good education, in clinical practice (80-82). The first results revealed that health professionals, with no exceptions, also knew little about inhaler technique performance and that is sustained by a generalised tendency for them to fail to recognise this problem (83). In fact, as this issue started to gain more importance over time, health professionals working directly in the respiratory field, such as respiratory therapists (84), pulmonologists (85, 86) and also family doctors/general practitioners (86, 87), also improved their knowledge on inhalers. Nevertheless, other health professionals still show little knowledge about inhalers, namely pharmacists (81, 88, 89), paediatricians (80) and nurses (90).

Teaching health professionals about inhaler technique seems to result (85), but this knowledge is lost after a few months without regular practice (91). Even younger health professionals show this lack of knowledge (92), which highlights the need to plan and structure an agenda on inhaled therapy education early during undergraduation (93-95).

Inhaler review and education

Educational programmes with inhaler review started to be under research in the 80's (96-99), and since then many prospective studies have been developed to test its impact on main outcomes, either with randomised control trials (RCT) or quasi-experimental ones. Most of the interventional studies were performed in adults, enrolling so far more than 6,000 patients, but most of them were designed without blinding, with short follow-ups and included other educational features besides inhaler technique alone, such as self-management plans and disease knowledge. Inhaler technique education has been tested using several tools, such as:

- Tailored teach-to-goal placebo device training (100-114), which consists of a repeated physical demonstration and training of all steps of inhalation, using placebo devices, and including feedback.
- Flyers or booklets with graphical schemes of all steps (99, 115).
- Showing videos of inhalation steps to patients (116, 117).
- Placing labels and reminders on the cover of the devices (118).
- Using interactive and multimedia-based tools (119-121).
- Using mobile or e-mail reminders (122).

Several studies have compared such methods in terms of inhaler performance itself. Some studies suggest that most of them seem to be equivalent (99, 115), but growing evidence points out placebo device training and videos as the best ones (98, 100, 106, 116, 123-125). Most of the interventions in those studies were performed by doctors, but there are several studies which also tested the ability of pharmacists (102-104, 110, 118, 126-129) and nurses (100, 121).

Different outcomes have thus far been addressed by interventional studies besides inhaler performance (100, 123) and inhaler adherence (99, 102, 103, 106, 108, 110, 114, 117, 121, 128-131), namely the most clinically relevant ones, such as lung function (101, 103, 111, 125, 126, 132-135), symptom control (102-108, 110, 118, 125, 127-129, 133, 136) and quality of life (97, 98, 101-103, 105, 108-110, 112, 115, 116, 126, 132, 135). Most of the studies found positive results showing that all methods improve clinical outcomes and quality of life. In addition, and regarding exacerbations, most of the evidence suggests that the best method may be placebo training with reminders, having the potential to reduce the risk (106, 115, 125, 130, 132). However, these findings must be taken with caution, because most studies had short follow-up periods and several potential biases, such as unblinded designs (137, 138). Several studies have highlighted the importance of regular reviews and feedback upon inhaler education in patients (97, 135, 139-141), and some guidelines also mention this aspect (142, 143). This is particularly important since inhaler performance is lost shortly after instructions (61). Different inhalers have also been under cost-effectiveness analysis, and some studies suggest that pMDI are less cost-effective that DPI (96, 144-146). However, the true cost-effectiveness of inhaler educational programmes is still unclear, mainly regarding clinical outcomes (147, 148).

1.4 Elderly patients

In the past few years a significant demographic shift has occurred, mainly due to ageing population in developed countries. In Portugal, this reality is particularly relevant, since it is one of the most aged countries in Europe (6). In addition, elderly patients with Asthma or COPD have higher mortality rates than younger patients, and almost twice the mean hospital stay during an admission. Also, almost 10% to 18% of elderly patients tend to have more than one hospital admission/year (5).

GINA and GOLD have also highlighted the importance that elderly patients have (11, 14), not only because of their increased risk of mortality, but also due to the significant associated morbidity. In addition, elderly patients are frequently underdiagnosed and that could be due to several features. First, these patients usually have a low perception of symptoms, and frequently have concomitant comorbidities that share similar symptoms (14, 149). In fact, associated comorbidities of Asthma and COPD frequently share respiratory symptoms and that frequently biases a correct clinical judgment (39). In addition, socioeconomic determinants may also play an important role in patients' empowerment, thereby compromising disease diagnosis. On the other hand, the increased decline in lung function in elderly individuals may lead to overdiagnosis of COPD (11).

Most elderly patients with Asthma or COPD have uncontrolled symptoms (28), and this highlights the importance of recognising their differences from younger patients. In elderly patients, lung function declines faster (28), and the prevalence of comorbidities such as depressive states, is significantly higher, and that also contributes to poor quality of life (150, 151). In addition, exacerbations in the elderly worsen cognitive function, making it harder to manage them and to invest in proper education (30). Several factors may be associated with poor clinical control and increased risk of exacerbations in the elderly, besides inhaler technique performance (152, 153), and cognitive function seems to be one of most importance (154).

Inhaler technique performance in the elderly

Inhaler performance is a major issue in elderly patients, and several studies have shown a significant trend to poor inhaler performance as age increases (152, 155-157). In elderly patients, error prevalence may reach up to 90%, while in younger patients this varies around 50% (158). Several factors may be related to inhaler technique performance, as previously mentioned, and that has been generating a special interest in elderly patients for some time (159, 160). Some of the those predictors may be: age itself (74, 155, 156); gender (160); cognitive function (159-164); concomitant comorbidities, depression or frailty, the latter ones because they may affect patient's motivation (160, 164, 165); educational level (74, 76, 166);

rurality, socioeconomic status and disease duration (76). Also, having regular appointments with a doctor, having received previous education, the type of device (74, 76) and lung function itself (164), may be associated with inhaler performance. However, most of such assumptions need to be clarified by true causal research, because some studies are contradictory, mainly regarding age, gender and educational level (160, 166) in elderly patients, as well as the use of multiple devices in adults also(166) (figure 1.4.1).

Inhaler review and education in the elderly

Regarding the complexity of inhaler performance in elderly patients, some studies started to address the impact of inhaler educational interventions upon them, and for the last two decades more than 3,100 patients have been recruited into interventional studies. However, the same problem arises regarding both adults and the elderly. Most studies were not randomised, had short follow-ups, were not blinded in most study design dimensions and addressed inhaler technique education not in isolation but in combination with other disease knowledge features.

Several methods were also tested in elderly patients, such as: placebo device training (166-173); videos (174, 175); flyers/booklets (169, 176-178) and videoconferencing (179). Most of the interventions were performed by doctors, but some have also been provided by pharmacists (167, 175, 178, 179) and nurses (180, 181). The majority of such studies show that interventions seem to improve major outcomes, namely inhaler performance itself (166-168, 171, 172), adherence (170, 177-179, 182), lung function (169, 176, 177, 182), symptom control (170, 174, 175, 181), and quality of life (169, 170, 176-180). Regarding exacerbations, most studies showed a significant reduction of risk ratio, but the educational tools used were diverse, such as a placebo device training (169, 170) and flyers/booklets (176-178). Teaching inhaler technique in the elderly also seems to be cost-effective (183), just as in younger adult patients, but more cost-effectiveness analyses are still needed to confirm this issue.

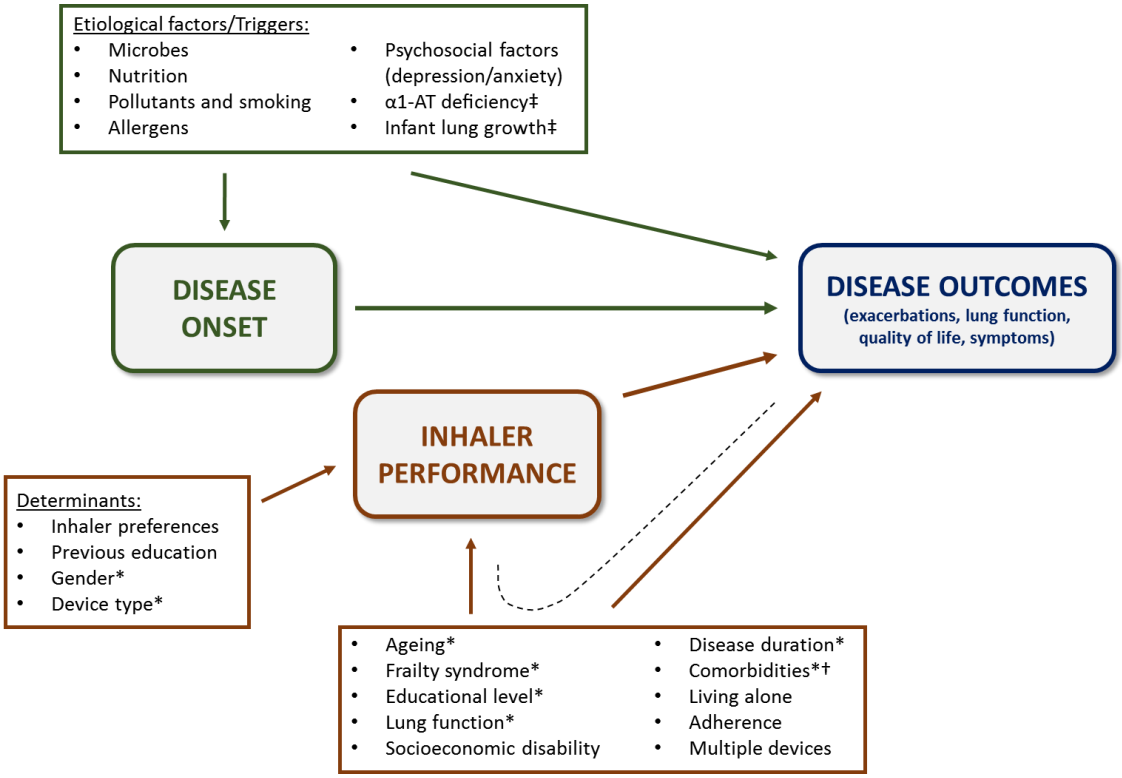


Figure 1.4.1 – Conceptual graph of causal pathways between disease onset, inhaler technique performance and disease outcomes in Asthma and COPD. Schema performed according to Direct Acyclic Graphs recommendations (184). The single-directional arrows show established and suspected causal pathways according to the reported bibliography. The black dashed line shows an open pathway between inhaler performance, exposure factors and disease outcomes, meaning common true causal inference or potential confounding. AT-Antitripsine. *Factors which impact is especially relevant on elderly patients. †Comorbidities identified as significant on both Asthma and COPD (rhinitis, sinusitis, nasal polyposis, gastroesophageal reflux, obesity, depression and anxiety) and comorbidities identified as significant mostly on COPD (cardiovascular disease, lung cancer, osteoporosis, musculoskeletal diseases, metabolic syndrome, bronchiectasis, sleep apnoea syndrome). ‡Factors which impact is especially relevant on COPD.

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CHAPTER TWO

Aims

Aims

For many years, considerable attention has been given to inhaler technique performance and its characteristics, due to its close relation to clinical outcomes of Asthma and COPD. Growing awareness regarding the burden of inhaler technique misuse has driven research on several key aspects that were so far ignored. Some of those key aspects rely upon predictors of inhaler performance itself, and much of those predictors share common associations with clinical features and clinical outcomes, arising many doubts about their true magnitude of impact. This issue is particularly relevant in elderly patients, in whom some of those potential confounders assume a special role. This is a subset of patients where scientific knowledge about inhaler performance is still scarce, and several questions remain unanswered.

Based on those concerns, the main purpose of this thesis is to study inhaler technique performance in elderly patients with Asthma or COPD, in its different features and views, in order to reach a more comprehensive approach in clinical practice. In order to achieve such findings, a subset of five main specific objectives were defined, and organised into the main subchapters of the results. Those are:

- To assess whether there is evidence that inhaler technique education in elderly patients with Asthma or COPD improves clinical control and reduces disease exacerbations.
    - In addition, to determine which is the best method for teaching inhaler technique and how often should inhaler technique be taught.
- To determine, in accordance with the main results reported in the previous objectives, the cost-effectiveness of educational interventions including inhaler technique review in elderly patients with Asthma or COPD.
- To perform an exploratory study aiming to develop a tool for the major predictors of inhaler performance in elderly patients with Asthma or COPD.
- To develop a tool for identifying the major independent predictors of clinical risk in elderly patients with Asthma or COPD.
- To design a study protocol that would test the impact of a teach-to-goal placebo device-based education programme on the risk of exacerbations in elderly patients with Asthma or COPD, and delivered by family doctors at baseline, 3 and 6 months, after a one-year follow-up, when compared to usual care.

CHAPTER THREE

Research Methods

Research Methods

There is a significant number of studies addressing inhaler technique performance in Asthma and COPD, either through descriptive approaches of inhaler errors, their predictors and their association with clinical outcomes, or through studies reporting the impact of inhaler educational interventions. Nevertheless, elderly patients are frequently excluded from such studies, and more importantly, from clinical trials. This is mostly due to the varied confounding factors that elderly patients introduce, which is mainly the scope of this thesis. The objectives that were set for this work provide a comprehensive approach to inhaler technique performance in this subset of patients, and altogether, our results attempt to further clarify this wide confounding territory. For that reason, different methods were used to achieve each one of these objectives.

The plan for all methods used in this thesis was approved on 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and the study regarding de second and third objectives was also approved by the Ethics Committee of the Local Health Administration (see Appendix I). In addition, all the materials used throughout the study for objectives three and four are presented on Appendix II, namely the informed consent form, the questionnaires, validated in Portuguese, that were applied to participants and all the checklists for inhaler performance evaluation.

In the subchapter of results, a systematic review of available research was performed, according to PRISMA recommendations (1). For that, interventional studies aiming at inhaler educational programmes for elderly patients with Asthma and COPD were selected, whatever the teaching method and comparator used, and reported its impact on inhaler performance, adherence, or clinical relevant outcomes, such as symptoms control, quality of life and exacerbations. After this work, data from meta-analysis regarding exacerbation risk reduction was used, was well as data from direct exacerbation costs and direct potential intervention costs in a Portuguese scenario, in order to establish the cost-effectiveness of such interventions in elderly patients. To perform it, a decision tree model was used, according to CHEERS guidelines (2), in a simple standard cost-effectiveness analysis, without cost-utility dimension.

The third and fourth objectives resulted from a single study, which had a multicentre cross-sectional design, and aimed to develop predictive tools of inhaler performance and clinical risk. For that purpose, elderly patients with Asthma or COPD, using regular inhalers, were recruited at several Primary Health Care centres, and several predictor variables were collected in order to relate them to several outcomes of interest, namely inhaler performance, symptom control, quality of life and history of exacerbations. In order to

control for several potential confounders, as previously mentioned (and presented in figure 1.4.1), multivariable regression models were built, according to TRIPOD recommendations(3), A total of 130 participants were recruited and several statistical confirmatory tests were performed in order to ensure statistical strength on model building with up to 10 predictors. In addition, subgroup analyses were performed in order to detect clinically relevant patterns.

The last objective of this thesis was established in a "future research" view, and it aims to answer one of the most important question regarding this subject, which is to establish the real impact of an inhaler education programme alone, in one single method, on exacerbation risk after a long follow-up. In order to achieve it, a single blinded RCT was designed, according to CONSORT statement (4), with proper concealment and outcome blinding, comparing "usual care" with a placebo device teach-to-goal tailored education, in a one year follow-up, with interventions at baseline, and at 3 and 6 months, and evaluating clinical outcomes, such as symptoms control, quality of life and exacerbations. To achieve enough power to detect that, a sample size of 146 participants (73 in each arm) was established.

3.1 Organization of the Thesis

The present thesis is organised in six main chapters. The first chapter is a general introduction that provides a global overview of the subject of the thesis, namely the global burden of Asthma and COPD, its close relation to inhaler technique performance and the relevance of studying elderly patients. The second and third chapters concisely describe the aims of the thesis and an overview of the main research approaches. The fourth chapter is divided into five subchapters, each one according to one of the objectives, and represented by a study, some already published, and others having been submitted for publication. The last two chapters, five and six, provide a general discussion of the main results, and a global overview of the final remarks.

Chapter One – General Introduction

This chapter provides a general overview of the state of art of the subject of this thesis. Its starts by addressing the global burden of Asthma and COPD, its main triggers and associated clinical features, and also the close relation of clinical control with inhaler technique performance. Here a brief review of inhaler technique errors, and the impact of inhaler educational programs in major clinical outcomes was performed. A special focus is also given to elderly patients.

Chapters Two and Three – Aims and Research Methods

These chapters summarise the main objectives of this research and highlight the different methods used to address them. In addition, the thesis structure is briefly described.

Chapter Four – Results

4.1 – This subchapter describes a systematic review and meta-analysis performed to assess the impact of inhaler technique educational programmes on major clinical outcomes of elderly patients with Asthma or COPD. It is based on the published article:

Maricoto T, Monteiro L, Gama JMR, Correia-de-Sousa J, Taborda-Barata L. Inhaler Technique Education and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease: A Meta-Analysis. J Am Geriatr Soc. 2018 Oct 6.

[The published article and supplementary material is on Appendix III]

[This paper has also been chosen by the National Institute for Health Research (NIHR) Dissemination Centre to be summarised as a Signal for its high quality design and relevance to UK decision makers. It is registered with doi: 10.3310/signal-000712].

4.2 – This subchapter involves a cost-effectiveness analysis, using data obtained from the previous meta-analysis, and addressing inhaler educational interventions in elderly patients, in a health care perspective with an estimation to the Portuguese scenario. It is based on the submitted paper:

Maricoto T, Marques Gomes J, Correia-de-Sousa J, Taborda-Barata L. Inhaler review in elderly with Asthma or COPD – a cost-effectiveness study and a perspective in Portugal. J Am Geriatr Soc. 2019 Feb 23. doi: 10.1111/jgs.15834.

[The published article is on Appendix IV].

4.3 – In this study, a cross-sectional analysis was performed in elderly patients, aiming to develop a predictive tool of inhaler performance, in order to identify target patients to highlight on clinical practice. This is based on the submitted paper:

Maricoto T, Santos D, Carvalho C, Teles I, Correia-de-Sousa J, Taborda-Barata L. Inhaler technique in elderly Asthma or COPD patients – a predictive tool for inhaler performance.

[This article was submitted to *Chest*, and is now under peer review]

4.4 – For this study, a similar design was used as in the previous subchapter, in a study aiming to develop a predictive tool of clinical risk, in order to identify target patients to highlight on clinical practice. This is based on the paper:

Maricoto T, Santos D, Carvalho C, Teles I, Correia-de-Sousa J, Taborda-Barata L. Inhaler technique in elderly patients with Asthma or COPD – a predictive tool for clinical risk.

[This article will be submitted to *Thorax*]

4.5 – This last subchapter of results presents a protocol for a single blinded RCT, aiming to test the impact of an inhaler educational intervention based on a placebo device tailored teach-to-goal approach, upon the main clinical outcomes and exacerbation risk, in a regular review (at 0, 3 and 6 months), and after a 12 month follow-up, versus usual care. It is based on the published article:

Maricoto T, Correia-de-Sousa J, Taborda-Barata L. Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial. BMJ Open. 2019 Jan 28;9(1):e022685.

[The published article is on Appendix V].

Chapters Five and Six – General Discussion, Conclusions and Final Remarks

These last two chapters present a global discussion of the main results, in a comprehensive approach, and integrating the results from all six objectives. It also highlights the final remarks and future research views that this thesis arises.

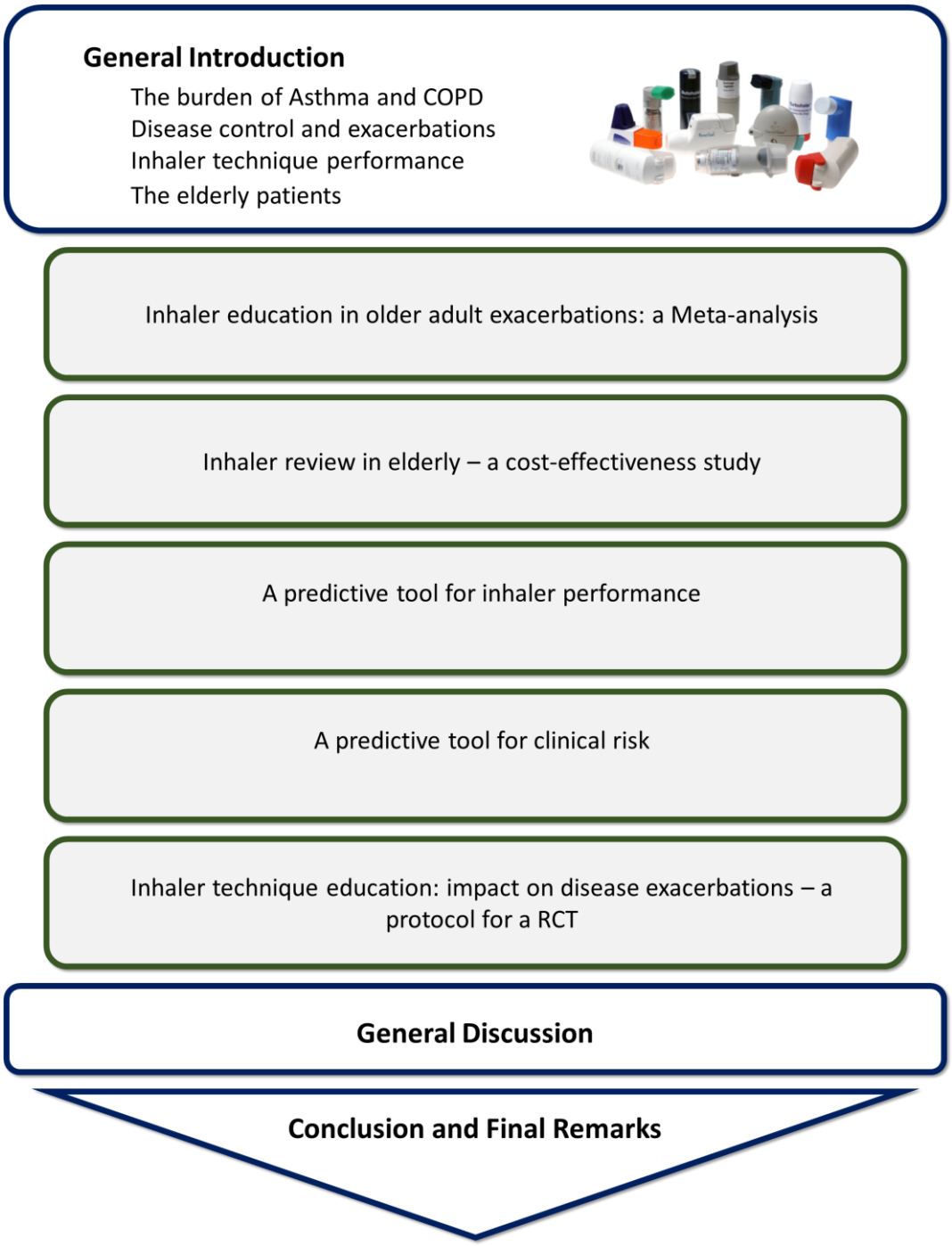

Figure 3.1.1 - Illustrative scheme of the thesis chapters.

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CHAPTER FOUR

Results

Results

4.1 Inhaler technique education and exacerbation risk in older adults with Asthma or COPD: a Meta-analysis

Abstract

Objectives: To evaluate the effect of inhaler education programmes on clinical outcomes and exacerbation rates in older adult with Asthma or chronic obstructive pulmonary disease (COPD).

Design: Systematic review and meta-analysis.

Setting and Participants: Older adults with Asthma or COPD, either in primary or secondary health care and pharmacy setting.

Measurements: We searched Medline, Embase and Central databases according to the main eligibility criteria for inclusion: systematic reviews, meta-analysis, clinical trials and quasi-experimental studies; participants older than 65 years; education on inhaler technique and reporting of disease control and exacerbation rates. We applied the GRADE scale for quality assessment and used a random effect model with Mantel-Haenszel adjustment to perform a meta-analysis.

Results: We included eight studies, four randomised and four quasi-experimental, with a total of 1812 participants. The most frequent type of intervention was physical demonstration of inhaler technique, training with placebo devices. Five studies showed significant reduction in exacerbation rates, and the pooled risk ratio was 0.71 (95%CI: 0.59-0.86; $p<0.001$). However, impact on disease control and quality of life showed high discrepancy in the reported results and all randomised studies revealed uncertainty in their risk of bias assessment.

Conclusion: All interventions seem to improve inhaler performance and clinically relevant outcomes, but placebo device could be the most effective one. Also, there is evidence that interventions reduce exacerbation risk in older adult patients, although in an overall moderate degree.

KEYWORDS: Asthma; Chronic Obstructive Pulmonary Disease; Inhalers.

Introduction

Asthma and COPD affect up to 10% of the population, and many patients have uncontrolled symptoms(1). These patients frequently experience exacerbations, which may be life threatening. Exacerbation rates may affect up to 53% of community treated cases, and good adherence to therapy is associated with reductions detected in half of the cases(2-4). Inhaled therapy is the most widely used treatment, but up to 90% of patients show incorrect technique in clinical studies(5), partly because the extensive variety of inhalers and their technical specifications create significant barriers to patients(6). Although all available inhalers may be equally efficient when properly used (7), there are various device-related and patient-related factors which may significantly influence performance(8-11). Poor inhaler technique is associated with worse symptom control(12, 13) and leads to increased health care resource consumption and costs(14).

Some studies showed that teaching inhaler technique may lower the risk of exacerbations and death in these patients(2, 3, 15-17), but the impact of teaching decreases with time, which emphasizes the importance of regular reassessment(9, 18, 19). There are many tools for teaching inhaler technique(20), and two systematic reviews addressed this issue. In one of them, the authors concluded that there is a lack of evidence about which is the best education method to improve inhaler technique(21). The other review concluded that there is sufficient evidence of the efficacy of different inhaler educational strategies. However, the authors did not quantify this impact with precision since it did not include a meta-analysis(22). In addition, neither review specifically focused on older adult patients.

Inhaler technique performance is regarded as particularly complex in older patients with Asthma or COPD who also tend to present lower inhaler adherence rates(19, 23, 24). These patients find it more difficult to achieve correct performance, since several characteristics seem to hamper this ability, such as cognitive impairment, low education level, osteoarthritis and global frailty(23, 25-28). For such reasons, and because they are frequently underdiagnosed, elderly patients are more susceptible to disease consequences and exacerbations(29, 30), and are frequently excluded from clinical trials involving education programmes. Thus, there is a lack of evidence regarding the real impact that educational interventions have in these patients. Our systematic review and meta-analysis assessed whether there is evidence that inhaler technique education in older adult patients with Asthma or COPD improves clinical control and reduces disease exacerbations. In addition, we also analysed which is the best method for teaching inhaler technique and how often should inhaler technique be taught.

Methods

Eligibility criteria:

Search criteria followed a PICO format:

Participants: We selected studies that included (not exclusively) participants above 65 years of age, with Asthma or COPD. In studies aggregating both adults and older adult patients, we considered the average age to decide about inclusion. Studies with mean age between 60 and 65 years were included in preliminary analysis to assess their magnitude of influence on our major results and conclusions, and were included in detailed analysis if considered highly relevant.

Intervention: We defined as the main criteria interventions that focus on teaching inhalation technique and, provided by health professionals and directed to patients or their caregivers, whatever method used, namely verbal instructions and physical demonstration with placebo device, text-based print resources, media, educational tools (e.g. turbutest, In-CheckDial), e-health interventions or combinations thereof. We included studies involving hospital staff (e.g. clinicians, nurses), pharmacists, general practitioners, community health workers and others as providers.

Comparator: Different methods were compared, either between each other, or against placebo or "usual care" (treatment provided to patients in a real world scenario, according to local guidelines or healthcare provider judgments).

Outcomes: We included studies that addressed any of the following outcomes: a) Inhaler performance evaluation (change from baseline scores preferred); b) All-cause hospitalization or all-cause mortality; c) Exacerbation rate or loss of control; d) Clinical control (preferably measured on a validated scale); e) Quality of life (preferably measured on a validated scale); f) Functional control (as change from baseline scores in forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, peak expiratory flow (PEF), etc.)

Types of studies: We searched systematic reviews, meta-analyses, randomised controlled trials (RCTs), nonrandomised clinical trials and quasi-experimental studies. We included quasi-randomised studies due to the paucity of RCTs found, in order to reinforce the quality of our review and the confidence in our findings.

Search methods:

As primary sources we used EMBASE, CENTRAL and MEDLINE databases. As secondary sources, we used the reference list from studies included in primary sources, as well as references found by authors` review and judgement of expert opinion. We also screened the main trial

registry databases, such as the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trial search). We used the MeSH terms Nebulizers and Vaporizers, Asthma and Pulmonary Disease, Chronic Obstructive, with a time limit for publication of March 2017. Overall, we intended to reproduce the same search strategy of previous systematic reviews that addressed the same questions (detailed search strategies in supplementary material on Sub-Appendix S1).

Selection process:

Two independent and blinded authors (TM and LM) selected the articles, according to the defined criteria and applied the following filter stages: 1) Cleaning of duplicated articles; 2) Selection of articles according to eligibility criteria and by reading the title and abstract; 3) Selection of articles according to full-text reading. Reasons for article rejection are expressed in a PRISMA diagram (31) (Figure 4.1.1). All disagreements, at every stage, including selection of studies, quality assessment and data extraction, were resolved through discussion or by a third review author (LT-B.).

Data collection process:

Data from selected articles were collected by two different authors (TM and LM) in their original presentation from papers, and noted in a proper form generated using Microsoft Excel© software. We also collected indirect data from figures and charts, adapting their interpretation by consensus, and authors of original articles were contacted for further information and data.

Type of data collected:

The following information was collected by two authors (TM and LM):

General Data: Year, study type, number of participants, age, gender, follow-up time, withdrawals, diagnosis, disease severity, type of intervention, location of the study, time lapse between interventions, type of intervention provider, adverse events/outcomes reported.

Outcomes: Inhaler performance, adherence rate, clinical control, quality of life (in any type of validated scale) and functional control (FEV1%; FVC%, PEF% and FEV1/FVC ratio) [in median, range, 95%CI, SD, SE, or in any index of % of change]; exacerbation rate, hospitalization and mortality [in OR, RR, HR, NNT and their respective 95%CI].

One author (TM) inserted data into Review Manager (RevMan), and data were double-checked for correct entry.

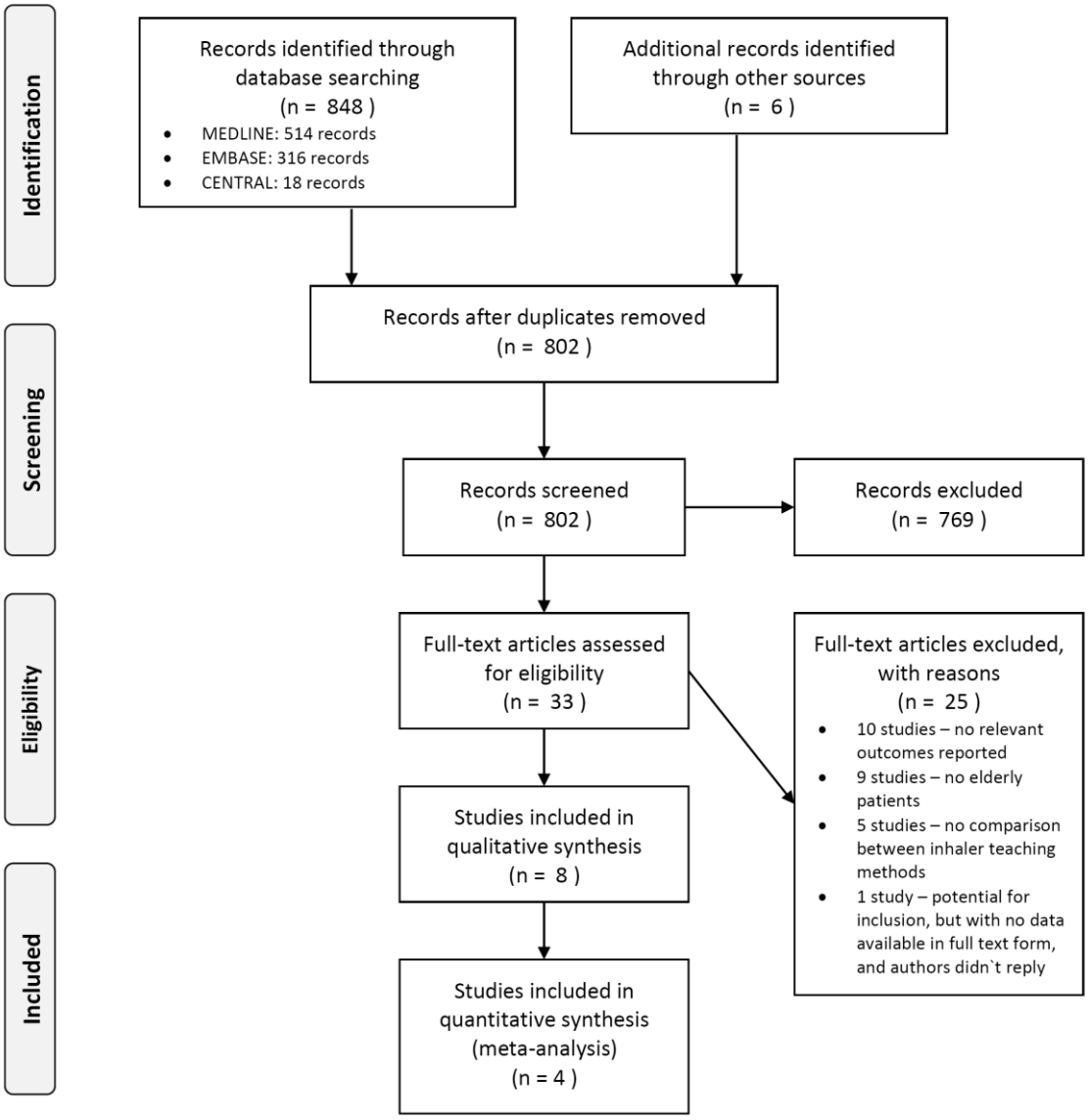

Figure 4.1.1 – Flow diagram on search and article inclusion, according to PRISMA statement(31).

Analysis of results and assessment of the risk of bias:

Data collected were analysed in a qualitative approach by two authors (TM and LM), according to the risk of bias. Quality of evidence for the collected outcomes of interest and recommendation for the interventions were assessed using the GRADE system, as reported in the Cochrane Handbook for Systematic Reviews of Interventions(32). Other two authors (LT-B or JCS) confirmed this assessment. Assessment of risk of bias was performed in the following domains: random sequence generation, allocation concealment, blinding of participants and

personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases. Risk of bias in each study was graded as high, low or uncertain and necessary justifications for such judgment were reported in the "Risk of bias" table (detailed bias classification in supplementary material on Sub-Appendix S2). Publication bias was analysed with a funnel plot.

Measures of treatment effect:

Quantitative analysis was performed with RCTs to obtain effect estimations, heterogeneity and consistency tests, by two authors (TM and JG). We used Mantel-Haenzsel risk ratios with a random-effects model and 95%CI for dichotomous data. Continuous outcomes were analysed as standardised mean difference (SMD) values using a random-effects model and 95%CI, because the included studies used different measurement instruments. We performed meta-analysis only with the RCTs. Heterogeneity between effect sizes of included studies was assessed by visual inspection of forest plots and by the Chi2 test for heterogeneity (with a P value of <0.1) and inconsistency between trials was described using the percentage of the variability in effect estimates that was due to heterogeneity rather than by chance (I2). We also performed sensitivity analysis of the included studies and their impact on meta-analysis. Results of the primary outcome, exacerbation risk reduction, with trial sequential analysis (TSA) were also presented using O`Brien Fleming monitoring boundaries approach. This was performed considering the results pooled in meta-analysis, in order to exclude a false positive or negative result from our review(33). No subgroup analysis was planned due to the paucity of studies. Quantitative analyses were not performed in quasi-randomised studies because of their high risk of bias. All statistical procedures were performed with Review Manager Software (RevMan) (available at http://community.cochrane.org), GRADEPro online (available at: https://gradepro.org/) and TSA software provided by the Copenhagen Trial Unit (available at http://www.ctu.dk).

Results

Description of studies:

Our search yielded 854 articles (Figure 4.1.1). Of the 802 unique articles, eight studies met the inclusion criteria and were analysed. Most studies were excluded because they did not address inhaler education in elderly patients or because no relevant outcomes were used. One study presented potential criteria for inclusion in its abstract, but no data from outcomes were available in full-text format, and was therefore excluded(34). One included study evaluated quality of life, but those results were not published in the article(35). Authors of these publications were contacted, but did not reply.

Of the eight studies included, four had a randomised design(16, 35-37), and the remaining four had a quasi-randomised pre- and post-intervention design(17, 38-40) (detailed data of selected studies in supplementary material on Sub-Appendix S3).

1812 participants were evaluated. Five studies addressed only COPD, one addressed Asthma and two included both diagnoses. Five studies were performed in Secondary Health Care facilities, two at Community Pharmacies and one at Primary Health Care centres. In half of the studies a pharmacist performed the educational intervention, and in the remaining ones it was a nurse or a doctor. Follow-up varied between one month and two years, and half of the studies had at least one year of follow-up. The mean age of participants was slightly greater than 65 in six of the studies and younger than 65 in the other two. We decided to include them in order to reinforce the quality of our review and the confidence in our findings, since the search strategy yielded few studies. Also, these two studies had large sample sizes (39) and reported exacerbation risk as an outcome(35).

Educational intervention varied between studies. Three studies addressed a physical demonstration with placebo devices, which was the most frequent type of intervention, covering more than half of the total amount of participants. Two studies used video demonstration and another two studies delivered written information. One study did not specify the inhaler education type(35), and another one was unclear(17).

Quality of life and exacerbations were the most commonly reported main outcomes (six studies), but different instruments and scales were used(16, 17, 35-37, 40). Similar limitations occurred with clinical and functional control, adherence rate and inhaler performance evaluation. Cost-effectiveness was never reported.

Most studies addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. Only two studies included a repeated education programme, providing intervention every 6 months(17, 40). All the other studies only provided intervention at baseline.

Risk of bias in included studies:

Two independent reviewers (TM and LM) evaluated the risk of bias of the included studies, reaching consensus in all evaluations (Figure 4.1.2). Non-randomised trials were classified as high risk of bias in the main parameters, such as Random Sequence Generation, Allocation Concealment, Blinding of Participants and Personnel and Blinding of Outcome Assessment. In our review, RCTs showed an overall uncertainty in their risk assessment, although most of them had good blinding on the Random Sequence Generation and Allocation Concealment.

The main limitation of RCTs was the lack of blinding of the intervention and outcome assessment (detailed bias evaluation in supplementary material on Sub-Appendix S2).

		Risk of BIAS							
		Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Source of Bias	Risk of BIAS Classification
Non-randomized Trials	Mulhall 2016	-	-	-	-	?	?	?	High
	Lee 2016	-	-	-	-	?	?	?	High
	Takemura 2013	-	-	-	-	+	+	?	High
	Buist 2006	-	-	-	-	?	?	?	High
Randomized Clinical Trials	Tommelein 2014	+	+	?	?	+	?	?	Uncertain
	Khdour 2009	+	-	-	-	+	+	?	High
	Rootmensen 2008	+	+	?	?	+	-	?	Uncertain
	Bourbeau 2003	+	+	?	?	+	?	?	Uncertain

Figure 4.1.2 – Risk of Bias assessment in included studies according to GRADE tool and recommended by Cochrane(32).

Logistic regression tests were performed to assess any statistically significant relationship between lower risk of bias and the magnitude of effect in the main reported outcomes. To build the model we set all variables as binary: risk of bias (0=high and 1=uncertain); inhaler performance, adherence rate, symptom control, respiratory function, quality of life and exacerbation rate (0=negative outcome and 1=positive outcome). None of these outcome variables was statistically associated with the risk of bias of the included studies.

Effects of interventions:

Table 4.1.1 shows the main findings of clinical and relevant outcomes from selected studies, and Figure 4.1.3 shows the meta-analysis results.

Table 4.1.1 – Summary of findings of intervention effect on clinical and relevant outcomes

Inhaler technique education programmes on clinical control and exacerbation risk in older adult patients with Asthma or COPD

Patient or population: older adult patients with Asthma or COPD
Setting: pharmacy and secondary health care
Intervention: inhaler education programmes
Comparison: usual care

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	Comments
		Without inhaler education programmes	With inhaler education programmes	Difference		
Exacerbation Rate № of participants: 1225 (4 RCTs)	**RR 0.71** (0.59 to 0.86)	58.2%	**41.3%** (34.3 to 50.0)	**16.9% fewer** (23,8 fewer to 8,1 fewer)	⊕⊕⊕◯ MODERATE [a,b,c]	
Quality of Life № of participants: 992 (3 RCTs)	-	-	-	SMD **0.12 SD lower** (0.26 lower to 0.03 higher)	⊕⊕◯◯ LOW [a,b,c,d]	A longer follow-up period seems to be associated with a positive effect
Functional Control (FEV1) № of participants: 308 (2 RCTs)	-	-	-	SMD **0.06 SD higher** (0.35 lower to 0.47 higher)	⊕⊕◯◯ LOW [a,b,c,d]	
Inhaler Technique Performance № of participants: 849 (2 RCTs)	-	-	-	SMD **0.63 SD higher** (0.34 higher to 0.92 higher)	⊕⊕⊕◯ MODERATE [b,c]	Different tools to teach inhaler performance were used, and one study did not specified the tool used

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Most studies didn`t blinded participants to interventions, exposing them to hawthorn effect.
b. None of the included studies have addressed inhaler technique education alone
c. Studies with smaller sample sizes obtained wide confidence intervals on the estimated parameter
d. Included studies showed divergent results on the estimated parameter

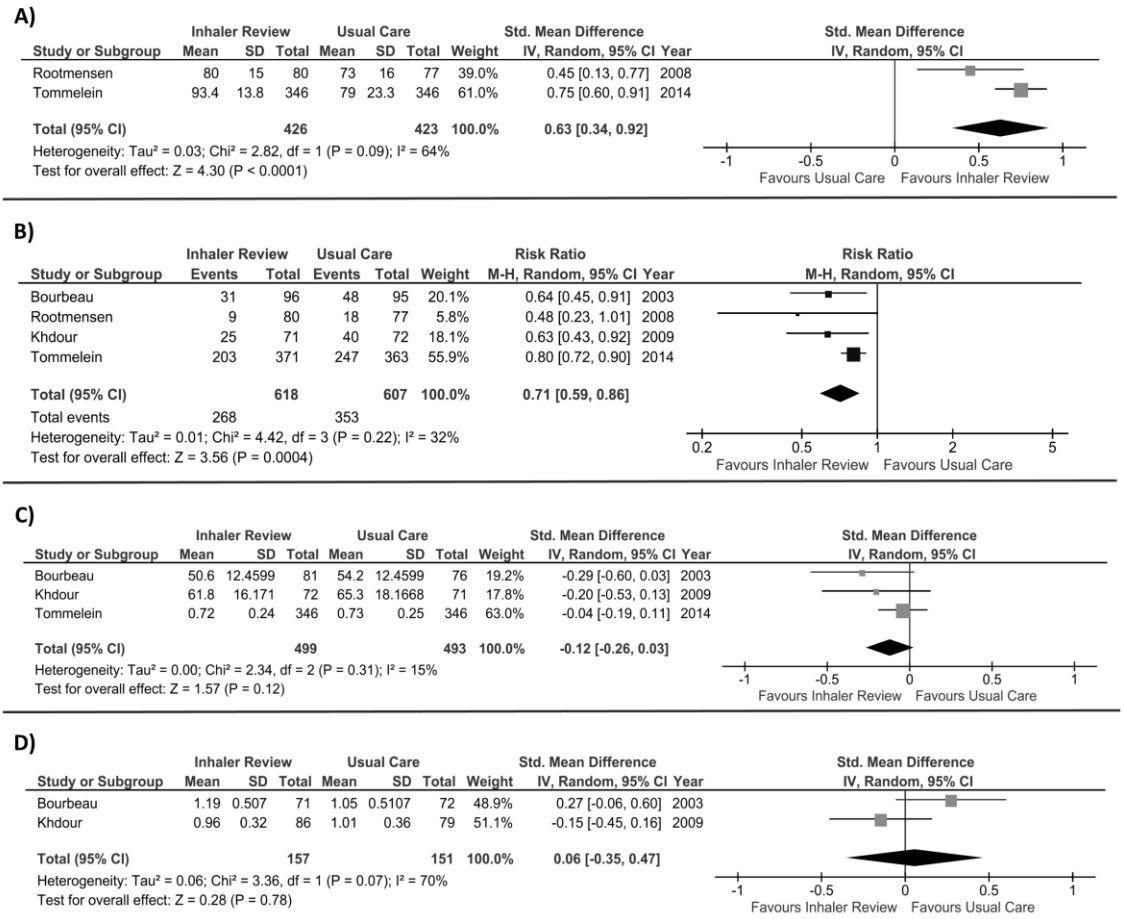

Figure 4.1.3 – Meta-analysis. a) Inhaler Performance. Tommelein et al.(16) measured the global % of correct steps. Rootmensen et al.(35) measured the global score of correct performance; b) Exacerbation Rate. c) Quality of Life. Tommelein et al.(16) used ED-5D scale. Khdour et al.(36) and Bourbeau et al.(37) used St. George questionaire. d) Respiratory Function (change in FEV1).

Inhaler performance: Only half of the studies measured the impact of the intervention on inhaler performance and most of them showed an improvement in this score(16, 38, 40), except for one study(35). This study did not specify the type of tool used to teach inhaler technique, and it may not have been the primary objective of the intervention. Authors were contacted, but did not reply. Although the authors did not find significant differences after intervention, when results were pooled in a meta-analysis together with the RCT by Tommelein et al.(16), they showed a significant benefit on inhaler performance. However, heterogeneity was high, probably due to the different measures of inhaler performance used. Also, this study by Rootmensen et al. showed a significant reduction in exacerbation rate, at the end of follow up, which could be due to the additional topics provided at intervention, namely patient's skills in disease self-management.

Exacerbation rate: All RCTs showed a significant reduction in exacerbation rates in the intervention group, and comparing with usual care group(16, 35-37). The reported mean RR on these studies varied between 0.45 and 0.82, with wide confidence intervals and favouring the intervention group. Pooling these results in a meta-analysis, we found a significant mean reduction of almost 30% in exacerbation rates favouring the intervention (RR=0.71, 95%CI=0.59-0.86) and a significant low heterogeneity index. In addition, sensitivity analysis showed that removing any of the included studies did not affect the outcome. Also, trial sequential analysis (in supplementary material on Sub-Appendix S4) confirmed the confidence in these findings, thereby excluding the risk of a false positive result, since significant boundaries and the necessary sample size were achieved.

One quasi-randomised study showed the same results, with relative reduction in exacerbation rates of almost 50%(17). One study did not show any differences(40). This was a randomised study, comparing the use of a peak flow meter versus symptom monitoring as a basis for disease control, and used physical demonstration with placebo devices in all participants, repeated every 6 months and provided by a clinician. It had a large sample size (396 participants), a 24-month follow-up, and predominantly involved moderate to severe Asthma patients. The authors did not find a reduction in global exacerbation rate, and this could be because this study included only Asthma patients while the other studies had COPD patients or both.

Disease control: All studies evaluated the effect of intervention on several aspects of disease control, mainly on quality of life and symptoms. Although the results were highly discrepant because half of the studies showed an improvement in these outcomes(36, 37, 39, 40) , but the other half did not(16, 17, 35, 38). Meta-analysis including only RCTs did not find significant improvement in quality of life. However, sensitivity analysis including only the two studies that used St. George's Respiratory Questionnaire (36, 38) showed a slightly significant improvement of 3.57 points in the mean score (CI 0.36 to 6.78). No relevant characteristics seemed to differentiate the studies on these findings, but detailed analysis of the RCTs showed that a longer follow-up period seems to be associated with a more significant, positive effect on quality of life(36, 38). Nevertheless, the magnitude of these effects was small and with wide confidence intervals, and was associated with an overall moderate strength of evidence.

Respiratory function: Half of the studies evaluated the impact on FEV1, but only one showed a significant benefit of the intervention(40). In this study, inhaler education was not the primary objective, and all participants received a thorough disease self-management program, with several intervention aspects besides inhaler education. The magnitude of the observed effect was small and with a wide confidence interval. Quantitative analysis did not show any significant benefit either.

Adherence rate: Three studies evaluated the impact on adherence rate to inhaled medication and all of them showed significant improvement after the intervention(16, 17, 36). Again, this effect may also be due to the Hawthorne effect in participants. Only two of the RCTs evaluated this outcome, but used different scales, and one of them did not report useful results for quantitative analysis.

Education frequency: Only two studies included a repeated education program, which was mainly on a biannual basis(17, 40). Both were non-randomised and reported divergent results in the main outcomes. Thus, we could not perform a quantitative or sensitivity analysis on them, which limits any kind of conclusion about how often inhaler review and education should be recommended.

Discussion

Summary of main results:

The main finding of our review is that inhaler technique education can significantly reduce exacerbation risk and this is reinforced by a significant pooled result with low index of statistical heterogeneity in the meta-analysis. This is the first study to find such results in older adult patients with Asthma or COPD.

Intervention can also improve quality of life and clinical control, but results are still divergent. Also, by enhancing self-management education, adherence rates also increase, but this was difficult to quantify. However, these findings should be interpreted with caution since most studies lack sufficient quality of the evidence on their results, and this is due to several limitations in design and methods, which introduce a high risk of bias. Most studies addressed complex intervention aspects beyond inhaler technique education alone, and this is particularly relevant to the outcomes of interest because it makes it harder to conclude about the true effect of an inhaler education approach alone. Thus, this review fails to detect any important finding about the role of inhaler technique education alone. Although many guidelines recommend regular inhaler review, it is still unclear how often that should be performed with older adult patients. Only one RCT included patients with Asthma(35), while the other ones only had COPD patients. Thus Asthma patients represent only 6% of total analysed patients, which skews the available evidence towards COPD.

In our review we could not perform additional subgroup analysis, namely according to age strata (i.e. such as in patients below or above 75 years old), or even according to important co-morbidities (osteoarthritis, frailty, cognitive disorders, etc). All studies had a mean age under 70 years old and none has reported such data. Such subgroup analysis would be clinically relevant because there is increasing evidence suggesting that such characteristics

seem to be determinant to inhaler performance and to disease outcomes in these individuals(23, 25, 27, 28).

Overall applicability and quality of the evidence:

Using the GRADE approach to rate the quality of the evidence, our analysis showed a significant overall risk of bias in studies. Half of them did not have a randomised design, and even RCTs were not blinded to the intervention due to its intrinsic nature. This fact introduces a potential Hawthorne effect, which could overestimate the main outcomes. Although this could compromise the internal validity of trials, globally, all showed a regular and similar trend in the results, which improves their external validity and applicability. Although the included studies did not address any cost-effective analysis or report adverse effects of the interventions, the potential benefits may outweigh the risks, which also favours regular inhaler education. Several studies have highlighted these aspects(2, 14, 15).

It is difficult, with the existing evidence, to conclude about the true potential of inhaler education alone, or about which is the most efficient education method. Some studies suggested that placebo device demonstration may be the best one(41-43) but in our review this was not clear. It is possible that older adult patients have some resistance to this method due to problems such as cognitive impairment(23, 26). We found only one RCT that used placebo device training for intervention, and it showed improvement in exacerbation risk only for severe episodes(16). More randomised and blinded design studies are needed to test different types of interventions, clarify which factors may influence inhaler performance, and assess the impact of performance on clinically relevant outcomes in older adults. These studies were performed by well-trained staff with adequate time dedicated to instruction. This does not usually happen in the real world where health professionals work in tight schedules and without proper training on handling all available devices. This could undermine generalizability of study findings.

Potential biases in the review process:

Our review process was based on Cochrane recommendations(32) and is in accordance with PRISMA statement(31), which makes it less susceptible to major biases and errors. The search method was based on main databases (CENTRAL, MEDLINE and EMBASE) and covered important secondary sources. In addition, criteria used were broad, thereby yielding a representative amount of selected studies. Previous systematic reviews(21, 22) on the same topic were also screened for secondary sources of important studies, which minimizes the risk of bias in this process. During the selection process, besides RCTs, we also included non-randomised studies, to avoid underestimation of true effects of inhaler education programs. Although this kind of study design lacks evidence quality, we believe that all four included studies helped to reinforce the strength of recommendation regarding some of the outcomes,

namely exacerbation risk reductions. In addition, by including quasi-randomised studies, we highlight the need for further, adequately designed, research in this particular population.

Quality of evidence was assessed in accordance with the GRADE approach, by two independent reviewers, and agreement was obtained in all studies. Also, two other authors confirmed the process. In addition, our main results of this analysis are very similar to the ones reported in previous systematic reviews(21, 22). Performing a meta-analysis of such different and complex interventions could lead to false interpretation of results, since these studies are not truly comparable. To overcome this, we confirmed the main meta-analysis findings with trial sequential analysis (in supplementary material - on Sub-Appendix S4), which strongly reinforced a significant reduction of exacerbations, thereby increasing confidence in the results and excluding the risk of a false positive result.

Comparison with other studies and reviews:

To our knowledge, this is the first systematic review on inhaler education in older adult patients with Asthma or COPD that obtained such clinically relevant results on disease control, namely the reduction of exacerbation risk. Given the increasing overall aging of the population, and the complex characteristics of these patients, we find this work relevant and timely.

This systematic review stands out from previous ones for several reasons(21, 22). First of all, it focuses on older adults, who often present poor clinical control, are more susceptible to exacerbations and more frequently have poor inhaler technique(25, 26). In addition, we included randomised and non-randomised studies, which allows us to reach more realistic conclusions on the impact of inhaler technique education. Also, our review included more recent studies, which were excluded in previous works. Finally, our systematic review highlights the fact that most studies showed a positive impact on exacerbation risk reduction. In the systematic review by Normansell et al.(21), the authors only focused on Asthma and included adult and older adult participants together, without performing subgroup analysis of the latter. This spread of age ranges may have introduced some bias, mainly derived from endotypic and phenotypic disease differences, which could lead to different clinical responses to education of inhaler performance. The systematic review by Klijn et al(22) focused on post-intervention inhaler performance as the main outcome, but did not perform full analysis of the clinically relevant outcomes. Also, it included a wide age range, did not perform subgroup analysis in older adult patients and did not carry out a meta-analysis. In any case, it is clear both in previous work and in our review that inhaler technique education improves performance, and has a potential benefit for clinical outcomes, although its evidence has low or moderate strength.

In our work, we found inconsistent results in clinical control and quality of life, but overall, exacerbation rates seem to be significantly reduced with interventions. This is particularly relevant regarding health economics, and several studies have shown cost-effective positive associations in this field(2, 14, 15).

Conclusions

Inhaler technique education is a key aspect of self-management programmes, and all kinds of interventions seem to improve inhaler performance and clinically relevant outcomes. Review of inhaler technique is recommended and there is evidence that interventions that promote improvement in inhaler technique ameliorate disease control. In addition, these interventions significantly reduce exacerbation risk in older adult patients. However, the strength of evidence for these outcomes is still moderate. Further studies are warranted in order to compare different education methods, different target populations and to define the best regular follow-up.

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4.2 Inhaler review in elderly with Asthma or COPD – a cost-effectiveness study and a perspective in Portugal

Abstract

Introduction: Elderly patients with Asthma or COPD are particularly susceptible to exacerbations, and that may be associated with incorrect use of inhalers. Education programmes with inhaler technique review seem to be effective, but no studies have addressed their cost-effectiveness in elderly patients.

Objective: To perform a cost-effectiveness analysis of education programme in elderly patients, and estimate the cost-benefit of applying such a programme in Portugal.

Perspective and Methods: We developed a decision tree analysis from a healthcare perspective, according to exacerbation rates and costs described in a previous meta-analysis, and according to intervention costs. Sensitivity analysis of worst and best-case scenarios was performed to estimate thresholds for intervention affordable limits, as well as cost-saving estimations and Incremental Cost Effectiveness Ratios (ICER) for a Portuguese scenario.

Setting: We estimated cost-effectiveness thresholds applicable in all settings and performed a sensitivity analysis of a theoretical intervention model in all patients, including inhaler technique review at an annual appointment with a doctor and a nurse.

Results: In the best-case scenario, the intervention affordable budget could be up to almost 1.800€ (US $1,585.24) per patient per year. Mean intervention-associated savings in Portugal would be 311.88€ (US $274.68) per patient per year, representing annual savings up to €131 million (US $150 million) for the whole health system, and this already includes intervention costs. ICER for Portugal vary between 93.73€ (US $82.55) and 437.43€ (US $385.25) per exacerbation avoided.

Conclusions: A model of an intervention program with inhaler technique review in elderly patients suggests that this intervention is cost-effective and can generate significant savings.

KEYWORDS: Cost-effectiveness; Inhaler; Asthma; Chronic Obstructive Pulmonary Disease; Elderly

Introduction

Respiratory diseases are one of the main causes of death worldwide. Asthma and Chronic Obstructive Pulmonary Disease (COPD) are two major respiratory diseases and affect up to 10% of the population (1). Inhaled therapy is the main treatment pathway used, but the majority of patients use devices incorrectly, frequently with critical errors, thereby contributing to poor clinical control and increased risk of exacerbations (2-5). In addition, many studies have shown that poor clinical control also leads to increased costs in health services (6-9). However, true estimates of the burden due to Asthma and COPD are unavailable, because direct and indirect costs are difficult to quantify, and different parts of the world report different estimations.

There is significant evidence showing that education programmes for Asthma and COPD may be effective in terms of clinical improvement (10-14), but few have addressed inhaler technique review alone. In addition, there is strong evidence to support the cost-effectiveness of those programmes, although the reported results show a broad range of annual cost savings with interventions, ranging from 200€ (US $176.17) to 2000€ (US $1,7617.06) per patient (15-20). In Portugal, acute care and exacerbations-associated annual costs are estimated between 330€ (US $290.69) and 8000€ (US $7,047.30) per patient (7, 21), but no study has yet evaluated the cost-effectiveness of a conceptualized national education programme for Asthma and COPD.

Portugal is one of the most aged countries in Europe, and elderly patients tend to have poor quality of life (22). Also, respiratory diseases represent the second leading cause of death in these patients (23). Elderly patients with Asthma or COPD are particularly susceptible to poor disease control and exacerbations(24, 25), which is due to particular characteristics, such as increased comorbidities, poor adherence to treatment and poor inhaler technique performance (26-28). Nevertheless, a recent meta-analysis has shown that educational interventions of inhaler technique review in elderly patients significantly reduce the risk of exacerbations, with a pooled risk reduction of 29%(29). These are patients who may benefit most from educational interventions, and this reported effectiveness was not previously detected in younger patients (30, 31).

However, as far as we know, there is no cost-effectiveness study published that has analysed educational interventions in elderly patients. Decision analysis and cost-effectiveness analysis are useful tools that integrate evidence in specific context conditions, in order to address a specific decision problem (32). Developed countries face the urge to reduce health costs and maximize clinical benefits from interventions. Thus, one major strategy is to identify the most cost-effective subgroups of patients.

We hypothesized that a simple intervention (review of inhaler technique) would result in a slight increase in intervention costs but also in a decrease in direct costs of exacerbations,

resulting in overall health care costs savings in a model for elderly patients with Asthma or COPD. Thus, our study aimed to determine, in accordance with the main results reported in the previous meta-analysis, the cost-effectiveness of educational interventions including inhaler technique review in elderly patients with Asthma or COPD.

Methods

Study design and Framework:

We developed a standard cost-effectiveness analysis, based on a decision tree approach (33) and in accordance with CHEERS recommendations (see Supplementary Appendix S1) (34). Our aims were to perform estimations of treatment affordable thresholds and according to exacerbation costs in elderly patients. In addition, we performed estimations of cost-savings and Incremental Cost Effectiveness Ratios (ICER) for a Portuguese scenario, according to local costs of a theoretical intervention program.

Sources of data:

We used data from previously published studies on exacerbation costs, exacerbation rates, and local costs for intervention on inhaler technique review, to try to determine cost-effectiveness ratios. According to a previously published meta-analysis, interventions that include inhaler technique review in elderly patients with Asthma or COPD reduce exacerbation rates from 0.58 to 0.43 (number of exacerbations per patient per year). Absolute mean reductions of exacerbation rates range from 0.07 to 0.22, in worst and best-case scenarios and according to 95%CI limits(29). In addition, exacerbations and acute medical care, alone, represent annual costs between 330€(US $290.69) and 8.000€ (US $7,047.30) per patient (7, 21). A more recent estimation for COPD in Portugal points out annual costs of 2.250€ (US $1,982.04) per patient(35). Due to the wide range of values, we used all these references to estimate scenarios for the best-case, worst-case, and mean estimation.

Base-case definition:

The base-case population of our analysis are elderly patients with Asthma or COPD, because these patients are more susceptible to poor clinical control and exacerbation risks. This is a healthcare payer's perspective study, where only direct costs were considered, because indirect costs and patient`s own costs were not reliably available. We did not consider medication costs in the different stages of disease management either. Two types of costs were calculated, the intervention costs and exacerbation costs, which were assigned to the decision tree analysis. This model assumes the previously reported exacerbation risk

reduction, as well as the costs associated with each exacerbation. We also performed sensitivity analysis to assess uncertainty regarding thresholds of intervention cost-effectiveness, using reported 95%CI limits in order to estimate worst and best-case scenarios.

Intervention:

Different intervention programmes were tested in these patients in previous studies, with a wide variety of aspects being addressed. Most interventions addressed inhaler technique review, self-management tools and functional control, and almost all studies performed it only at baseline of the follow-up period. In addition, interventions were delivered by different health professionals, such as doctors, nurses and pharmacists(29). For that reason, we developed a conceptual intervention program with annual control appointments by a doctor and a nurse. Each appointment would require a 20 min evaluation, to perform inhaler technique review and to assess clinical control and lung function through spirometry.

Setting:

Due to inherent difficulties in specifying different aspects of interventions (inhaler technique review, self-management strategies, lung function evaluation, etc.), the costs of such programme were calculated as a whole, considering health professionals' salaries in 2017 that are based on the official values defined by the Portuguese Central Administration of Health System (ACSS), as well as spirometry costs(7). All costs and outcomes were expressed as additional factors to the main comparator, which was Usual Care. We used Usual Care as the main comparator because it was the reference control reported in most studies that were included in the previous meta-analysis(29). The time frame in the base-case analysis was one year, because exacerbation rates were reported that way. No discount rates were considered in cost estimation.

Outcome measures:

We used a synthesis-based estimate to define outcome measures, which included exacerbation rates, cost per exacerbation and thresholds of cost-effectiveness for the designed intervention program. All cost estimations were used according to 2017 references, in euros (€). Exacerbation costs were considered as a whole in mean estimations, regardless of the type of treatment or management that is usually provided to patients. For that reason, some types of clinical interventions provided for the management of exacerbations could be the same as those provided in our theoretical intervention programme. However, that would not hamper the ability to compare them as a conceptual framework for the cost-effectiveness analysis.

Figure 4.2.1 shows the decision tree used in the model. The resulting equation for cost-effectivity balance is the following one (EC – Exacerbation costs; IC- Intervention Costs; PIR – Probability of exacerbation under Inhaler Technique Review; PUC – Probability of exacerbation under Usual Care):

Expected Value (Inhaler Review)=Expected Value (Usual Care)

$$[(EC+IC)\times P\_IR\ ]+[IC\times(1-P\_IR\ )]=(EC\times P\_UC\ )+[0\times(1-P\_UC\ )]$$

$$IC=EC\times(P\_UC-P\_IR\ )$$

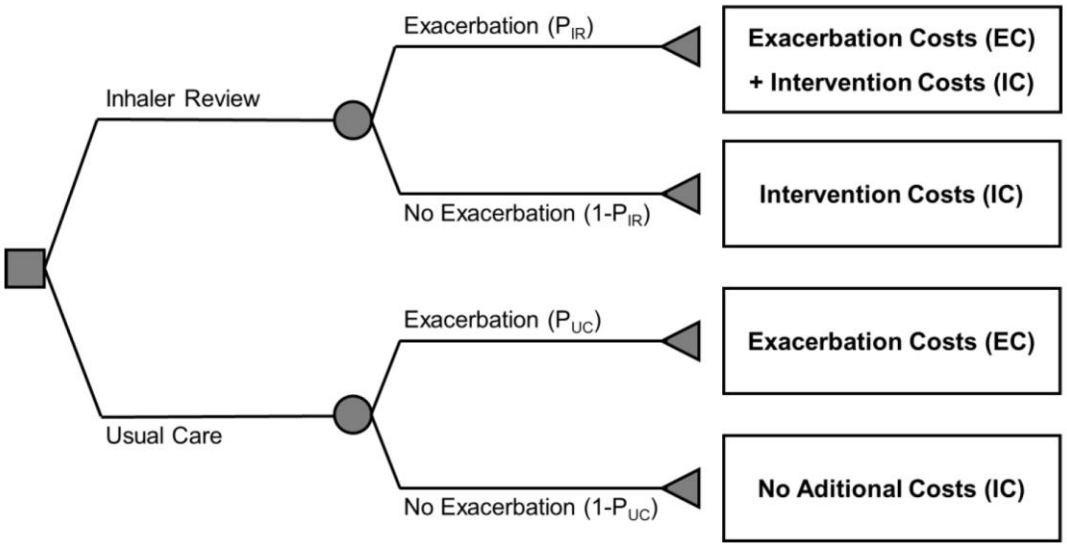

Figure 4.2.1 - Decision tree model to compare Usual care versus Inhaler technique review intervention. EC – Exacerbation costs; IC- Intervention Costs; PIR – Probability of exacerbation under Inhaler Technique Review; PUC – Probability of exacerbation under Usual Care.

Table 4.2.1 summarizes all data considered in parameters assigned to cost estimations. Using the model assumptions presented in figure 4.2.1, we estimated the affordable limits for intervention costs at mean values and at worst and best-case scenarios. Worst-case scenario was estimated using the 95%CI lower limit of probability of exacerbation under Usual Care, and 95%CI upper limit of probability of exacerbation under Inhaler Technique Review intervention. Best case scenario was estimated using the 95%CI upper limit of Probability of exacerbation under Usual Care, and 95%CI lower limit of Probability of exacerbation under Inhaler Technique Review intervention. Mean estimation was obtained with the respective mean values.

Table 4.2.1 – Input parameters used in the model

Parameter	**Value**	**CI95% lower limit**	**CI95% upper limit**	**Source**
Exacerbation rate (anual)				
• Usual care	0.58	0.54	0.62	(29)
• Inhaler technique review	0.43	0.40	0.47	(29)
Parameter	**Mean estimation**	**Best-case estimation**	**Worst-case estimation**	**Source**
Intervention Costs (€/$)				
• Doctor (20 min intervention once/year)*	7.25€ (US $6.39)	4.10€ (US $3.61)	10.40€ (US $9.16)	‡
• Nurse (20min intervention once/year)†	4.45€ (US $3.92)	2.60€ (US $2.29)	6.30€ (US $5.55)	‡
• Control Spirometry	13.92€ (US $12.26)	13.92€ (US $12.26)	13.92€ (US $12.26)	(7)
TOTAL	25.62€ (US $22.56)	20.62€ (US $18.16)	30.62€ (US $26.96)	
Exacerbation Costs (€)				
Cost per patient	2.250€ (US $1,982.04)	330€ (US $290.69)	8.000€ (US $7,047.30)	(7, 21, 35)

CI: Confidence Interval; €: 2017 Portuguese euro. $: United States dollar.

* Mean salary of a Doctor for each hour ranges from 12,22€ (US $10.76) to 31,13€ (US $27.41).

† Mean salary of a Nurse for each hour ranges from 7,90€ (US $6.96) to 18,80€ (US $16.55).

‡ based on official values defined by the Portuguese Central Administration of Health System (ACSS)

Cost-saving estimation for Portugal was also obtained according to worst and best-case scenarios. In the worst-case scenario, we used the lower limit of reported exacerbation cost, the worst-case estimation of intervention cost and worst-case estimation of risk difference (the difference between exacerbation risk of Inhaler Technique Review group and Usual Care group). In the best-case scenario, we used the upper limit of reported exacerbation cost, the best-case estimation of intervention cost and the best-case estimation of risk difference

Results

Cost effectiveness estimation and sensitivity analysis:

Our analysis estimated the cost-effectiveness thresholds for intervention costs affordable limits per patient per year. Figure 4.2.2 presents these results in the range of exacerbation costs between 0€ (US $0) and 8.000€ (US $7,047.30). The respective estimation equations are (EC – Exacerbation costs; IC- Intervention Costs; PIR – Probability of exacerbation under Inhaler Technique Review; PUC – Probability of exacerbation under Usual Care):

Worst-case scenario: [CI95% lower limit of P_{UC} and upper limit of P_{IR}]

$$IC = EC \times (0.54 - 0.47) \text{ <=> } IC = 0.07 \times EC$$

Mean estimation scenario: [mean P_{UC} and mean P_{IR}]

$$IC = EC \times (0.58 - 0.43) \text{ <=> } IC = 0.15 \times EC$$

Best-case scenario: [CI95% upper limit of P_{UC} and lower limit of P_{IR}]

$$IC = EC \times (0.62 - 0.40) \text{ <=> } IC = 0.22 \times EC$$

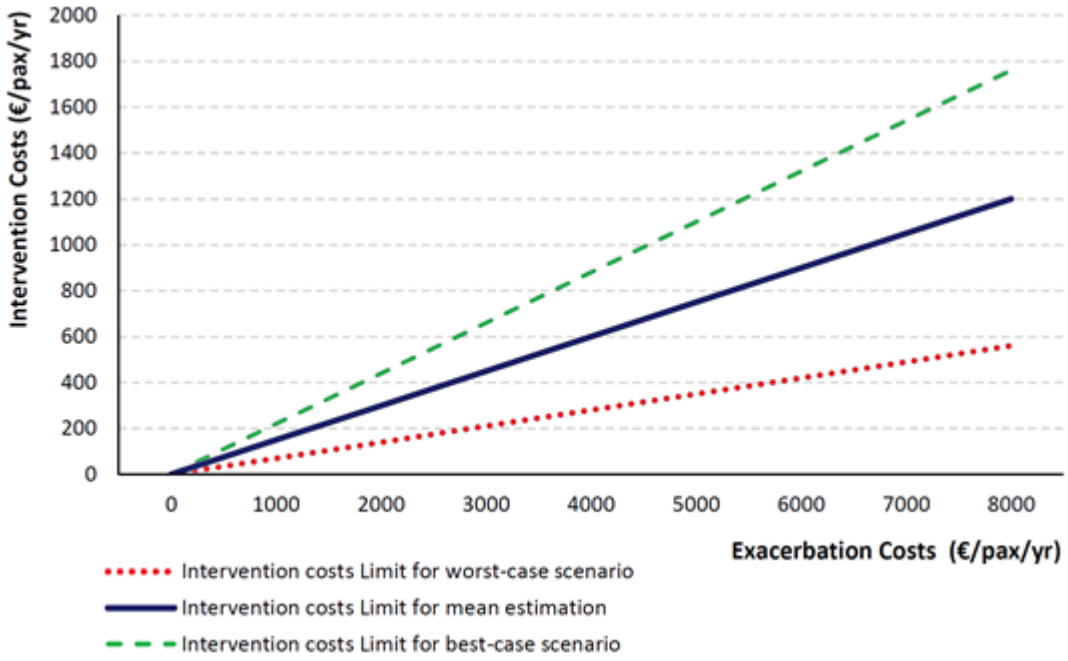

Figure 4.2.2 - Cost-effectivity thresholds according to exacerbation costs. Lines represent the intervention costs affordable limit scenarios according to exacerbation proportions of CI95% lower limit, mean estimation and CI95% upper limit.

In the best-case scenario of intervention effectiveness and with exacerbation costs at the reported upper limit, the intervention affordable budget could be up to almost 1.800€ (US $1,585.24) per patient per year. The more exacerbation costs increase, the higher the affordable limit rises in order to develop an intervention programme.

Cost effectiveness estimations for a Portuguese scenario:

Cost-saving estimations for Portugal were obtained considering mean values, worst and best-case scenarios, and according to variations between exacerbation annual costs, which range from 330.95€ (US $291.54) to 8.000€ (US $7,047.30) per patient. These reported costs concern the global population, but were used here to estimate savings for elderly patients. The main equations used to estimate cost-savings were (EC: Exacerbation costs; IC: Intervention costs; RD: risk difference between Inhaler Technique Review and Usual Care):

Worst-case scenario:

$$Estimation\,Savings_{worst-case} = (EC_{best-case} \times \mathrm{RD}_{\mathrm{worst-case}}) - IC_{worst-case}$$

$$Estimation\,Savings_{worst-case} = (330.95 \times 0.07) - 30{,}62$$

$$Estimation\,Savings_{worst-case} = (-)7{,}45$$

Mean estimation:

$$Estimation\,Savings_{mean} = (EC_{mean} \times \mathrm{RD}_{mean}) - IC_{mean}$$

$$Estimation\,Savings_{mean} = (4165.48 \times 0.15) - 25{,}62$$

$$Estimation\,Savings_{mean} = 599.20$$

Best-case scenario:

$$Estimation\,Savings_{best-case} = (EC_{worst-case} \times \mathrm{RD}_{\mathrm{best-case}}) - IC_{best-case}$$

$$Estimation\,Savings_{worst-case} = (8000 \times 0.22) - 20{,}62$$

$$Estimation\,Savings_{worst-case} = 1739{,}38$$

Considering data from exacerbation risk difference reported for elderly patients, we estimated mean annual savings of 311.88€ (US $274.68) per patient for an intervention program in Portugal. We found a wide interval between worst and best-case scenarios, ranging from an annual negative balance of minus 7,45€ (US $6.56) and a positive budget of 1.739,38€ (US $1,532.09) per patient. However, considering the reported difference in annual costs associated with clinically well-controlled patients and clinically uncontrolled patients, which is about 469,42€ (US $413.47)(7), the worst-case scenario increases to a positive balance of 2,24€ (US $2.13) per patient/year.

In Portugal there are approximately 2,2 million elderly people. Thus, considering an overall 10% combined prevalence of Asthma or COPD(1), the mean estimation for effectively implemented interventions in this age group could theoretically represent total annual savings of €131 million (US $150 million) for the Portuguese national health system, and this estimation already includes all the intervention costs.

Incremental cost-effectiveness ratio (ICER) estimations for a Portuguese scenario:

ICER was estimated for worst and best-case scenarios, and according to upper and lower limits of intervention costs and risk difference. Incremental effectiveness was estimated according to the number of prevented exacerbations. Figure 4.2.3 represents ICER for Portugal at worst-case and best-case scenarios, which vary between 93.73€ (US $82.55) and 437.43€ (US $385.25) per exacerbation avoided.

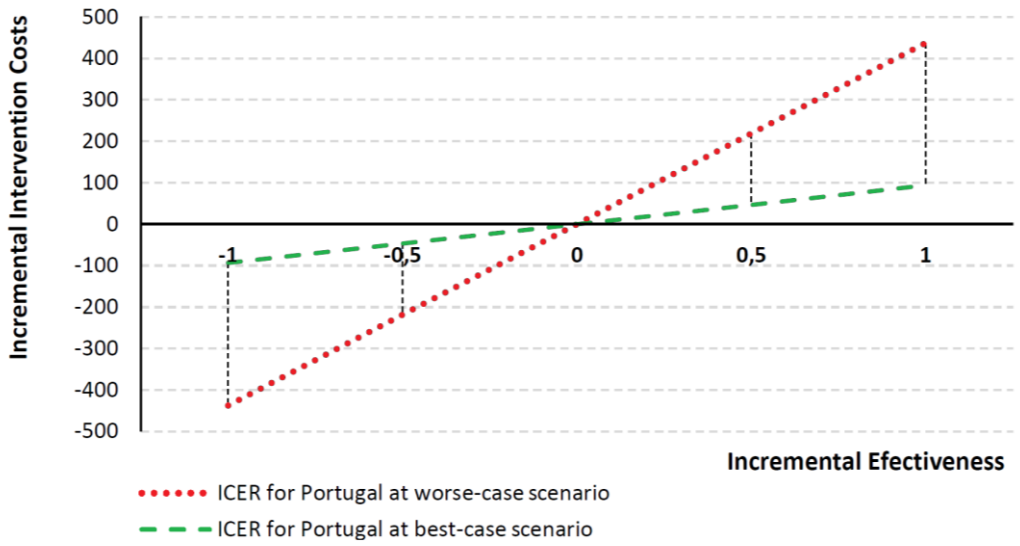

Figure 4.2.3 - Incremental cost-effectiveness ratio (ICER) for Portugal at worst-case and best-case scenarios according to lower and upper limits of Intervention Costs and Risk Difference. Incremental effectiveness was estimated according to number of prevented exacerbations.

The equations used were (IC: Intervention costs; RD: risk difference between Inhaler Technique Review and Usual Care.):

At worst-case scenario:

$$ICER_{worst-case} = \frac{IC_{worst-case}}{\mathrm{RD}_{\mathrm{worst-case}}} = \frac{30{,}62}{0{,}07} = 437{,}43$$

At best-case scenario:

$$ICER_{best-case} = \frac{IC_{best-case}}{\mathrm{RD}_{\mathrm{best-case}}} = \frac{20{,}62}{0{,}22} = 93{,}73$$

Discussion

Our results show that interventions that include inhaler technique review to improve clinical control in elderly patients with Asthma or COPD may be cost-effective and may generate significant savings from the perspective of the healthcare provider.

This is the first study showing that these interventions could save up to several hundreds of million euros in Portugal. Also, this is the first study establishing thresholds for affordable budget interventions, which can be adopted worldwide according to exacerbations costs. Moreover, as exacerbations costs get higher, affordable limits for intervention budget also increase. These thresholds may apply to other health care systems, since they are based on worldwide data of exacerbation rate variations, and are unaffected by local health costs. In a simple approach, health care systems may invest on interventional programs up to 22% of total exacerbation costs, in order to be cost-effective.

The intervention costs and exacerbation costs used were based on data from Portugal, and might differ from costs in other countries, which might lead to different cost saving estimations. However, when actually compared with reports from other countries, our study found similar mean savings with interventions in the Portuguese scenario, which reinforces the generalizability of our findings. In addition, most previous reports used a standard cost-effectiveness model, which was also our approach (15-19). However, similarly to these reports, we also found a very wide range of plausible values, which could be due to uncertainty of estimation of exacerbation costs and difficulty in establishing true costs of intervention programmes. More recent studies have estimated less savings with interventions(15, 16), and that could be due to various reasons. First, because these studies mostly included adult patients in the base-case analysis, without focusing on elderly patients. Secondly, they mostly included COPD patients, who have irreversible airway obstruction and an increased risk of exacerbations. In Asthma patients, inhaled medication, such as inhaled corticosteroids, is more effective. Finally, the observed discrepancy may also be due to different country settings and their respective costs. In contrast, we focused our analysis mainly on older patients, because they tend to have higher exacerbation rates and are probably more susceptible to the benefits of interventions(24, 25, 29). This approach may have improved our findings. These patients also have more comorbidities and drug interactions, which can increase costs of exacerbations and worsen disease control. Moreover, exacerbations may not only lead to direct costs of additional treatment and/or hospitalizations, but there is also evidence that they result in significant lung function decline

and thus, in a tremendous loss in overall functions, such as increased frailty and cognitive impairment(36, 37).

Our study has, nevertheless, some limitations. First, we were not able to estimate and obtain indirect costs, mainly those regarding the patients' perspective, because exacerbation costs were uncertain in the available literature. In addition, exacerbation rates in these elderly patients may also be imprecise, since the meta-analysis we used as the basis for our work included relatively few studies(29). Lastly, we could not perform a cost-utility analysis based on Quality Adjusted Life Years (QALY), due to the scarcity of available data. We accept that such analysis would probably reinforce the clinical relevance of our findings.

We found that the worst-case scenario for cost-savings could represent a slight negative balance, but that could be underestimated. In fact, for that estimation we used data from a Portuguese study on Asthma(7), but we only considered acute medical care costs, which represent about 40% of patients included. However, the real prevalence of exacerbations in elderly patients is slightly higher. In addition, using the real difference in annual costs between controlled and uncontrolled patients [about 469,42€ increase (US $413.47)] our worst-case scenario turns to a positive balance.

Another important aspect to consider is the intervention conceptual programme itself. In fact, the mean follow-up period of previous interventional studies is wide, varying from 3(12) up to 24 months(14), and none of those studies have tested regular inhaler technique review. Further studies should be designed to test how often and for how long the intervention is needed, in order to maintain effectiveness, because there is evidence that inhaler technique review is lost after some time(38, 39). Other features may also affect exacerbation risk and progressive lung function decline, such as the choice of the type of inhaler, the use of multiple devices(40) or even the choice of drugs or the combination of drugs, as newer combination inhalers may make a difference in outcome(24, 25).

Finally, it should be stressed that interventions in these patients should include several aspects of disease control, such as self-management plans and inhaler technique review. This is particularly relevant, since most interventional studies included in a previous meta-analysis have covered other features besides inhaler technique review(29). In addition, most of those studies have measured adherence as an outcome, rather than inhaler technique performance, and this is an important aspect to be taken into account, because it may bias the result of intervention effectiveness. Better adherence to inhaler therapy does not necessarily mean better inhaler technique performance, and this should be clarified in future studies. Also, improving adherence seems to be related to decreased exacerbation risk(12, 13), and that may be independent of inhaler technique performance(3, 41, 42). Adherence may also be an important aspect to consider in terms of cost estimation, because it also affects medication costs(43). Here, medication costs were not considered as a subset, although cost estimations

included them in the main source. Medication costs may decrease due to better inhaler technique, because as clinical control improves, other concurrent therapies are less needed (such as oral corticosteroids or antibiotics), and the optimal inhaled dosing may also be reduced. Those aspects were not considered in our analysis.

However, it is difficult to ascertain the cost-effectiveness of such aspects alone, mainly the impact of inhaler technique review, which has been remarked as a key point in previous work by others (15).

Conclusion

Intervention programmes in elderly patients with Asthma or COPD seem to be cost-effective, and may generate significant savings in Portugal. Also, the affordable limits for intervention costs are wide, and are augmented as exacerbation costs increase.

Intervention programmes should embrace different dimensions, as self-management tools and inhaler technique review, and this should be considered before changing or adding new treatment options.

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4.3 Inhaler technique in elderly Asthma or COPD patients – a predictive tool for inhaler performance

Abstract

Background: Elderly patients with Asthma or COPD are particularly susceptible to inhaler technique errors and up to 85% use them incorrectly. Several factors may influence performance, but most studies are inconsistent and contradictory. We developed a tool for the major predictors of inhaler performance in these patients.

Methods: Multicenter cross-sectional study with patients using inhalers on a regular basis. Several demographic, socioeconomic and clinical characteristics were collected as potential predictors, and inhaler performance was the main outcome. Linear and logistic regression models were set up to identify significant variables. Subgroup analysis was performed according to age, cognitive performance and different types of inhalers.

Results: We included 130 participants, mean age of 74.4(±6.4) years. The prevalence of inhaler technique errors was 71.6% (95%CI: 64-78.5), and that of critical mistakes 31.1% (95%CI: 24-38.8). Among all, pressurized metered dose inhaler (pMDI) was the type of inhaler with most frequent critical mistakes.

From the multivariate analysis, a predictive score of misuse probability was developed for clinical practice, including attributable points to: cognitive performance, adherence, and having a previous placebo device education. Other significant variables were: being a male, having concomitant allergies or comorbidities, smoking status and depression. A progressive decline in performance was detected in cognitively impaired elderly patients older than 75 years who were using dry powder inhalers (DPI).

Conclusions: Inhaler performance should be addressed with caution in non-adherent patients and those with cognitive impairment. Placebo device training provided by doctors seems to best suit these patients.

KEYWORDS: Asthma; Chronic Obstructive Pulmonary Disease; Inhaler performance; Aged; Predictors

Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are the most common chronic respiratory conditions, affecting up to 10% of the global population, and many patients have uncontrolled symptoms[1 2]. Life-threatening exacerbations affect almost 50% of patients every year in community healthcare settings[3 4]. Elderly patients are more susceptible to disease consequences due frequent underdiagnosis and associated comorbidities and drug interactions [5 6].

Inhaler therapy is the most effective approach to treating these patients but up to 85% of them use inhalers incorrectly. This could be due to the wide variety of inhalers available, each with its specificities, and to patients` individual characteristics [7]. In addition, some errors are more critical than others and have higher impact on disease control[8]. In fact, inhaler performance is strongly associated with disease control, exacerbations and healthcare costs [9-14].

Although all inhalers when properly used show equal treatment efficacy [15], elderly patients are particularly susceptible to inhaler technique errors[16], probably due to more frequent, cognitive impairment[17 18], lower education level[19 20], decreased lung function [21], and global frailty or hand osteoarthritis[22 23]. Cognitive impairment seems to be the most relevant predictor of inhaler performance, leading to an increased risk of exacerbations. Moreover, exacerbations worsen cognitive impairment, which creates a vicious circle [24 25]. Aging leads to lung function decline, which compromises the ability to perform inhalation properly, since some inhalers need significant inhalation flow[26]. Some findings from available studies are inconsistent and contradictory regarding factors influencing inhaler performance. Furthermore, elderly patients are frequently excluded from major trials, which hampers the ability to integrate and adjust these factors as true predictors of inhaler performance in these patients.

Thus, we performed an exploratory study aiming to assess the major predictors of inhaler performance in elderly patients with Asthma or COPD, and developed a predictive tool of inhaler performance that may be used in clinical practice.

Methods

Study setting:

Multicenter cross-sectional study in patients with Asthma, COPD or Asthma/COPD overlap (ACO), older than 65 years and regularly using inhalers. Patients with severe or acute illness, recent abdominal or chest surgery, or chronic respiratory dysfunction under oxygen therapy were excluded. The study protocol was approved by an Institutional Review Board and Ethics

Committee of the University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, on November 2017. Every participant signed a written consent form.

Sample Size and Participants' recruitment:

Sample size was estimated using the x2 independent group proportions approach of STATA Statistical Package, considering the event proportion of inhaler errors up to 90%, a 95% CI, a power of 80% and alpha level of 0.05. Estimated sample size was 139, which would allow model building up to 13 variables as predictors for primary analysis.

Participants were recruited in primary healthcare centres, by family doctors, between October 2017 and April 2018. Among eligible patients, randomly selected participants were invited to participate by telephone call. Recruitment stopped when enough data were gathered to allow well-fitted regression models. From all contacted patients (n=217), almost 15% (n=33) did not answer the call, approximately 25% (n=54) declined to participate or failed the scheduled visit and approximately 60% (n=130) accepted to participate in the study.

Criteria and data collected:

We collected the following potential predictors: age, gender, body mass index, number of household members, occupational status, number of exacerbations in previous year, disease duration, disease stage/class according to GINA or GOLD classifications[3 27], educational level, Graffar social classification[28], allergies or comorbidities with potential respiratory impact (such as diabetes, heart failure, obesity, chronic and allergic rhinitis, gastroesophageal reflux disease, sleep apnoea), smoking habits, depression scale score >5[29], frailty scale score >2[30], cognitive performance according to Montreal Cognitive Assessment (MoCA) test[31], anti-pneumococcal and anti-influenza vaccination, previous teaching of inhaler technique (method and provider), adherence rate [continuous variable with score between 0 (total adherence) and 7 (non-adherence)][32] and device type.

The primary outcome was inhaler performance, measured as presence of at least one error [dichotomous], as a score in a 0-10 scale [continuous, according to the number of errors made when using each device among the total available steps] and the presence of critical mistakes [dichotomous, defined according to previous reports as follows: using Soft Mist Inhaler (SMI) and pressurized Metered Dose Inhaler (pMDI), poor coordination on dose activation and absence of a slow and steady inhalation; using pMDI the same items plus not shaking the device; using Dry Powder Inhalers (DPI) wrong dose activation (according to manufacturer specifications) and absence of a deep and strong inhalation[8]].

There were six researchers involved in evaluation of the technique and data gathering, with a medical background, and specifically trained in the inhaler reviewing process, in order to standardize procedures.

Statistical analysis and model building:

All data were analyzed with IBM SPSS Statistics© and STATA Statistical Package© software and alpha level was set at 0.05. Recommendations from the TRIPOD statement were followed to report multivariable prediction model results[33].

To test associations between predictors and outcome variables we used linear and logistic regression models. To build the models we first performed bivariate associations in order to identify significant variables to be included at a 0.25 alpha level[34]. Models were set using step-up and step-down approaches, and different models were rechecked with homoscedasticity tests and validation tools. Poisson regression was performed with the same predictors, to confirm the best-fitness of the linear regression (adapted from previous reports on a statistical approach to counting variables[35]).

According to the most significant predictors obtained on the logistic regression and their respective coefficients, we used the midpoint of the logistic curve inflection as the threshold reference for the probability of having "absent errors" overcomes the probability of having "at least one error". According to that, a predictive score was developed in order establish the clinically relevant threshold for the absence or presence of inhaler errors. Also, subgroup analysis were performed according to the major predictors identified in the model building.

Results

We included 130 participants, with a mean age of 74.4 (±6.4) years (table 4.3.1). Most patients had low educational and socioeconomic level, moderate to severe disease stage and presented allergies or comorbidities. Depression and frailty were present in one-third of participants and cognitive impairment (MoCA test score <20) in 68.5%. Good adherence rate was 36%. Most used therapy was: a combination of inhaled corticosteroid and long-acting ß2-agonist (LABA) in 68.8% of Asthma patients and 52.6% of ACO patients; a combination of LABA and long-acting muscarinic antagonists (LAMA) (25.5%), as well as a single LAMA therapy (23.4%), in COPD patients. Almost half of the cases had exacerbations in the previous year. Most participants made at least one error (overall prevalence of 71.6%; 95%CI: 64-78.5, one sample binomial test), and a high proportion of these were critical (31.1%; 95%CI: 24-38.8, one sample binomial test) (Table 4.3.2). pMDI had the highest number of critical mistakes, mainly due to poor coordination and poor inhalation flow. The most common errors were present in previous expiration (absent in 50.7%) and during end pause (absent in 47.3%).

Around 85% had received previous inhaler education, but most did not get it regularly. The most used method was placebo device training, provided mainly by a doctor at initial prescription.

Cognitive score and adherence rate were significantly associated with inhaler technique performance in all outcome measures. Educational and socioeconomic levels were also significantly associated with critical mistakes and performance score (Table 4.3.1). Inhaler education provided by doctors seemed to be associated with better performance than that provided by other professionals, for all outcome measures (Table 4.3.2). In addition, previous education was significantly associated with fewer critical mistakes and a higher performance score.

Table 4.3.3 reports the best-fitted multivariate models with major identified predictors. Logistic regression for risk of having “at least one error” identified as major significant predictors: non-adherence score (OR: 1.92 per unit increase in questionnaire score), cognitive score (OR: 0.86 per unit increase in questionnaire score) and placebo device training as previous education method (OR: 0.27). The same model, used with an inverted binary outcome (“absence of errors”), and readjusting the adherence score to a binary variable (yes/no), revealed the same coefficients for the significant predictors with the same statistical fitness. Figure 4.3.1 presents the regression line of the multivariate analysis to inhaler performance score. The logistic curve representing the probability of having “absent errors” is presented of figure 4.3.2. Using such data, a predictive score threshold was obtained, and that includes a total range from 0 up to 49 points: 1 point for each cognitive MOCA score obtained (ranging from 0 up to 30), plus 11 points for having proper adherence, plus 8 points for having received a previous placebo device training. Thus, a 38-point limit was detected as being the minimum necessary for the probability of having “absent errors” overcomes the probability of having “at least one error” (Table 4.3.4).

Linear regression for “inhaler performance score” identified as major predictors: gender (increase in 0.74 points for males), non-adherence score (decrease of 0.485 points per unit increase in questionnaire score), cognitive score (increase of 0.089 points per unit increase in questionnaire score), placebo device training as the previous education method (increase of 0.787 points), concomitant allergies or comorbidities (increase of 0.759 points), smoking status (increase of 0.663 points for never-smokers) and depression (increase of 0.618 points). Logistic regression for risk of having “at least one critical mistake” identified as major significant predictors: non-adherence score (OR: 1.43 per unit increase in questionnaire score), cognitive score (OR: 0.9 per unit increase in questionnaire score) and previous inhaler education provided by a doctor (OR: 0.2).

In subgroup analysis, we observed a non-linear, non-significant trend towards worsening inhaler performance with age and cognitive impairment – there was a progressive decline above 75 years of age and below a cognitive score of 25 points. Combining these findings with the main device types (Figure 4.3.3), a significant difference was found in inhaler performance score between patients with cognitive impairment using DPI and patients with cognitive impairment using pMDI+Spacer or SMI. This was maintained when compared with patients with normal cognitive score (p=0.001; Kruskal Wallis). Regarding age, the same trend was observed in patients above 75 years of age using DPI, but this was not statistically significant, (p=0.261; Kruskal Wallis). The exception to these trends was the use of pMDI without a spacer, which was associated with worse inhaler performance, regardless of other variables.

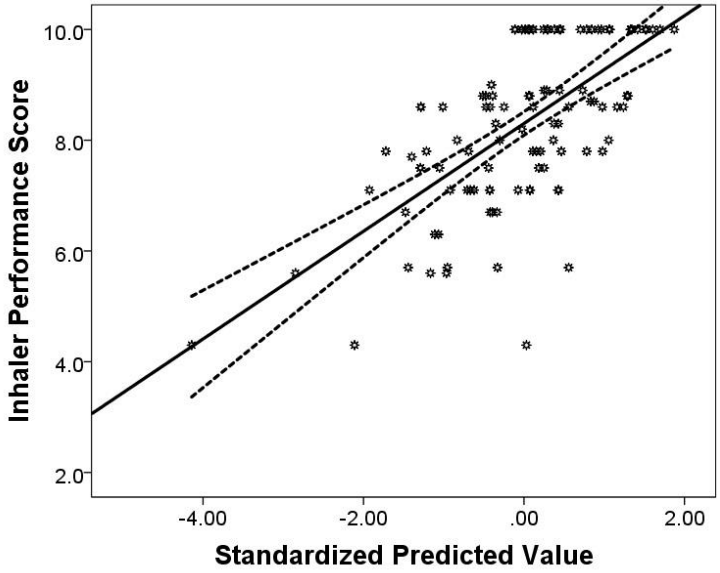

Figure 4.3.1 - Regression line of the multivariate analysis to inhaler performance score.

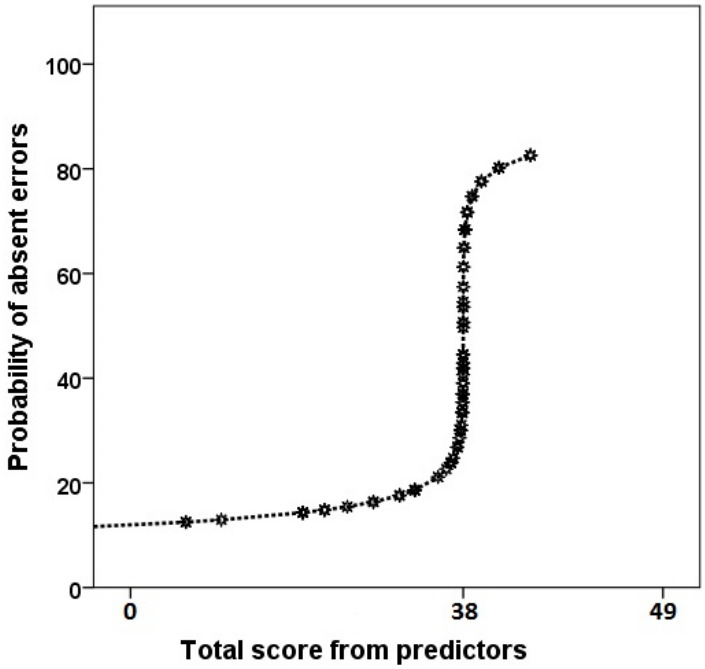

Figure 4.3.2 - Regression line of the multivariate analysis to the "absence of inhaler errors". The x-axis represents the score obtained according to predictors' coefficients. The y-axis represents the probability of having a total correct inhaler performance (absent errors).

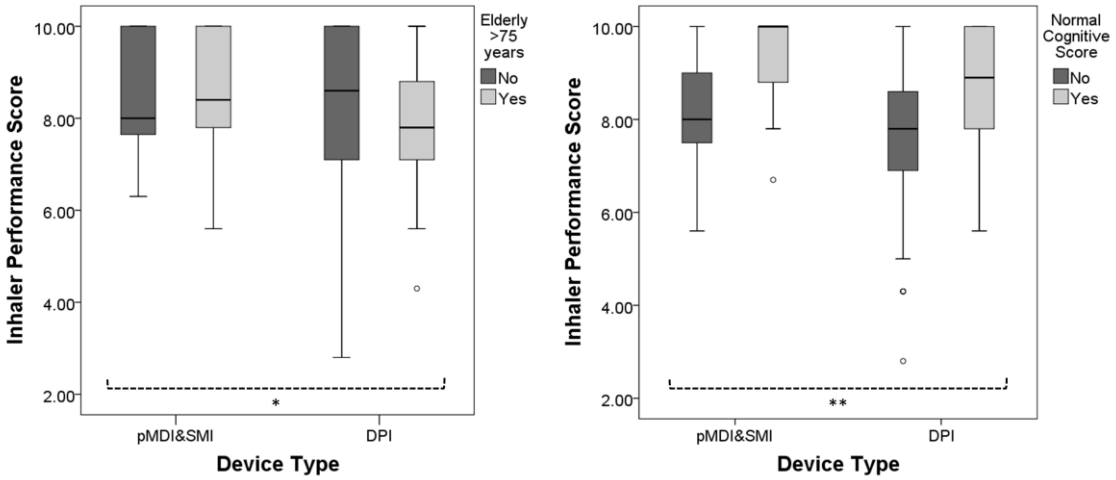

Figure 4.3.3 - Box plot of Inhaler performance score according to device type, age, and cognitive performance. *p=0.261 and **p=0.001, Kruskal Wallis test.

Table 4.3.1 - Data from demographic and clinical predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd or %]	Total	At least 1 error*			Critical errors*			Performance Score*	
		No	Yes	p value	No	Yes	p value	Mean	p value
N° of total participants	130	28.4	71.6	--	68.9	31.1	--	8.1(±1.6)	--
Age	74.4(±6.4)	73.8(±6.3)	74.6(±6.4)	.525†	74(±6.2)	75(±6.6)	.426†	--	.30 ¥
Man	41.5	33.3	66.7	.239‡	76	24	.06‡	**8.5(±1.4)**	**.044†**
Women	58.5	23.7	76.3		59.2	40.8		**7.9(±1.6)**	
BMI	27.7(±5.3)	27.4(±5.5)	27.8(±5.3)	.694†	27.2(±5.1)	28.5(±5.8)	.201†	--	.614§
Living alone	23.1	23.3	86.7	.645‡	53.3	46.7	.123‡	7.8(±1.5)	.213†
Not living alone	76.9	29	71		70	30		8.2(±1.6)	
Retired	90.8	28	72	1.0#	67.8	32.2	.336‡	8.1(±1.6)	.923†
Working	9.2	25	75		50	50		8.1(±1.4)	
Educ.>elementary school	27.7	30.6	69.4	.666‡	**80.6**	**18.4**	**.039‡**	**8.6(±1.1)**	**.008†**
Educ. none or element.	72.3	26.6	73.4		**60.6**	**39.4**		**8.0(±1.7)**	
Graffar middle/high class	40.0	32.7	67.3	.322‡	**76.9**	**23.1**	**.039‡**	**8.7(±1.1)**	**<.001†**
Graffar low class	60	24.4	75.6		**59**	**41**		**7.8(±1.7)**	
Asthma	49.2	**20.3**	**79.7**	**.024#**	59.4	40.6	.28#	7.8(±0.2)	.05 ‡
COPD	26.2	**21**	**79**		72.3	27.7		8.3(±0.2)	
ACO	14.6	**52.6**	**47.4**		73.7	26.3		8.8(±0.4)	
Disease duration (years)	20.6(±20.5)	21.5(±20)	20.3(±20.7)	.752†	20.1(±20.7)	21.7(±20.1)	.670†	--	.544§
Disease mod/severe stage**	56.2	26.0	74.0	.695‡	63	37	.457‡	8.1(±1.7)	.595†
Disease mild stage	44.8	29.8	70.2		70.2	29.7		8.2(±1.4)	
With allergies/comorb.	82.3	29	71	.611‡	68.2	31.8	.334‡	8.3(±1.5)	.066†
No allergies/comorb.	17.7	21.7	78.3		56.5	43.5		7.6(±1.8)	

Table 4.3.1 - Data from demographic and clinical predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd or %]	Total	At least 1 error*			Critical errors*			Performance Score*	
		No	Yes	p value	No	Yes	p value	Mean	p value
Never smoked	60	24.4	75.6	.322‡	**59**	**41**	**.039‡**	7.9(±1.7)	.074†
Smoker/Past-smoker	40	32.7	67.3		**76.9**	**23.1**		8.4(±1.4)	
SPY	17(±27.7)	19.2(±29.5)	16.2(±27.1)	.588†	19.9(±28.6)	11.4(±25.2)	.085†	--	.129§
With depression	32.3	26.2	73.8	.837‡	54.8	45.2	.075‡	7.8(±1.8)	.119†
No depression	67.7	28.4	71.6		71.6	28.4		8.3(±1.4)	
With frailty	33.1	23.3	76.7	.533‡	**53.5**	**46.5**	**.048‡**	7.8(±1.7)	.092†
No frailty	66.9	29.9	70.1		**72.4**	**27.6**		8.3(±1.5)	
Cognitive score	21.9(±5.7)	**24.9(±4.4)**	**20.8(±5.7)**	**<.001†**	**23.2(±5.2)**	**19.4(±5.8)**	**<.001†**	**--**	**<.001§**
Anti-pneumococcal vac.	26.9	33.3	66.7	.312‡	73	27	.352‡	8.4(±1.5)	.162†
No anti-pneumococ. vac.	73.1	24.4	75.6		62.2	37.8		8.0(±1.6)	
Anti-influenza vac.	78.5	24.5	75.5	.153‡	65.7	34.3	1.0‡	8.1(±1.5)	.492†
No anti-influenza vac.	21.5	39.3	60.7		67.9	32.1		8.3(±1.7)	
Adherent	36.2	**48.9**	**51.1**	**<.001‡**	**80.9**	**19.1**	**.012‡**	**8.9(±1.2)**	**<.001†**
Non-adherent	63.8	**15.7**	**84.3**		**57.8**	**42.2**		**7.7(±1.6)**	
Exacerb./previous year	41.5	24.1	75.9	.551‡	61.1	38.9	.349‡	8.1(±1.6)	.696†
No exac./previous year	58.5	30.3	69.7		69.7	30.3		8.2(±1.6)	

ACO - Asthma/Chronic Obstructive Pulmonary Disease overlap; BMI - Body mass index; COPD - Chronic Obstructive Pulmonary Disease; SPY - Smoking pack years. *Outcome data presented as values considering only the count of participants within each of the predictor variables. **Disease moderate to severe stage considered as Asthma on steps 3 and 4, as well as COPD on grade C or D. †Independent samples T-test; ‡Chi-squared test; #Fisher exact test; §Pearson correlation test; ¥Spearman correlation test; ǂ ANOVA test

Table 4.3.2 - Data from inhalers use as predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd] [%]	**Total**	**At least 1 error***			**Critical errors***			**Performance Score***	
		No	**Yes**	**p value**	**No**	**Yes**	**p value**	**Mean**	**p value**
N° of inhalers in all participants	148	28.4	71.6	--	68.9	31.1	--	8.1(±1.6)	--
Inhalers used									
Handihaler/Breezhaler	26.4	28.2	71.8		**82.1**	**18.9**		8.3(±0.2)	
Diskus/Accuhaler	15.5	13	87		**78.3**	**21.7**		7.6(±0.3)	
Turbohaler	12.8	26.3	73.7		**42.1**	**57.9**		7.8(±0.5)	
pMDI	11.5	23.5	76.5		**29.4**	**70.6**		8.0(±0.4)	
Spiromax	7.4	27.3	72.7		**81.8**	**18.2**		8.2(±0.5)	
Respimat	6.8	40	60	.154[#]	**90**	**10**	**.003[#]**	8.9(±0.4)	.299[λ]
Novolizer/Genuair	6.1	11.1	88.9		**66.7**	**33.3**		8.2(±0.4)	
Ellipta	6.1	44.5	55.5		**77.7**	**22.3**		8.3(±0.6)	
pMDI+Spacer	6.1	55.5	44.5		**66.7**	**33.3**		8.8(±0.5)	
Easyhaler	0.7	100	0		**100**	**0**		10.0	
Twisthaler	0.7	100	0		**100**	**0**		10.0	
Using multiple devices	11.5	26.7	73.3	1.0[#]	53.3	46.7	.384[‡]	8.5(±1.1)	.252[†]
Using a single device	88.5	27.8	72.2		67.8	32.2		8.1(±1.6)	
Years of device usage	5.8(±7.3)	6.1(±8.5)	5.7(±6.7)	.768[†]	5.6(±7.2)	6.3(±7.4)	.584[†]	--	.473[§]
Previous inhaler education	84.6	31.2	68.8	.06[#]	**71.6**	**28.4**	**.005[‡]**	**8.3(±1.5)**	**.005[†]**
No previous education	15.4	9.5	90.5		**38.1**	**61.9**		**7.3(±1.7)**	
Years since last review	4.7(±7.3)	5.4(±9.6)	4.4(±6.2)	.529[†]	4.8(±7.7)	4.4(±6.5)	.809[†]	--	.52[§]
Annual/Biannual review	14.6	31.6	68.4	.782[‡]	68.4	31.6	1.0[‡]	8.2(±1.5)	.873[†]
No regular review	85.4	27	73		65.8	34.2		8.1(±1.6)	

Table 4.3.2 - Data from inhalers use as predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd] [%]	Total	At least 1 error*			Critical errors*			Performance Score*	
		No	Yes	p value	No	Yes	p value	Mean	p value
Education Method									
Placebo device training	70.9	**37.2**	**62.8**	.04‡	74.4	25.6	.484‡	**8.6(±1.3)**	.002†
Verbal explanation	29.1	**15.6**	**84.4**		65.6	34.4		**7.6(±1.6)**	
Provider									
Doctor	76.1	**36.1**	**63.9**	.004‡	**80.7**	**19.3**	<.001‡	**8.5(±1.4)**	<.001†
Nurse or Pharmacist	23.9	**12.8**	**87.2**		**46.2**	**53.8**		**7.4(±1.6)**	

*Outcome data presented as values considering only the count of participants within each of the predictor variables. †Independent samples T-test; ‡Chi-squared test; #Fisher exact test; §Pearson correlation test; λKruskal-Wallis test.

Table 4.3.3 – Predictors identified with statistical significance on multivariate analysis according to the major outcome variables.

Outcome – At least one error on inhaler technique (logistic regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**Exp. (coef.)**	**95%CI**	
Placebo device training	-1.305	0.517	**.012**	**0.27**	0.098	0.747
Non-adherence score*	0.654	0.216	**.002**	**1.92**	1.26	2.933
Cognitive score	-0.148	0.051	**.004**	**0.86**	0.78	0.953
(Constant)	4.568	1.299	**<.001**	**96.35**		
AUC: 0.812 (0.734;0.89)						
Cox&Snell Pseudo-R^2: 0.235						
Outcome – Inhaler performance score (linear regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**Exp. (coef.)**	**VIF**	
Gender male	**0.74**	0.317	**.022**	2.1	1.995	
Non-adherence score*	**-0.485**	0.083	**<.001**	0.62	1.239	
Cognitive score	**0.089**	0.022	**<.001**	1.09	1.274	
Placebo device training	**0.787**	0.251	**.002**	2.2	1.065	
Allergies/comorbidities	**0.759**	0.297	**.012**	2.14	1.033	
Never-smoked	**0.663**	0.321	**.042**	1.94	2.051	
Depression	**0.618**	0.281	**.030**	1.86	1.41	
(Constant)	**4.909**	0.704	**<.001**			
R^2: 0.431 (adjusted to 0.392)						
Mean VIF: 1.44						
Outcome – Al least one critical mistake (logistic regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**Exp. (coef.)**	**95%CI**	
Non-adherence score*	0.355	0.145	**.014**	**1.43**	1.073	1.894
Cognitive score	-0.104	0.039	**.007**	**0.9**	0.836	0.972
Previous education by doctor	-1.605	0.436	**<.001**	**0.2**	0.086	0.472
(Constant)	1.963	0.886	**.027**	**7.12**		
AUC: 0.812 (0.736;0.888)						
Cox&Snell Pseudo-R^2: 0.245						

AUC – area under the curve; VIF - Variance inflation factor for collinearity

*Adherence score was used as a continuous variable with a score between 0 (total adherence) and 7 (non-adherence)(36).

Table 4.3.4 – Predictive score for the probability of having "absent errors" in inhaler performance.

Variable	Score	Threshold
Cognitive MOCA score	Use exact score obtained	Results: • >38 points: Inhaler technique probability correct. No need for review. • ≤38 points: Inhaler technique probability with errors. Must be reviewed.
Adherence* (yes)	11 point	
Previous placebo device training	8 points	
MOCA – Montreal Cognitive Assessment questionnaire. *Adherence must be defined as a score of 0 points on the Morisky-Green questionnaire.[32].		

Discussion

To our best knowledge, this is the first study addressing the major predictors of inhaler performance in elderly patients with all types of inhalers. Previous studies have been limited by the inability to perform multivariable predictive modelling or by the narrow selection of specific types of inhalers[22]. Our results show that poor inhaler performance in these patients is highly prevalent and different features should be considered in clinical practice to identify patients needing review. In addition, this is the first attempt to develop a predictive score that may be used as a clinical practice tool for clinicians, and that may ultimately allow the quick and easy identification of patients needing more attention for inhaler review.

Inhaler performance may be considered acceptable in our results when regarded as a score, but we found a high prevalence of errors, some of them critical, which is associated with poor clinical outcomes[8]. In our study, some patients used multiple device types, but that was not associated with worse inhaler performance which is in contrast with previous reports [36 37]. The most used device types in our study were DPI, although other studies in the elderly reported the pMDI with a spacer as being more frequently used[38]. Considering demographic and clinical characteristics, our study is similar to previous reports[19 23], finding a considerable prevalence of cognitive impairment, depression, frailty, allergies and comorbidities with respiratory impact.

The major identified predictors of inhaler performance were adherence rate, cognitive performance and previous inhaler education provided by a doctor using placebo device

training. Adherence seems to play a key role in inhaler performance[39] and previous inhaler education may improve it[40]. Our study is the first to establish this relation in the elderly. However this is still controversial, since many other factors may also influence inhalers use[41]. Our study suggests that placebo device training may be better than verbal explanation alone, and that was also suggested by a previous systematic review[42]. In addition, doctors seem to be better at teaching inhaler performance than other healthcare professionals, particularly regarding critical mistakes. This may be due to their focus on teaching the most important steps of inhaler technique although other factors such as time spent on teaching the technique during clinical appointments, specific characteristics of patient-doctor relationship or more frequent teaching by medical doctors, in Portugal, namely in primary healthcare practices, may also play a part. All doctors in our study were general practitioners and this did not allow us to check whether there were differences between these and pulmonologists or allergists, as described in a study involving younger asthmatics[20]. The cognitive score was also a major predictor of inhaler performance in our study, as previously reported [17 18 21].

Some other aspects should also be taken into consideration when dealing with elderly patients, namely being a woman or having a smoking history, because these factors may also be associated with worse performance, as we found. However, some of these findings are inconsistent with previous reports [22 43], and further studies are needed to clarify these aspects. In fact, regarding gender, a previous study from Gray et al[22] found men to have worse performance, but a more recent study[19] found the opposite, just like ours. Both studies, however, were done in younger patients, and both lacked an appropriate validated multivariate analysis. Regarding smoking history, our study is the first one to report its association with poor performance, and this may be due to confounding or due to the possible surrogate effect of smoking habits towards health self-awareness[44].

Interestingly, patients with allergies or comorbidities, as well as those with depression, showed better performance score in our study. As opposed to a previous report[45], our study is the first one to establish such a positive association, and this must be taken into consideration in future studies. This may be due to a confounding effect or reverse causality, considering that these patients may show a greater concern about disease, greater experience in self-care or increased healthcare attendance

Some previous studies identified other significant predictors, such as regular inhaler education, education level, health related literacy, osteoarthritis, frailty or living alone[7 19 23 43 46 47]. However, in our study this was not confirmed when we adjusted these variables in multivariate analysis. This discrepancy could be due to a true confounding effect from such factors that was not properly controlled in the former reports. We therefore highlight the need for longitudinal cohort studies, which may clarify these causal associations.

The development of a multivariable and comprehensive analysis on such a wide range of predictors allowed the development of a simple predictive score that may be used as a quick tool for clinicians to identify high-risk patients. In fact, such a score highlights the significant influence of cognitive performance on the risk for poor inhaler performance, but it must also be stressed that, having a good adherence and a previous well performed placebo device education may overcome in part, some extent of cognitive impairment. This means that patients with mild cognitive impairment may present good inhaler performance, as long as the other two factors prevail. However, such an inference should not imply that inhaler performance could be neglected in these conditions. There are still critical situations in which this needs to be done, such as in poorly controlled patients, or after an exacerbation or a device switch [7 15]. Nevertheless, this, or similar tools should be tested in real word practice in order to confirm its applicability and reliability, because they may influence the course of future studies regarding inhaler review and, thus, future guidelines on this topic.

Subgroup analysis of our data suggested that some core characteristics could be associated with different inhaler performances and device types. It seems that elderly patients older than 75 years or with cognitive impairment can properly handle pMDI with spacer and SMI, but not DPI. In the remaining cases, we found similar performances with any type of inhaler. These findings are not in agreement with a previous report that highlighted the superiority of DPI[37], although another study involving elderly asthmatics using a specific DPI also showed that patients older than 75 years had worse inhaler performance [23]. Thus, inhaler choice should be adjusted to the elderly patient’s profile particularly age, gender, cognitive status, and inhaler therapy review should consider these main aspects.

Our findings regarding major predictors of inhaler performance present good statistical fitness. However, there are some limitations. Firstly, the cross-sectional design does not allow us to establish true causality pathways, which should be adressed in longitudinal cohort studies. Secondly, although sample size was calculated to test our main hypothesis, the relatively limited sample size hampers performance of more accurate subgroup analysis. In addition, studies performed with elderly patients are heterogeneous, involving diverse population profiles (age, disease severity, comorbidities), different inhalers or inhaler performance evaluation tools. This hampers the ability to compare our results with other studies, since many confounding factors may be involved. However, in contrast with most previous studies, our study also included multivariable modelling, which strengthens our analysis and improves the generalizability of our work.

Overall, there is growing evidence showing that inhaler education in elderly patients may lead to better disease self-management, improved inhaler performance and reduction in global healthcare consumption[48 49]. However, its impact on clinical outcomes, as well as the definition of the best method and frequency of review need to be further clarified.

Conclusion

Inhaler performance in elderly patients is still a major problem and seems to be strongly associated with cognitive status and adherence rate, and such aspects may be used as predictive scores in clinical practice. Previous inhaler education provided by doctors may reduce critical mistakes, and placebo device training seems to be the best method for these patients.

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4.4 Inhaler technique in elderly Asthma or COPD patients – a predictive tool for clinical risk

Abstract

Background: Elderly with Asthma or COPD have poorer symptomatic control and more frequent exacerbations than younger patients. Several factors may be involved, namely incorrect inhaler technique or associated comorbidities, but most studies are inconsistent and contradictory. We aimed to develop a tool to identify the main predictors of clinical risk in these patients.

Methods: Multicentre cross-sectional study including patients with diagnosis of Asthma or COPD using any inhaler type on a regular basis. Demographic, socioeconomic and clinical characteristics were collected as potential predictors, and the outcomes were quality of life, presence of symptoms, lung function (as % of predicted FEV1 values) and exacerbations in the previous year. Linear and logistic regression models were set up to identify significant variables.

Results: We included 130 participants, mean age of 74.4(±6.4) years. The prevalence of inhaler technique errors was 71.6%. 82.3% had respiratory comorbidities and 56.2% had moderate to severe disease. Multivariate analysis showed that the most predictive variables of clinical control were previous doctor-provided teaching of inhaler performance, smoking load, anti-influenza vaccination and depression status. Respiratory comorbidities and educational level were also predictive of symptomatic control, as well as of exacerbations. Lung function was associated with smoking load, as well as with wrong inhaler dose activation and absent end pause after inhalation.

Conclusion: Different factors seem to be associated with clinical control and risk of exacerbations in elderly patients with Asthma and COPD, and some of them, such as inhaler performance, smoking and respiratory comorbidities should be considered when monitoring these patients.

KEYWORDS: Asthma; Chronic Obstructive Pulmonary Disease; Inhalers; Aged

Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) affect more that 300 million people worldwide, and in a high proportion of these patients the disease is uncontrolled, with patients having regular symptoms and being at risk of exacerbations(1). These exacerbations or flare-ups affect up to 50% of patients in community health care settings and can be life-threatening(2, 3).

Elderly patients frequently experience several disease consequences, which may be due to frequent underdiagnosis, associated comorbidities with respiratory impact, and increased risk of drug interactions(4). Inhaler therapy is the most used approach to treating these patients but up to 85% of them do not use inhalers properly, which leads to poor clinical control and an increased risk of exacerbations(5-10).

Elderly patients are more susceptible to poor inhaler performance(11), and some studies have identified potential associated predictors, such as the presence of other comorbidities(4), cognitive impairment(12), lower education level(13), lack of previous teaching of inhaler technique(14), as well as global frailty or hand osteoarthritis(15). Some of these characteristics, such as cognitive impairment, are common causes of unsatisfactory inhaler performance and clinical control, and are also worsened by recurrent disease exacerbations(16). Lung function itself declines with age, which compromises the ability to perform the needed inhalation flow that some inhalers require(17). It is, thus, difficult to establish a true independent predictor of clinical control even when considering and controlling for the influence of inhaler performance.

As far as we know, no previous study has yet addressed the relationship between inhaler performance and clinical control in an integrated, multifactorial approach on elderly patients. This highlights the need to fully ascertain these factors as true independent predictors of inhaler performance and clinical control. On the other hand, elderly patients are frequenly excluded from research studies, although they are gaining more relevance as the populations keeps ageing on most developed countries, and this reinforces the importance of focusing attention on them. Our exploratory study aimed to develop a tool for identifying the major independent predictors of clinical risk in elderly patients with Asthma or COPD.

Methods

Study setting:

A multicentre cross-sectional study was carried-out, including patients diagnosed with Asthma, COPD or Asthma/COPD overlap (ACO), using any kind of inhaler on a regular basis and

aged 65 years old or above. We excluded patients with severe or acute illness, recent abdominal or chest surgery, as well as chronic respiratory dysfunction under oxygen therapy.

Criteria and data collected:

The following variables were collected for analysis of potential predictors: age, gender, body mass index, number of household members, occupational status, disease duration, disease stage/class according to GINA or GOLD classifications(2, 18), educational level, socioeconomic classification by Graffar scale(19), allergies or comorbidities with potential respiratory impact (such as diabetes, heart failure, obesity, chronic and allergic rhinitis, gastroesophageal reflux disease and sleep apnoea), smoking habits, depression (evaluated by geriatric depression scale, with a score above 5 points)(20), frailty (evaluated by a screening test, with a scale score above 2 points)(21), cognitive performance according to Montreal Cognitive Assessment (MoCA) test(22), anti-pneumococcal and anti-influenza vaccination, previous teaching of inhaler performance technique (including method used and provider), adherence rate(23), device type and inhaler performance. Adherence rate was evaluated as a continuous variable with a score between 0 (total adherence) and 7 (non-adherence)(23). We measured inhaler performance as the presence of at least one error (dichotomous), as a performance score in a 0-10 scale (continuous), and also as the presence of errors in any of the following four steps: dose activation (with Dry Powder Inhaler (DPI) and including poor coordination with pressurized Metered Dose Inhaler (pMDI), previous expiration, inhalation technique itself and end pause. Performance score was obtained according to the number of errors made when using each device following the total number of recommended steps.

Clinical risk was defined according to four main outcomes of interest: exacerbations in the previous year (as a dichotomous YES/NO variable; and also as a continuous variable in terms of number of exacerbations); functional control, using Forced Expiratory Volume in 1st second (FEV1) as a % of predicted value (continuous); quality of life scale score, using St. George`s Respiratory Questionnaire(24) and Asthma Quality of life Questionnaire (AQLQ)(25) (as a continuous variable with scores standardised to a 0-10 scale); and symptom assessment, using COPD Assessment Tools (CAT)(26), modified Medical Research Council (mMRC)(27), Control of Allergic Rhinitis and Asthma Test (CARAT)(28) and Asthma Control Test (ACT)(29) (as a dichotomous variable YES/NO). Good symptomatic control was defined as a score above 24 points in CARAT, or as an ACT score above 19 points for Asthma patients whereas a CAT score below 10 points and an mMRC score below 2 points were used for COPD patients.

Six researchers with a medical degree were involved in assessment of inhaler technique and collection of data. These researchers underwent specific training in the process of inhaler technique assessment, in order to standardize procedures.

Statistical analysis and model building:

All data were analyzed with IBM SPSS Statistics© and STATA Statistical Package© software and alfa level was set at 0.05.

We used linear and logistic regression models to test associations between predictors and outcome variables. During model building, we performed bivariate associations at the first stage, in order to identify significant variables to be included at a 0.25 alpha level(30).

Models were set using step-down and step-up approaches, and different models were rechecked with homoscedasticity tests and the necessary validation tools (namely Hosmer Lemeshow test, AIC and BIC values, Area Under the Curve (AUC) values for ROC curves, Sensitivity and Specificity values and Multicollinearity).

Ethics:

This study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was reviewed and analysed by an Institutional Review Board of the University of Beira Interior, in May 2017, and by the local Ethics Committee of the University of Beira Interior, with the reference number CE-UBI-Pj-2017–025 and was approved on 22 November 2017. Every participant signed a written consent form.

Results

A total of 130 participants were included, with a mean age of 74.4(±6.4) years. Baseline data from demographic, socioeconomic and clinical features are reported in Table 4.4.1.

Most participants had low socioeconomic and educational level, and more than half had a moderate or severe disease stage. More than 80% had some type of allergies or comorbidities with respiratory impact. Depression and frailty were present in nearly 30% of the participants and cognitive impairment (MoCA test score <25 points) was present in more than 68%. Non-adherence rate was about 64%. Exacerbation rate in the previous year was almost 50%.

Table 4.4.2 reports data on inhalers used by participants and their features. A high proportion (71.6%) of patients made at least one technical error. The most common errors were present in previous expiration (absent in 50.7% of the cases) and in the end pause (absent in 47.3% of the cases). Almost all patients had received some type of previous inhaler education, but not on a regular basis. The most used method was placebo device training, mainly provided by a doctor at the time of initial prescription. Inhaler education provided by doctors seemed to have more positive impact than that provided by a nurse or pharmacist in all outcome measures (alpha levels reported in Table 4.4.2). In addition, functional control was

significantly associated with performance itself and with some specific type of errors, namely wrong dose activation and absent end pause.

Table 4.4.3 reports the best-fitted multivariate models with the major identified predictors.

Logistic regression for having "Good symptomatic control" identified as major significant predictors: at least elementary school education (OR: 3.768), allergies (OR: 0.291) and being depressed (OR: 0.110). This model presented an AUC of 0.759 (0.676; 0.842), with a sensitivity of 93.5% and a specificity of 21.6%, a positive predicted value of 57.1% and a negative predicted value of 75%. Excluded variables from the model (due to non-significance) were age, gender, body mass index, socioeconomic level, living alone, type of diagnosis, years of diagnosis, smoking status, frailty status, anti-influenza and anti-pneumococcal vaccination, cognitive performance, adherence rate, device type, previous placebo device training and previous inhaler review provided by a doctor. The model was confirmed regarding statistical control for inhaler performance covariates (presence of at least one error and performance score), and all predictors maintained the statistical significance for coefficients (and OR).

Logistic regression for having "Exacerbation history" identified as major significant predictors: educational level (OR: 0.661 for higher levels), moderate or severe disease stage (OR: 3.361) and the presence of allergies or comorbidities (OR: 4.188). This model presented an AUC of 0.712 (0.623; 0.802), with a sensitivity of 65.9% and a specificity of 74.2%, a positive predicted value of 64.4% and a negative predicted value of 75.4%. Excluded variables from the model (due to non-significance) were gender, body mass index, number of household members, type of diagnosis, smoking status and smoking load, being depressed, frailty status, cognitive performance, adherence rate, device type, using multiple devices and having a previous inhaler education provided by a doctor. The model was confirmed regarding statistical control for inhaler performance covariates (presence of at least one error and performance score), and all predictors maintained the statistical significance for coefficients (and OR).

Linear regression for "quality of life score" identified as major predictors: current number of cigarettes per day (decrease in 0.113 points for each unit), previous inhaler education provided by doctor (increase of 1.352 points), and having anti-influenza vaccination (increase of 0.1003 points). The regression line of the model is available on supplementary material – Figure 4.4.1. A Poisson regression was performed with the same predictors, to confirm the best-fitness of the linear regression (adapted from previous reports on a statistical approach to counting variables(31)). Excluded variables from this model (due to non-significance) were: living alone, type of diagnosis, allergies, frailty status, being depressed, anti-influenza vaccination, cognitive performance, adherence rate, using multiple devices and having regular inhaler review.

Linear regression for “FEV1% of predicted values” identified as major predictors: smoking pack-years (decrease in 0.233 points for each unit increase), non-adherence score (increase of 5.807 points for each unit increase in the questionnaire score), regular inhaler review (decrease of 18.613 points), wrong dose activation (decrease of 23.842 points) and absent end pause (decrease of 18.353 points). The regression line of the model is available on supplementary material – Figure 4.4.2. A Poisson regression was performed with the same predictors, to confirm the best-fitness of the linear regression (adapted from previous reports on a statistical approach to counting variables(31)). Excluded variables from this model (due to non-significance) were: gender, body mass index, educational and socioeconomic level, number of household members, type of diagnosis, allergies or comorbidities, previous inhaler education provided by a doctor and number of years since last review. The model was confirmed regarding statistical control for disease stage as a covariate, and all predictors maintained the statistical significance for coefficients (and OR).

Table 4.4.1 - Data from demographic and clinical predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd or %]	Total	Good Symptomatic Control*			Exacerbation History*			Quality of Life Score*		FEV1%*	
		No	Yes	p value	No	Yes	p value	Mean	p value	Mean	p value
Nº of total participants	130	71.5	28.5	--	58.5	41.5	--	6.7(±2.1)	--	80.1(±26.8)	--
Age	74.4(±6.4)	74.8(±6.6)	73.2(±5.6)	.211†	74.7(±6.6)	73.8(±6.1)	.434†	--	.161§	--	.963§
Man	41.5	**59.3**	**40.7**	.009‡	66.7	33.3	.110‡	6.6(±2.3)	.698†	**72.9(±27.7)**	.016†
Women	58.5	**80.3**	**19.7**		52.6			6.8(±1.9)		**84.9(±25.4)**	
BMI	27.7(±5.3)	28.0(±5.6)	26.7(±4.6)	.197†	26.9(±5.2)	28.7(±5.4)	.056†	--	.531§	--	.168§
Living alone	23.1	88.3	11.7	.103‡	66.7	33.3	.298‡	6.3(±2.1)	.163†	78.8(±25.8)	.768†
Not living alone	76.9	68	32		56	44		6.9(±2.1)		80.5(±27.3)	
Retired	90.8	71.2	20.8	1.0#	58.5	41.5	1.0#	6.7(±2.1)	.523†	80.1(±27.6)	.981†
Working	9.2	75	25		58.3	41.7		7.1(±1.7)		80.3(±14.8)	
Educ.>elementary school	27.7	**55.6**	**44.4**	.012‡	66.7	33.3	.240‡	6.9(±2.3)	.514†	80.3(±29.5)	.965†
Educ. none or element.	72.3	**77.7**	**22.3**		55.3	44.7		6.6(±2.0)		80.1(±26)	
Graffar middle/high class	40.0	65.4	34.6	.204‡	55.8	44.2	.611‡	6.7(±2.2)	<.773†	80.5(±26.2)	.894†
Graffar low class	60.0	75.6	24.4		60.3	39.7		6.8(±2.0)		79.9(±27.4)	
Asthma	49.2	78.1	21.9		51.6	48.4		7.1(±1.9)		**90.7(±24.7)**	
COPD	26.2	63.8	36.2	.243‡	68.1	31.9	.218‡	6.2(±2.2)	.07‡	**70.1(±25.9)**	<.001‡
ACO	14.6	68.4	31.6		57.9	42.1		6.7(±2.1)		**70(±23.6)**	
Disease duration (years)	20.6(±20.5)	22.5(±21.4)	15.9(±17.3)	.098†	18.9(±19.8)	23(±21.3)	.266†	--	.684§	--	.883§
Disease mod/severe stage**	56.2	74	26	.486‡	**46.6**	**53.4**	.002‡	6.9(±2.0)	.266†	80.5(±29.3)	.867†
Disease mild stage	44.8	68.4	31.6		**73.7**	**26.3**		6.5(±2.2)		79.7(±23.4)	

Table 4.4.1 - Data from demographic and clinical predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted) (continued).

Predictor variable [mean±sd or %]	Total	Good Symptomatic Control*			Exacerbation History*			Quality of Life Score*		FEV1%*	
		No	Yes	p value	No	Yes	p value	Mean	p value	Mean	p value
With allergies/comorb.	82.3	72	28	.817‡	**53.3**	**46.7**	.01#	6.8(±2.1)	.426†	**82.7(±26.1)**	.018†
No allergies/comorb.	17.7	69.6	30.4		**82.6**	**17.4**		6.4(±2.1)		**67.3(±27.3)**	
Never smoked	60	**79.5**	**20.5**	.014‡	52.6	47.4	.095‡	6.7(±1.9)	.949†	**86.4(±24.9)**	.002†
Smoker/Past-smoker	40	**59.6**	**40.4**		67.3	32.7		6.7(±2.3)		**71.2(±27.3)**	
SPY	17(±27.7)	**13.1(±22.6)**	**27.0(±35.9)**	.034†	19.4(±29.4)	13.8(±25)	.257†	--	.229§	--	.004§
N° cigarettes/day (smokers)	14(±3)	13.4(±8.0)	15.8(±17.3)	.741†	15.7(±11.3)	9.0(±9.5)	.373†	--	.001§	--	.073§
With depression	32.3	**92.9**	**7.1**	<.001#	**42.9**	**57.1**	.013‡	**6.1(±1.6)**	.007†	82.9(±28.9)	.439†
No depression	67.7	**61.4**	**38.6**		**65.9**	**34.1**		**7.0(±2.2)**		78.8(±25.9)	
With frailty	33.1	**86**	**14**	.01‡	51.1	48.9	.235‡	**6.1(±1.9)**	.009†	83.8(±29.5)	.313†
No frailty	66.9	**64.4**	**35.6**		62.1	37.9		**7.1(±2.1)**		78.4(±)25.5	
Cognitive score	21.9(±5.7)	21.4(±5.8)	23.2(±5.2)	.097†	22.5(±5.2)	21.1(±6.2)	.158†	--	.04¥	--	.7091§
Anti-pneumococcal vac.	26.9	64.6	35.4	.179‡	75	25	.447‡	6.8(±2.0)	.903†	82.6(±27.8)	.452†
No anti-pneumococ. vac.	73.1	75.6	24.4		61	39		6.7(±2.1)		78.8(±26.4)	
Anti-influenza vac.	78.5	67.6	32.4	.096#	61.8	38.2	.145‡	6.8(±2.0)	.179†	80.5(±26.5)	.762†
No anti-influenza vac.	21.5	85.7	14.3		46.4	53.6		6.3(±2.2)		78.7(±28.4)	
Adherent	36.2	63.8	36.2	.143‡	68.1	31.9	.094‡	**7.2(±2.0)**	.04†	80.3(±25.4)	.958†
Non-adherent	63.8	75.9	24.1		53	47		**6.4(±2.1)**		80(±27.9)	

ACO - Asthma/Chronic Obstructive Pulmonary Disease overlap; BMI - Body mass index; COPD - Chronic Obstructive Pulmonary Disease; SPY - Smoking pack years.

*Outcome data presented as values considering only the count of participants within each of the predictor variables. **Disease moderate to severe stage considered as Asthma on steps 3 and 4, as well as COPD on grade C or D. †Independent samples T-test; ‡Chi-squared test; #Fisher exact test; §Pearson correlation test; ¥Spearman correlation test; ǂ ANOVA test

Table 4.4.2 - Data from inhalers use as predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted).

Predictor variable [mean±sd] [%]	Total	Good Symptomatic Control*			Exacerbation History*			Quality of Life Score*		FEV1%*	
		No	Yes	p value	No	Yes	p value	mean	p value	mean	p value
N° of inhalers in all participants	148	71.5	28.5	--	58.5	41.5	--	6.7(±2.1)	--	80.1(±26.8)	--
Inhalers used											
Handihaler/Breezhaler	26.4	**73.3**	**26.7**		80	20		6.6(±2.1)		73.4(±18.7)	
Diskus/Accuhaler	15.5	**85**	**15**		50	50		6.4(±2.1)		89.8(±36.6)	
Turbohaler	12.8	**55.6**	**44.4**		55.6	44.4		7.1(±1.9)		82.6(±21)	
pMDI	11.5	**88.2**	**11.8**		58.8	41.2		6.7(±1.9)		87.6(±24.2)	
Spiromax	7.4	**45.5**	**54.5**		45.5	54.5		8.0(±1.6)		78.2(±16.4)	
Respimat	6.8	**55.6**	**44.4**	.028#	44.4	55.6	.069#	6.4(±2.3)	.315λ	75.1(±42.8)	.343λ
Novolizer/Genuair	6.1	**77.8**	**22.2**		55.6	44.4		6.3(±2.3)		73.1(±20.9)	
Ellipta	6.1	**42.9**	**57.1**		85.7	14.3		7.4(±2.6)		81.4(±26.8)	
pMDI+Spacer	6.1	100	0		25	75		5.7(±2.0)		71.3(±35.4)	
Easyhaler	0.7	100	0		0	100		6.2		103	
Twisthaler	0.7	100	0		0	100		5.3		92	
Using multiple devices	11.5	67.7	32.3	.762#	**33.3**	**66.7**	.036‡	5.9(±2.0)	.124†	73.9(±36.9)	.380†
Using a single device	88.5	72.2	27.8		**61.7**	**38.3**		6.8(±2.1)		80.9(±25.5)	
Years of device usage	5.8(±7.3)	6.2(±7.7)	4.8(±5.7)	.323†	5.4(±7.1)	6.4(±7.5)	.471†	--	.593§	--	.593§
Previous inhaler education	84.6	70	30	.431#	58.2	41.8	.879‡	6.7(±2.2)	.520†	80.9(±28.4)	.289†
No previous inhaler education	15.4	80	20		60	40		7.0(±1.5)		75.9(±15.3)	
Years since last review	4.7(±7.3)	5.0(±7.6)	3.9(±6.6)	.463†	4.9(±7.8)	4.3(±6.7)	.683†	--	.552§	--	.326§
Annual/Biannual review	14.6	73.7	26.3	.823‡	52.6	47.4	.577‡	6.1(±2.2)	.141†	**67.2(±21.4)**	.031†
No regular review	85.4	71.2	28.8		59.5	40.5		6.8(±2.0)		**82.3(±27.1)**	

Table 4.4.2 - Data from inhalers use as predictor variables collected from all participants and comparisons according to the major outcome variables (significant results highlighted) (continued).

Predictor variable [mean±sd] [%]	Total	Good Symptomatic Control*			Exacerbation History*			Quality of Life Score*		FEV1%*	
		No	Yes	p value	No	Yes	p value	mean	p value	mean	p value
Education Method											
Placebo device training	70.9	66.7	33.3	.234‡	61.5	38.5	.265‡	6.8(±2.1)	.325†	80.9(±29.6)	.724†
Verbal explanation	29.1	78.1	21.9		50	50		6.4(±2.2)		79.1(±22.3)	
Provider											
Doctor	76.1	65.1	34.9	.172‡	62.7	37.3	.198‡	**7.0(±2.1)**	**.035†**	82.6(±28.2)	.179†
Nurse or Pharmacist	23.9	78.7	21.3		51.1	48.9		**6.2(±1.9)**		75.7(±24)	
At least one error	71.6	71.3	28.7	.915‡	56.4	43.6	.437‡	6.8(±2.0)	.676†	77.5(±26.4)	.106†
No errors committed	28.4	72.2	27.8		63.9	36.1		6.6(±2.3)		86.2(±27.1)	
Performance score (0-10 scale)	8.1(±1.6)	8.1(±1.6)	8.2(±1.5)	.750†	8.2(±1.6)	8.1(±1.6)	.696†	--	.986§	--	**.040§**
Incorrect dose activation	19.6	66.7	33.3	.529‡	63	37	.594‡	6.3(±2.3)	.247†	**66.1(±23.5)**	**.006†**
Correct dose activation	80.4	72.8	27.2		57.3	42.7		6.8(±2.0)		**83.3(±26.6)**	
Wrong previous expiration	50.7	75.8	24.2	.279‡	57.6	42.4	.835‡	6.8(±2.0)	.667†	78.6(±25.3)	.516†
Correct previous expiration	49.3	67.2	32.8		59.4	40.6		6.6(±2.2)		81.8(±28.5)	
Wrong inhalation	23.0	75	25	.617‡	59.4	40.6	.904‡	6.3(±1.9)	.240†	75.1(±24.5)	.260†
Correct inhalation	77.0	70.4	29.6		58.2	41.8		6.8(±2.1)		81.7(±27.5)	
Absent end pause	47.3	71.9	28.1	.933‡	56.3	43.7	.614‡	6.8(±1.9)	.512†	**74.8(±23.7)**	**.036†**
Present end pause	52.7	71.2	28.8		60.6	39.4		6.6(±2.4)		**85.2(±28.8)**	

pMDI - pressurized Metered Dose Inhaler

*Outcome data presented as values considering only the count of participants within each of the predictor variables. †Independent samples T-test; ‡Chi-squared test; #Fisher exact test; §Pearson correlation test; λKruskal-Wallis test.

Table 4.4.3 – Predictors identified with statistical significance on multivariate analysis according to the major outcome variables.

Outcome – Good Symptomatic Control (logistic regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**Exp. (coef.)**	**95%CI**	
Education above elementary school	1.326	0.493	**.007**	**3.768**	1.433	9.909
Allergies with respiratory impact	-1.235	0.561	**.028**	**0.291**	0.097	0.873
Being depressed	-2.206	0.665	**.001**	**0.110**	0.030	0.406
(Constant)	-0.565	0.283	**.046**	**0.569**		
AUC: 0.759 (0.676;0.842)						
Cox&Snell Pseudo-R^2: 0.185						
Outcome – Exacerbation History (logistic regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**Exp. (coef.)**	**95%CI**	
Educational level	-0.414	0.188	**.028**	**0.661**	0.457	0.956
Disease moderate or severe stage **	1.212	0.454	**.008**	**3.361**	1.381	8.182
Allergies/comorbidities with respiratory impact	1.432	0.706	**.042**	**4.188**	1.050	16.704
(Constant)	-1.305	0.783	**.095**	**0.271**		
AUC: 0.712 (0.623;0.802)						
Cox&Snell Pseudo-R^2: 0.174						
Outcome – Quality of Life Score (linear regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**VIF**		
Current nº of cigarettes/day	**-0.113**	0.031	**<.001**	1.02		
Previous teaching provided by doctor	**1.352**	0.441	**.003**	1.01		
Anti-influenza vaccination	**1.003**	0.464	**.033**	1.02		
(Constant)	**5.067**	0.533	**<.001**			
R^2: 0.198 (adjusted to 0.174)						
Mean VIF: 1.02						
Outcome – FEV1% of predicted values (linear regression)						
Predictor variables in the model	**Coef.**	**SD**	**p-value**	**VIF**		
Smoking Pack-years	**-0.233**	0.084	**.006**	1.025		
Non-adherence score*	**5.807**	1.694	**.001**	1.204		
Annual or biannual inhaler review	**-18.613**	6.604	**.006**	1.101		
Wrong dose activation	**-23.842**	6.942	**.001**	1.160		
Absent end pause	**-18.353**	5.068	**<.001**	1.119		
(Constant)	**93.992**	4.262	**<.001**			
R^2: 0.342 (adjusted to 0.306)						
Mean VIF: 1.09						

AUC – area under the curve; VIF - Variance inflation factor for collinearity

*Adherence score was used as a continuous variable with a score between 0 (total adherence) and 7 (non-adherence)(32). **Disease moderate to severe stage considered as Asthma on steps 3 and 4, as well as COPD on grade C or D.

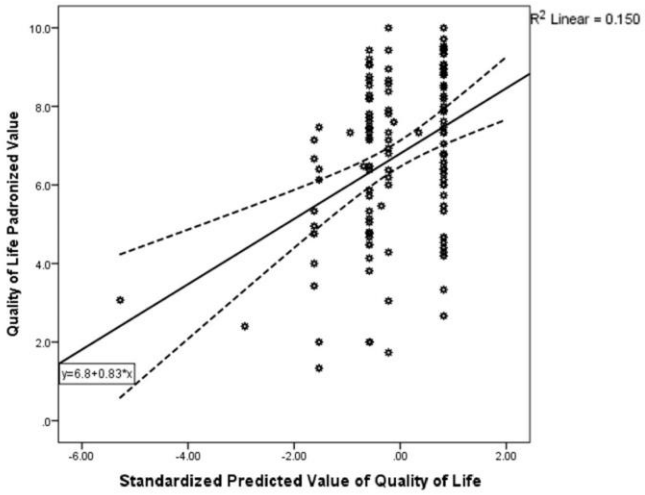

Figure 4.4.1-Regression line of the multivariate analysis to quality of life score.

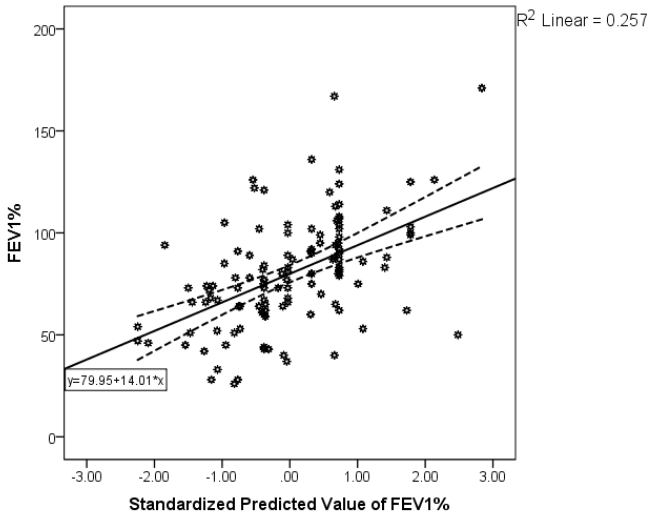

Figure 4.4.2-Regression line of the multivariate analysis to FEV1% of predicted values.

Discussion

This is the first study to integrate major predictors of clinical risk in elderly patients with Asthma or COPD, while controlling for several issues of inhaler performance. Our results show that clinical risk is particularly complex in these patients, depending not only on inhaler performance, but also on other independent predictors that should be considered in order to identify patients requiring more focused clinical attention.

The main findings on demographic and clinical features are in line with other reports, namely in terms of educational and socioeconomic levels as well as the prevalence of allergies and comorbidities with respiratory impact(13, 15). We also highlight the high rate of annual exacerbations, the high prevalence of patients with a moderate or severe disease stage and the low adherence rate. We found a high prevalence of errors and poor inhaler performance with some devices, which is associated with poor clinical outcomes(32). Although most patients had received previous inhaler education, in most cases this was performed only once by the doctor at the time of initial prescription, which highlights the need to improve regular follow-up and further educational interventions.

The major predictors of global clinical risk that we have found are educational level, disease stage, smoking load, depression, concomitant allergies or comorbidities, anti-influenza vaccination and inhaler performance. Most of these predictors had already been identified in previous reports(2, 4, 18).

Previous teaching on inhaler performance provided by a doctor seems to improve quality of life better than that provided by nurses or pharmacists. This could be due to an improved global health care provided by doctors, involving time spent on teaching the technique during clinical appointments, specific characteristics of patient-doctor relationship or more frequent teaching by medical doctors. In addition, doctors probably focus on more embracing issues, seizing the opportunity to deliver other self-management tools with such impact. Besides that, patients may more easily follow recommendations from their physician with whom they have established a good relationship, which improves adherence to treatment. On the other hand, inhaler review provided in a private environment, which usually happens in the medical office, can also promote better outcomes. Few studies have addressed these differences among health care professionals, but it should be further analysed because the evidence is still divergent(33-35).

Anti-influenza vaccination also seems to be associated with better quality of life. It reduces the symptomatic burden from influenza epidemics, but this may also be a proxy for patients with a higher level of literacy and self-care initiatives. Indeed, previous studies have highlighted the importance of literacy and motivation on clinical outcomes(36). We found a strong association between smoking load and quality of life, as well as between smoking load and pulmonary function (in FEV1% values) and that has also been demonstrated(2, 18).

Inhaler performance may also affect FEV1% values, as detected in our study, mainly regarding correct dose activation and the presence of end pause, and these may present as critical steps. There are several inhalers available on the market(37, 38) and all have different specifications that should be considered in order for patients to receive the adequate inhaled dose. In this context, DPI need proper inhalation flows and pMDI need good coordination on dose activation to get the drug deep in the airways, and the end pause may be critical to

allow its sedimentation(17). Previous reports have highlighted the superiority of DPI in inhaler performance(39), but in our study they do not seem to be better than other device types regarding clinical outcomes. Some of these previous reports may have underestimated the impact of DPI on clinical features, because they were not designed to properly control for other predictor variables as potential biases, as we did. The report by Price et al. highlighted the importance of critical errors, pointing out some of these issues, namely wrong dose activation(32). Our study is the first to specifically address and identify this problem in elderly patients, and highlights the need for further investigation of critical errors.

In our study, we also found that patients with good inhaler adherence and with previous regular inhaler review had poor FEV1% values, and these findings were sustained even when controlling for disease stage and symptom control. This may be explained by a reverse causality phenomenon, at least in part, considering the fact that patients with poorer lung function may receive health care follow-ups more regularly, and thus, more interventions on inhaler performance and adherence. In fact, some studies suggest a close association between previous education on inhaler performance and adherence rate(40), but the true causal pathway and its impact on clinical control should be addressed in detail in future longitudinal studies.

Finally, we found a strong association between lower educational level and exacerbation risk, as well as between lower educational level and symptom control. Few studies have specifically addressed this direct relationship(41). Educational level and literacy are also main predictors of good inhaler performance(13, 42), and this could be an important causal pathway to consider.

Our study has some limitations. Although our findings present good statistical fitness, it is difficult to establish clear causality pathways due to the cross-sectional design and the limited sample size, which hampers the ability to perform more detailed subgroup analysis and control for such important covariates. In addition, studies carried out in older patients are heterogeneous, in terms of age, disease severity, or comorbidities, and involve different inhalers or inhaler technique evaluation tools. This makes comparison of our results with those from other studies difficult, since various confounding factors may interfere. However, in contrast with most previous studies, our study also included multivariable modelling, which strengthens our analysis and improves the generalizability of our work. Considering our broad inclusion criteria of elderly patients, as well as the significant amount of potential predictors that were here analysed, we believe our study brings a new and clear insight upon this remarkable topic, and thus, standing out for its generalizability. In addition, due to the ageing population on most countries worldwide, and the burden of health economics, it is of paramount importance to identify priority targets for deliver more accurate and efficient interventions.

It is well known that proper inhaler performance in elderly patients can reduce clinical risk and global healthcare consumption(43, 44). However, its independent influence on some clinical outcomes seems to be attenuated by other major factors, such as concomitant allergies or comorbidities, smoking load, depression and educational level. These characteristics should be addresses with more attention on clinical practice, in order to optimize intervention's efficiency. More studies are needed in order to establish clear causal pathways, mainly with large cohort designs, following the disease window from early stages until the end of life.

Conclusion

Inhaler performance in elderly patients with Asthma or COPD is a major predictor of clinical risk, and some errors appear to be critical. However, different factors also seem to be associated with clinical control and exacerbations, such as educational level, smoking load and respiratory allergies or comorbidities, and should be properly considered when monitoring these patients.

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4.5 Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial

Abstract

Introduction: COPD and Asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and Analysis: A multicentre single-blinded RCT will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care, with a one-year follow-up, in patients above 65 years of age with Asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions Chi-squared test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination: Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on the 22th November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meeting and published in peer-reviewed journals.

KEYWORDS: Chronic Obstructive Pulmonary Disease; Asthma; Nebulizers and Vaporizers

Introduction

Epidemiology:

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms (1). In Asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled (2, 3), and the elderly population is particularly vulnerable to this condition (3). In fact, late onset Asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring (4). Hospitalisation rates due to Asthma and COPD are reported to reach 27% among non-adherent patients, and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases (5-7).

Inhaler technique:

Inhaled therapy is the most widely used way to treat patients with Asthma and COPD(8), but up to 90% of them do not use their inhalers correctly (9, 10). Performance errors have been described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand the specificities of different inhaler use as well as the impact of different inhaler teaching methods (11) Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance (12). However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy (13, 14), but it is well established that poor inhaler technique leads to poor clinical control (15, 16) and also to increased health costs (17). In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical (18, 19)

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes (20). Some studies show that teaching inhaler technique may lower the risk of exacerbations and death (6, 21, 22). However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients (23, 24). Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients (25, 26). These patients also present lower adherence rates (9) and are more resistant to correct performance (27, 28). Furthermore, other major characteristics

may influence inhaler use, such as educational level, previous teaching, or even age itself (i.e. age above 75 years) (29) However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. None has yet addressed inhaler review alone or in a regular education programme (21, 30-33). Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact on major outcomes (34-37). Nevertheless, some studies including adult patients as well, suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person (38-42). In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the necessary steps of inhaler use (43). This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.

This study will focus on elderly patients and aims at testing the effect of a structured and regular placebo device training approach on disease exacerbation rates.

Specific Aims and Hypotheses

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with Asthma or COPD.

The main hypothesis is that, among elderly patients with Asthma or COPD, regular education of inhaler technique using a teach-to-goal placebo device-based approach, and delivered by family doctors at baseline, 3 and 6 months, can reduce the exacerbation risk by 50% after a one-year follow-up, when compared to usual care.

Research Design and Methodology

Study Design:

Two arms single blinded randomised controlled trial with a 1 year follow up (figure 4.5.1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The

allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order, and will contain the result of the allocation. The order of the envelopes' number will define the order of participants` enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

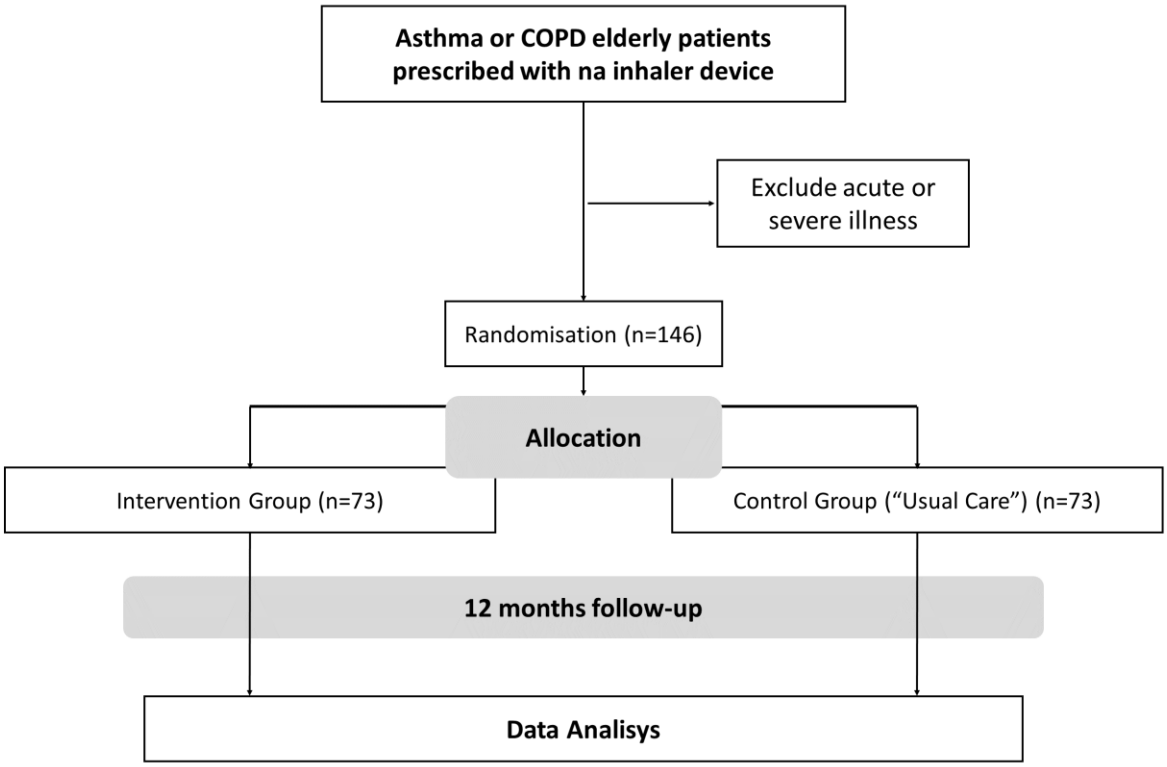

Figure 4.5.1 – Study design diagram.

Sample size calculation:

Sample size was estimated using the Chi square independent group proportions approach of STATA Statistical Package©, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies (21, 22, 44) and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% confidence interval, with β value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

Inclusion Criteria:

Patients with a diagnosis of COPD or Asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler (DPI) or Soft Mist), aged ≥65 years and being a regular user of primary healthcare services (defined as having had at least one appointment in the last two years with his/her own Family Doctor). In order to minimise diagnostic inaccuracy, Asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies (45, 46).

Exclusion Criteria:

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within one month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within one month), recent thoracic, abdominal or eye surgery (within one month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent Asthma, as well as patients with COPD with mild obstruction (GOLD stage I), and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention:

Intervention Group – This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used with correction of identified errors. Then we will ask patients to demonstrate the inhaler technique, and again, errors will be corrected by demonstration. We will repeat all correct steps as many times as needed in order for patients to perform them correctly. This intervention will be performed at baseline, 3 and 6 months. Outcomes will be assessed at baseline and after 3, 6 and 12 months, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions (21, 30, 32). In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group – This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according

to his/her real life judgement. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded, since it will be important to analyse and control for the true effect size of intervention.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest:

Primary Outcome: Adverse events (continuous, time to event).

For Asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care, and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4x the regular dose
- Need for increase of short-acting ß2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or Emergency Room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting ß2 agonists on a daily basis
- Need for oral corticosteroids
- Need for oral antibiotics
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event. All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Healthcare facilities (such as PEM© for prescribed drugs, SCLINICO© for clinical records and PDS© for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the

primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary Outcomes:

- Clinical assessment using COPD Assessment Tools (CAT) and modified Medical Research Council (mMRC) for COPD; Control of Allergic Rhinitis and Asthma Test (CARAT) (47) and Asthma Control Test (ACT) for Asthma (48).
- Quality of Life using St. George's Respiratory Questionnaire (49) and Clinical COPD Questionnaire (CCQ) (50) for COPD and Asthma Quality of Life Questionnaire (AQLQ) (51).
- Functional control using Forced Expiratory Volume in 1st second (FEV1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Maximum Expiratory Flows of 25-75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices) (52).
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale)

To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used (53), evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from Farmoz®, Ellipta, Spiromax and Forspiro).

All questionnaires will be used in validated Portuguese versions (47-52, 54, 55). All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline:

- Demographics (Body Mass Index, Age, Sex)
- Classification of clinical status, according to:
  - ✓ Exacerbation history.
  - ✓ Years of diagnosis.
  - ✓ Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5)(45)

  - ✓ COPD stage according to 2017 GOLD guidelines (combined assessment stages A,B,C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4)(46).
- Social class according to Graffar classification (Portuguese version)(56).
- Co-morbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese(57).
- Frailty state in elderly, using a self-reported instrument in Portuguese (58).
- Cognitive function using Montreal Cognitive Assessment (MoCA) in Portuguese (59)
- Influenza and pneumococcal vaccination status
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia, etc.).
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical Analysis:

The hypothesis testing approach will be the following:

Null hypothesis: Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Alternative hypothesis: Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with Asthma or COPD after a one-year follow-up.

Dichotomous Predictor: Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous Outcome: Exacerbation Yes/No

Data will be analysed using the STATA Statistical Package© software.

Test statistic for primary outcome: Dichotomous data will be analysed with a two-sample proportions Chi-square test and a COX proportional hazard time-to-event analysis, and both arms will be compared using the measures of association: risk ratio; risk difference; hazard ratio and Number Needed to Treat (NNT) analyses.

Test statistic for secondary outcomes: Continuous data will be analysed using parametric tests, such as T test for comparison of mean values and dichotomous data will be analysed using Chi-square test. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature (60). As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Missing data will be treated as missing completely at random. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65-75, 75-85, and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device type, as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.

An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025 (61).

Study Setting:

The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10,000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of Asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each healthcare facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.

All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines, and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline:

- Study protocol final version: August 2017
- Ethics consent and scientific academic authorisation: December 2017
- Clinical administrative authorisations: first semester of 2018
- Multicentre team gathering: first semester of 2018
- Beginning of recruitment: second semester of 2018
- End of recruitment: second semester of 2019
- Data analysis and dissemination: during 2020

Patient and Public Involvement:

No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

Discussion

This study is innovative because it includes exclusively elderly patients with Asthma or COPD, addressing a specific placebo device education programme, alone, without any other aspects, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.

This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses; and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie. behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of one year this effect will not be sustained. On the other hand, the control group (“usual care”) will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group (“usual care”) participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group, and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of

two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting). Using usual care as the comparator arm also brings some limitations to consider, because it is not a perfect comparator due to its nature. It is not sufficient for good patient outcomes and it is not standardised. This aspect is due, for instance, to the fact that patients on usual care can receive interventions on inhaler education and self-management tools from other uncontrolled sources. To overcome that we will retrospectively query patients in this arm and their own family doctor for any type of interventions that may have been delivered during the study period.

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available – INCA device(62). Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide, and also in Portuguese (52). Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating sub-domains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of patients with Asthma and COPD. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardisation of all procedures of intervention and it will be provided ahead by the coordination team of the study.

Ethics and Dissemination

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025, and was approved on 22th, November 2017.

Every participant will sign a written consent form (Sub-Appendix I). We decided to use "usual care" as the main comparator instead of another intervention method, since all interventional methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. We thus believe that comparing with other education methods would minimise the effect detection of our teach-to-goal placebo-device intervention. Moreover, all of the randomised studies that included mostly elderly patients also used "usual care" as a comparator, which will be important when comparing them with our results. However, we highlight the fact that those studies did not use the same age criteria as we are using, since they also included non-elderly adult patients in their samples. In addition, they did not just focus on inhaler teaching, since they provided additional sessions with other programme elements, such as self-management care. There is, thus, insufficient evidence about the efficacy of inhaler education as an isolated intervention, and for that reason, our approach will be novel and will significantly contribute towards clarifying those issues.

A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up, or if significant evidence of intervention effectiveness is obtained, providing that statistical significance values are met by the Bonferroni adaptation.

Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Healthcare Service Number (eg. Name FirstSurname SecondSurname, 123456789 -------> code "NF89").

The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.

Results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary healthcare and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

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CHAPTER FIVE

General Discussion

General Discussion

This thesis addresses inhaler technique performance in elderly patients with Asthma and COPD, because such patients are in most risk of clinical adverse outcomes. Inhaler technique performance has been under study for many years, and it is still regarded as an important hallmark for clinical control and exacerbation risk. This work was designed to address it in different perspectives, allowing the establishment of five specific aims, whose results disclose a comprehensive approach to the issue. Regarding the first two aims, a systematic review with metanalysis and a subsequent cost-effectiveness analysis, summarised the reported data published so far regarding the effectiveness of inhaler technique educational programmes on major clinical outcomes in such patients. In addition, a cross-sectional study was undertaken, addressing another two specific objectives, in order to determine major predictors of inhaler technique performance and clinical risk in elderly patients. This study was performed because it is of most importance to identify patients at increased risk that can benefit from such interventions. Lastly, a protocol for a clinical trial was designed to access and quantify the true effect of inhaler technique education in major clinical outcomes, because most previously reported interventions did not clearly achieve that.

Looking at the results reported in our systematic review, it became clear that inhaler technique education programmes can significantly reduce the risk of exacerbations in elderly patients. Previous systematic reviews in children and adults reached inconclusive results, showing no significant effect on major clinical outcomes (1), and this may be due to the higher vulnerability of elderly patients, who have an increased risk for exacerbations and poor outcomes. However, results from our systematic review were slightly inconsistent concerning improvements in quality of life and symptom control, and that may be due to the considerable heterogeneity of reported interventions. In fact, almost all studies addressed other aspects besides inhaler technique performance itself, such as self-management education, adherence, smoking cessation, influenza vaccination, trigger avoidance and exacerbations management. Such dimensions seem to be quite relevant. They may be key aspects for disease control in elderly patients, but possibly less in children or younger adults, and the evidence is still contradictory in some of them. Some studies pointed out the importance of disease self-knowledge in most outcomes (2), but other reports show that it is not enough to prevent exacerbations (3). Moreover, our systematic review also raised some important questions. It is still unclear which is the true effect of inhaler education as a single intervention, as well as the best method to teach inhaler performance and how often should it be performed. Most guidelines have not yet reached a consensus about this, and further studies are needed in order to establish optimal recommendations. Results from our

systematic review also suggest that the elderly may be different than children and adults in terms of interventions' effectiveness, and this may also be due to increased rates of comorbidities in elderly individuals, which may be relevant to clinical risk. However, those may also be potential confounders (2), and further studies should try to identify optimal target populations to different types of interventions.

This was the first study to report such findings in older adults with Asthma and COPD, and this is particularly relevant because projections for the ageing population worldwide reveal the important burden they will present to health services. Our cost-effectiveness analysis shows that such interventions may generate significant savings from the healthcare providers' perspective, and this may increase to hundreds of million euros in Portugal. Although the true costs of intervention programmes may vary among different countries, we were able to establish thresholds for affordable interventions, which may be adopted worldwide. These results are very timely and relevant, because the cost-effectiveness of inhaler educational programmes was not yet fully explored (4). However, the study has some limitations, such as the inability to perform a cost-utility based analysis. This would be of most importance to reinforce the clinical relevance of the findings (5) as some recent reports suggested (6). We may also have underestimated some indirect costs that were not be easy to estimate, such as those related to exacerbations, because they may be influenced by comorbidities and drug interactions that elderly patients frequently have.

The scientific evidence is now showing that inhaler technique review in elderly patients is very important, playing a key role, but several aspects still need further clarification. One significant question that remains is which patients are at a higher risk for inhaler poor performance and for clinical poor outcomes. This thesis focuses on such aspects and our results bring some clarification regarding the most relevant predictors that should be considered in daily practice. Figure 5.1.1 shows the scheme for causal pathways between inhaler technique performance and disease outcomes in Asthma and COPD, re-evaluated according to our results.

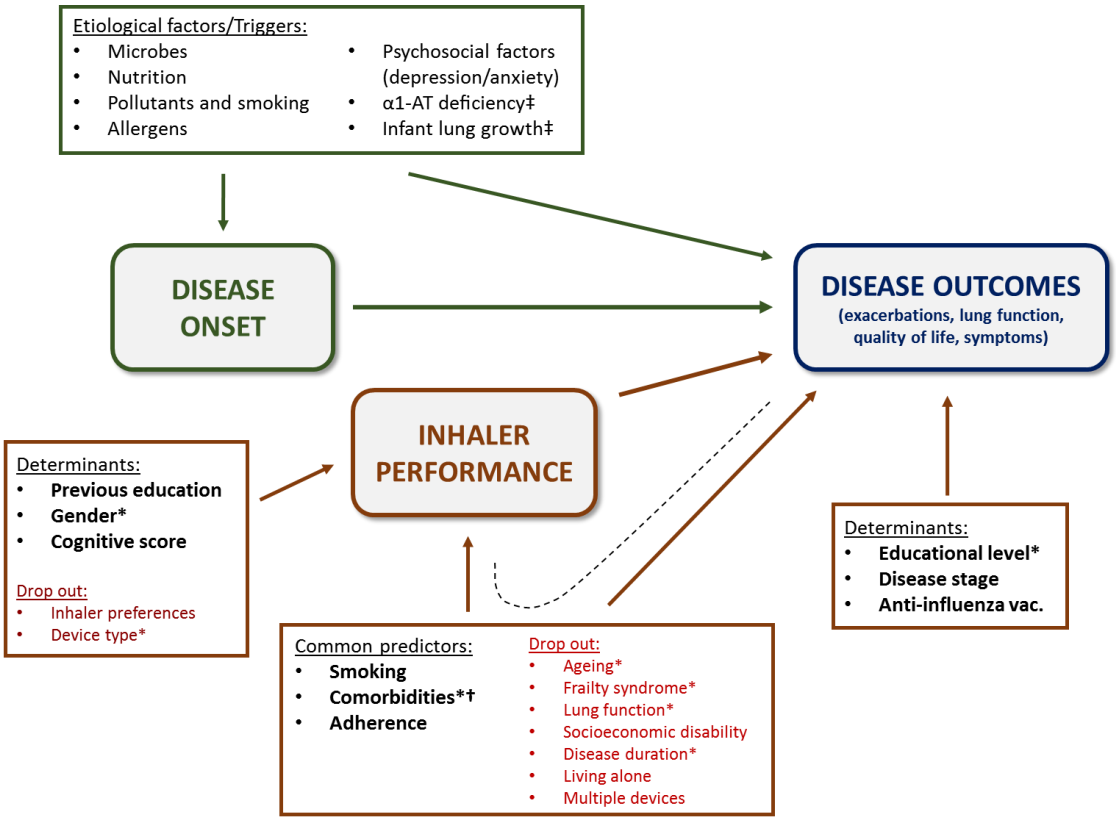

Figure 5.1.1 – Conceptual graph of causal pathways between disease onset, inhaler technique performance and disease outcomes in Asthma and COPD. Diagram performed according to Direct Acyclic Graphs recommendations (7), and re-evaluated taking in account the results of this thesis. The variables identified as "drop-out" were the ones that did not reveal statistically significant associations in the results of this thesis, and may thus be potentially irrelevant, deserving further clarification in causal studies. The single-directional arrows show established and suspected causal pathways according to the reported bibliography. The black dashed line shows an open pathway between inhaler performance, exposure factors and disease outcomes, meaning common true causal inference or potential confounding. AT-Antitripsine. *Factors which impact is especially relevant on elderly patients. †Comorbidities identified as significant both in Asthma and COPD (rhinitis, sinusitis, nasal polyposis, gastroesophageal reflux, obesity, depression and anxiety) and comorbidities identified as significant mostly in COPD (cardiovascular disease, lung cancer, osteoporosis, musculoskeletal diseases, metabolic syndrome, bronchiectasis and sleep apnoea syndrome). ‡Factors which impact are especially relevant in COPD.

Regarding inhaler performance itself, it becomes clear that cognitive function plays a key role as an independent predictor, and this is in accordance with previous reports, that established the association for a long time(8-12). Also, there may be differences in cognitive impairment between COPD and Asthma patients and that should be further studied (13). Exacerbations

may also contribute to worsening of cognitive function, and this relation may be considered for more regular follow-ups for high-risk patients (14, 15). Some aspects may also be considered in routine practice in order to personalise inhaler review, such as patient empowerment, disease self-knowledge, patient preferences of type of inhaler and previous inhaler education (16-19). Adherence may play an important role on inhaler performance, and that has been previously established (20). However, many other factors may influence adherence, such as medication costs, education level, previous adverse events and patient beliefs and perceptions about its importance (20, 21). Adherence may be intentional (usually due to patients' beliefs and attitudes), or unintentional (i.e. forgetting to take the drug), and this should be considered by clinicians before prescription, in order to deliver more personalised and efficient interventions (22). Several tools may be used to check adherence, and the most common are questionnaires or electronic devices (23, 24). All of them may be suitable, but further research is needed to test their effectiveness in real-world. Patients with other comorbidities besides Asthma or COPD also seem to have worse inhaler performance. This was previously reported (25, 26), but the true reason for that is still unclear. It must be considered that comorbidities may still play some confounding effect, because they also influence clinical outcomes.

The choice of an inhaler should consider individual profile and patients' characteristics, and be suitable to their ability to use them (27-29). Although more evolved and simpler devices became available on the market in the last few decades, inhaler performance has not improved over time (30) and errors are committed by all types of patients using different devices (31). However, there may be some differences in some type of inhalers. For instance, some studies suggest that pMDI may be better used when coupled to a spacer (31), with less critical errors committed. Other studies point out the superiority of DPIs and BAIs (32-34), but these may also be more expensive (32). BAIs may in fact overcome some difficulties of pMDI on the adequate coordination of drug activation. In our study we found no significant differences among different device types. New DPI devices are available on the market in the last few years, trying to simplify drug activation steps and inhalation flow, and those may play an important role on performance itself (35, 36).

Teaching patients how to correctly use their inhalers is extremely important, but this can only be achieved if we have well prepared healthcare professionals to deliver it in real clinical practice. This issue has been under research for many years, and it is quite clear that there is a significant variability in professionals' ability to detect inhaler performance errors, both among pharmacists (37) and doctors (38). Healthcare professionals tend to underestimate this topic, and they quickly lose the skills over time if they do not practice them regularly (39, 40). In addition, all healthcare professionals that deal with these patients should be involved in teaching, not only pharmacists or doctors, but also nurses (41) and respiratory therapists (42). Healthcare professionals now have many different tools to

improve their knowledge and to learn new skills alongside their career, but some studies highlight the need to invest in an early stage of education. Younger students seem to be highly prone to learning inhaler technique skills (43-45), and, thus, educational programmes may be designed for them.

It is not only important to recognise the most relevant predictors of inhaler performance, but it is also of paramount importance to identify true predictors of disease outcomes. Our results highlight the importance of some of those aspects, such as the presence of other comorbidities, depression and anxiety, and it is, indeed, well established that they worsen disease control (25, 46, 47). Also, we found that educational level and empowerment may play an important role in disease outcomes, and placebo face-to-face education may help to overcome some barriers (48). Previous reports also highlight the same findings (2, 49). However, some studies suggest that self-knowledge and the patient's ability to learn new skills does not improve major outcomes (3, 50).

Another important aspect that has been under recent discussion is the difference between critical and non-critical errors. In fact, some reports show that up to 50% of patients commit critical errors (51, 52), and most studies do not report them. Also, only half of the reported studies use appropriate checklists for inhaler performance evaluation (53, 54). Our results identify as the most important steps for lung function (measured in FEV1% of predicted values), but not for clinical control, the wrong dose activation and an absent end pause, and these are more relevant on patients using pMDI without spacer and DPIs. Previous reports have highlighted similar findings (52, 55), but that should also be addressed in a more specific approach in future studies. Although cognitive function was detected as an important predictor for inhaler performance, but not for clinical outcomes, some studies also suggest that it may influence the ability to self-manage COPD (56). Evaluating clinical risk and clinical outcomes in elderly patients is a challenge for clinicians, because many aspects should be considered in a comprehensive management. Some studies have investigated simpler approaches to estimate individual risk for elderly patients, such as through the identification of important biomarkers, and that may play an important role in the near future (57).

Comparing the conceptual graph of causal pathways in figure 5.1.1 before and after analysing our results, we may identify some predictors of inhaler performance and disease outcomes that may "drop out" from the equation, such as: ageing, frailty, lung function, socioeconomic disability, disease duration, living alone, using multiple devices, inhaler patient preferences and device type. Some of these predictors have been identified as important variables to be considered in previous studies, as we already mentioned.

Our results now suggest that the confidence of such findings may be uncertain. In fact, considering the limited time that clinicians have available to perform patient centred evaluations, is it of paramount importance to develop individualised guidelines for risk assessment, in order to optimise disease outcomes. On the other hand, there are some potential confounders that were not truly clarified in our study, regarding their predictive role for both inhaler performance and clinical outcomes. The most important ones are comorbidities and adherence. This lack of robustness may be due to the cross-sectional design or the relatively limited sample size of our study. Thus, these aspects should be further investigated by true causal study designs.

Our results highlight the benefit and cost-effectiveness of inhaler technique educational interventions on major clinical outcomes, as well as the importance of patients' individual characteristics on both dimensions. However, some questions still arise regarding elderly patients. First, the true effect of inhaler technique education as a stand-alone intervention should be further assessed. Second, some key predictors of both inhaler performance and clinical outcomes should be properly controlled in order to clarify their role in causal pathways. Lastly, the optimal frequency for inhaler review should also be evaluated in order to assess its effectiveness over time.

In fact, most studies performed in elderly patients are non-randomised, with a short follow-up, and include more interventional aspects besides inhaler technique review. The best-designed studies, such as RCT's with large samples, among adult patients, have shown contradictory findings. The RCT by Armour et al (58) and Garcia-Cardenas et al (59) have shown a positive impact of a placebo device training on clinical outcomes, but the follow-up was only six months. The longest follow-up was observed in the randomised trial by Hesselink et al. (60), in which patients were observed for two years with a placebo device based intervention, but no significant impact was observed in clinical outcomes. Regarding exacerbations as the primary outcome, no study addressed it with more than six months follow-up. Regarding the elderly, the best-designed study, with a randomised design and a significant sample size, by Tommelein et al (61) has shown a positive impact on severe exacerbations after three months. However, it is unclear if that effect would be sustained after a longer follow-up period. Two other RCT's, by Bourbeau et al (62) and Khdour et al (63) addressed it in a 12-month follow-up, finding a positive impact on risk reduction. Nevertheless, all those studies only included COPD patients, who naturally have more exacerbations than patients with Asthma. In addition, a recent systematic review regarding the impact of inhaler technique education in children and adult patients revealed no significant benefit in clinical outcomes (1), and this highlights the need to test those interventions in elderly patients. Most studies included in that systematic review did not incorporate the optimal design characteristics, as previously mentioned. Also, some

international guidelines highlight the need for regular review and longer follow-up assessments (64, 65).

In this thesis we propose a protocol for a single-blinded randomised controlled trial, that aims to assess the impact of a single placebo device training intervention, delivered regularly in elderly patients with Asthma or COPD, on major clinical outcomes after a one-year follow-up, when compared with real-life care. This study will try to overcome many potential biases detected in previous works, in order to quantify the real benefit of inhaler technique education. However, due to the inherent nature of the intervention, such study will not be blinded to the participants, who will suffer from the Hawthorne effect, introducing some performance bias. On the other hand, the importance of adherence rate should be stressed, as it might have biased the results from previous work. In this trial the authors intend to minimise non-adherence using email and telephone communication with patients and to control for that factor (23, 66). Another important issue to be considered is patients' educational level and disease self-knowledge. Although this will not be an issue addressed in the intervention, it will be controlled as a potential confounder or effect modifier. Many tools may be used to teach inhaler technique in elderly patients, and some studies suggest that face-to-face education may overcome some of the main barriers previously mentioned (48). Although most studies suggest that placebo device is the best method, recent reports highlight the potential benefit of videos (67). In addition, as technology evolves, new virtual and multimedia tools may also be considered (68, 69), as well as videoconferencing and telemedicine (70).

Our results bring up for discussion many issues that should be further investigated in elderly patients, but most of such questions are still in the grey zone regarding younger adults and children. For that reason, studies comparing such different populations may be conducted, in order to clarify the need for a more personalized health care delivery. Also, significant differences in most of the outcomes here reported may exist between Asthma patients and COPD patients, and that may be due to the disease pathophysiology itself or to patients' different profiles. New routes may arise regarding the management of patients with Asthma or COPD in clinical practice. As primary health care professionals gain more experience dealing with them, scientific knowledge is widening the ground for a more accurate and personalised patient centred medicine.

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CHAPTER SIX

Conclusion and Final Remarks

Conclusion and Final Remarks

This thesis gives a comprehensive insight on inhaler technique performance in elderly patients with Asthma and COPD.

The results highlight that educational interventions with inhaler review may significantly reduce the risk for exacerbations in the elderly. In addition, a regular programme of annual appointments with a nurse and a doctor is cost-effective, generating significant savings from the healthcare providers' perspective. However, according to previous reports, such educational programmes should include other aspects besides inhaler technique performance itself, such as self-management education, adherence improvement, trigger avoidance, and, in selected cases, pulmonary rehabilitation. The true effect of inhaler performance education alone is still unclear.

Our study also identified patients at higher risk for poor inhaler performance and bad clinical outcomes. Regarding inhaler performance itself, the most important aspects to consider in clinical practice may be cognitive function, previous inhaler education, adherence and the presence of other comorbidities with respiratory impact. Regarding the main disease outcomes and clinical risk, the most important aspects to consider in clinical practice are the presence of comorbidities with respiratory impact, depression, anxiety, educational level and patient empowerment, smoking status and an inadequate inhaler use, mainly with critical errors.

There is enough evidence to suggest that regular inhaler review should be performed in elderly patients with Asthma or COPD, mainly those with a high-risk profile. In addition, all healthcare professionals must be trained in proper inhaler educational skills, as well as in the ability to manage features that predict the most relevant outcomes.

In the light of such findings, longitudinal studies must be designed to establish true causal pathways of the most important predictors for inhaler performance and for disease outcomes, which should consider differences in patient profiles. In addition, critical errors must be clarified, since they may be the target for simpler and quicker interventions in clinical practice. Finally, well designed randomised control trials should clarify the true effect of inhaler education as single interventions, and how often they should be delivered to patients.

CHAPTER SEVEN

Appendixes

Appendixes

Appendix I - Curriculum Vitae

PROFILE

I am a recently graduated Family Doctor at Aveiro Heath Centre, and graduated MSc in Medicine at University of Coimbra. During my career I developed activities in various fields, such as of continuing medical education, scientific research and also in an executive position in the national board of the Portuguese Association of General and Family Medicine.

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CURRICULUM VITAE [UNTIL JULY 2019]

PERSONAL INFORMATION

Full Name: Tiago João Pais Maricoto
National ID card: 12860443
Birth Date: 15 February 1985
Nationality: Portuguese

PROFESSIONAL AND ACADEMIC GRADUATION

2018 – Now: Head of the department of USF Aveiro-Aradas Aveiro-Aradas Family Health Unit, Aveiro Health Centre.
2018 – Now: Member of Unit of Continuing Education and Research, Aveiro Health Centre.
2016 – Now: Family and General Medicine Physician in Aveiro-Aradas Family Health Unit, Aveiro Health Centre.
2016 – 2019: PhD Student. Faculty of Health Sciences. University of Beira Interior.
2012 – 2015: Post-graduate trainee in Family and General Medicine in USF Aveiro-Aradas, Aveiro Health Centre.
2011: Post-graduate trainee in the first General Practice recidency (*Internato do Ano Comum*) at Hospital Centre of Coimbra.
2010: Integrated Master in Medicine in Medical School of the University of Coimbra, with final classification of 15 values. Master thesis available online in: http://hdl.handle.net/10316/20396.

POST-GRADUATION COURSES

(Including courses with final evaluation or longer than 30 hours)

2016-2018: Portugal Clinical Scholars Research Training Program. Harvard Medical School and Portuguese Foundation of Science and Technology.
2015: EURACT level I, directed to future teachers and supervisors in General and Family Medicine.
2014: Online Couse in Prostatic Pathology, held by Portuguese Association of Urology/Tecnimede®.
2014: 11th Hypertension Summer School – SPHTA. 35 hours. Completed with Success.
2013: Análise Estatística na Prática Clínica. 36 hours. Finished with 20 values.
2013: Online Course in Nutrition, Health and Lifestyle: Issues and Insights. In *Coursera.* Completed with Distiction.
2013: Online Course in Health for All Through Primary Health Care. In *Coursera.* Completed with Success.

RESEARCH GRANTS AWARDS

2015: Collaborator in the research project "RESPIRA – Environmental Risk Factors for The Progression of Pulmunary Diseases", winner of the international 8.000€ grant, by OHM Estarreja®.
Announced online in: http://ohm-estarreja.in2p3.fr/pt/component/fabrik/details/3/298.
2013: Principal investigator in the research project "OXIMAPA – Controlo da Hipertensão Arterial por MAPA e associação com Síndrome de Apneia do Sono por Oximetria de Pulso", winner of the national 5.000€ grant APMGF/AstraZeneca - Primary Health Care.
Announced in: MGF Notícias. Out. 2013. Pág. 4. "Bolsa APMGF/AstraZeneca 2013 - Investigadores realçam fomento à investigação em CSP".

SCIENTIFIC ACTIVITY

International Publications – ISI Papers:

- Barata A, Maricoto T. Teaching children about hygiene: A primary prevention experience in Portugal. J Family Med Prim Care 2019;8:1017-21.
- Maricoto T, Marques-Gomes J, Correia-de-Sousa J, Taborda-Barata L. Inhaler Review in Older Adults with Asthma or COPD: A Cost-Effectiveness Study and a Perspective in Portugal. J Am Geriatr Soc. 2019 Feb 23.
- Maricoto T. Correia-de-Sousa J. Taborda-Barata L. Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial. BMJ Open 2019;9:e022685.
- Maricoto T, Monteiro L, Gama JMR, Correia-de-Sousa J, Taborda-Barata L. Inhaler Technique Education and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease: A Meta-Analysis. J Am Geriatr Soc. 2019 Jan;67(1):57-66.
  [This paper was published on a top 5 journal of the geriatrics and gerontology category. It has also been chosen by the National Institute for Health Research (NIHR) Dissemination Centre to be summarised as a Signal for its high quality design and relevance to UK decision makers. It is registered with doi: 10.3310/signal-000712].

- Monteiro L, Maricoto T, Solha IS, et al Computerised decision to reduce inappropriate medication in the elderly: a systematic review with meta-analysis protocol. BMJ Open 2018;8:e018988. doi: 10.1136/bmjopen-2017-018988.
- Coelho SD, Maricoto T, Pastorinho MR, Itai T, Isobe T, Kunisue T, Tanabe S, Sousa ACA, Nogueira AJA (2017) Cadmium intake in women from Aveiro University, Portugal – a duplicate diet study. Journal of Geochemical Exploration 183: 187-190; http://dx.doi.org/10.1016/j.gexplo.2017.02.003; 5 year IF (2016): 3.024
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- Maricoto T, Madanelo S, Teixeira G, Valente C, Andrade L, Saraiva A. Educational interventions to improve inhaler techniques and their impact on asthma and COPD control: a pilot effectiveness implementation trial. J Bras Pneumol. 2016;42(6):1-4.
- Maricoto T, Rodrigues LV, Teixeira G, Valente C, Andrade L, Saraiva A. Assessment of Inhalation Technique in Clinical and Functional Control of Asthma and Chronic Obstructive Pulmonary Disease. Acta Med Port 2015 Nov-Dec;28(6):702-707.

Other International Publications:

- Coelho SD, Maricoto T, Tanabe S, Nogueira AJA, Sousa ACA (2017) Dietary Habits of A Portuguese Academic Community - A Food Frequency Questionnaire Approach. J Nutr Diabetes Res. 1(1):

Proceedings in international conferences:

- Maricoto T, Madanelo S, Rodrigues L, Teixeira G, Valente C, Andrade L, Saraiva A. Inhalation technique education and its impact in asthma and COPD. European Respiratory Journal Sep 2015, 46 (suppl 59). DOI: 10.1183/13993003.congress-2015.PA 5019 Published 1 September 2015
- Maricoto T, Vale Neto M, Rainho C. Approach To Diabetic Nephropathy In Children – Evidence-based Review. Pediatric Nephrology. 2014. 29(9):1649-1867.
- Maricoto T, Silva E. From vomits to antidepressant. A somatization case. Psychother Psychosom 2013; 82 (suppl1):1-134.
- Farinha F, Maricoto T, Cunha I, Barcelos A. Da Gota à Incapacidade . Acta Reumatol Port. 2013. 38:33-98 (SUP).
- Silva E, Caramona M, Maricoto T, Cruz e Silva V, Rocha R, Costa , Oliveiros B. Evaluation of a hypertension/diabetes screening campaign. pharm word sci (2008) 30:649-740.

With acknowledgments reference:

- Coelho SD, Sousa ACS, Isobe T, Tanabe S, Nogueira AJA. Flame Retardants in Indoor Dust - A Review on the Levels of Polybrominated Diphenyl Ethers and Hexabromocyclododecanes. Current Organic Chemistry, 2014, 18, 2218-2230

National/Non-ISI Publications:

- Maricoto T, Hespanhol A, Santos P, Nogueira R. O primeiro ano em revisão do novo ciclo da medicina geral e familiar – mudanças e perspetivas. Rev Port Med Geral Fam 2018;34:351-2.
- Nogueira R. Maricoto T. O contexto de exercício clínico do médico de família tem determinantes que influenciam a prestação de cuidados de saúde. Rev Port Med Geral Fam 2018;34:186-8.

- Santos P, Maricoto T, Hespanhol A, Nogueira R. O novo ciclo da medicina geral e familiar. Rev Port Med Geral Fam 2018;34:123.
- Figueiredo A, Pereira M, Príncipe P, Nogueira R, Lopes T, Maricoto T. Sintomas do Tracto Urinário Inferior (LUTS) no Homem. Springer Healthcare Ibérica S.L. APU. APMGF. 2017.
- Maricoto T. A nova métrica das listas de utentes – uma nova era. Journal "MGF Noricias". Nº66. Serie I. Set. 2017. Pág. 14.
- Maricoto T. Uma nova dimensão para a lista de utentes dos médicos de família. Supplement of journal "Jornal Médico de Família". Nº8. IV edição. 3º trimestre de 2017. Pág. 5.
- Maricoto T,. Casos Clínicos Urocses®. Monography. Tecnimede®. 2016. Pág. 126-131.
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- Maricoto T. Lista de Utentes. Que limite? Jornal Medico de Família. Nº3. IV edição. 2º trimestre de 2016. Pág. 8-10.
- Maricoto T, Vale Neto M, Rainho C. Abordagem da Nefropatia Diabética em Idade Pediátrica: Revisão Baseada na Evidência. Acta Pediatr Port 2015;46:250-3
- Silva T, Rebelo P, Seabra D, Silva E, Sequeira J, Sebe M, et al. Projeto Mexer com a Diabetes. Saúde em Números. Revista da Direcção Geral de Saúde. Mar. 2015. Pág. 82
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- Costa R, Maricoto T, Sousa E. Casos Clínicos Spiriva Respimat®. Monography. Boehringer®. 2015. Pág. 6-9.
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- Maricoto T, de Sousa JC. Asma de Controlo Difícil. Jornal Médico. Abr. 2014. Pág. 12
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- Maricoto T, silva E. Uso profilático de anti-histamínicos na dermatite atópica. Revisão baseada na evidência. Acta Pediatr Port 2013;44(1):43-5

Publications in journals for the general public:

- Maricoto T. Volte a ter energia. Prevenir. November 2016.
- Maricoto T. «Tenho a vacina do tétano em atraso. Que riscos corro?». Prevenir. October 2016.
- Maricoto T. As ferias perfeitas começam aqui. Prevenir. August 2016.
- Maricoto T, Silva E. Tosse. JustNews. January 2015.
- Maricoto T. Dia Mundial do Médico de Família. Interview. Diário de Aveiro. 19 May 2015.
- Maricoto T. Cuidados a ter com o Calor nas Ferias de Verão. Prevenir. August 2015.
- Maricoto T. Um Aliado no combate à Obesidade Infantil. Pais&Filhos. October 2015.

Oral Presentations:

- Maricoto T. Santos D. Carvalho C. Telles I. Correia-de-Sousa J. Taborda-Barata L. Técnica inalatória em idosos com Asma ou DPOC – uma ferramenta preditiva de performance. 1as Jornadas de Investigação Clínica do CACB. November 2018.

- Maricoto T. Marques-Gomes J. Correia-de-Sousa J. Taborda-Barata L. Intervenções educativas com revisão da técnica inalatória em idosos com Asma ou DPOC - Uma análise custo-efetividade com uma perspetiva aos cuidados de saúde em Portugal. 34º Congresso de Pneumologia. November 2018.
- Maricoto T. Inovação, Partilha e Conhecimento: criação de uma equipa de formação e investigação num ACeS. 22º Congresso Nacional de MGF. September 2018.
- Maricoto T. Santos FC D. Correia-de-Sousa J. Taborda-Barata L. Inhaler technique in elderly Asthma or COPD patients – a predictive tool for inhaler performance and clinical risk; 9th IPCRG World Conference. June. 2018.
- Maricoto T. Monteiro L. Gama J. Correia-de-Sousa J. Taborda-Barata L. Inhaler technique education in elderly patients with Asthma or COPD: impact upon disease control and exacerbations: a Systematic Review and Meta-analysis; 9th IPCRG World Conference. June. 2018.
- Maricoto T. Correia-de-Sousa J. Taborda-Barata L. Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded RCT; 9th IPCRG World Conference. June 2018.
- Coelho SD, Maricoto T, Pastorinho MR, Itai T, Riyadi AS, Kamei T, et al. Cadmium dietary intake in women from Aveiro University (Portugal) - a duplicate diet study. 6th International Conference on Medical Geology. July 2015.
- Maricoto T. Silva E. Avaliação de Qualidade – Prescrição da vacina antipneumocócica. 32º Encontro Nacional MGF. March. 2015
- Maricoto T. Silva E. A weekend toast to triglycerides and HbA1c – A case report. 19th WONCA Europe Conference. July 2014.
- Maricoto T. Silva E. Um brinde de fim-de-semana aos TG e à HbA1c. 31º Encontro Nacional MGF. February 2014.
- Maricoto T. viALERT – Caracterização da referenciação em consulta de Reumatologia. 31º Encontro Nacional MGF. February 2014
- Maricoto T. Silva E. Revisão da Técnica Inalatória em Asma e DPOC – Avaliação de Qualidade. 31º Encontro Nacional MGF. February 2014
- Maricoto T. Silva E. Avaliação de Qualidade - Prevenção do Cancro do Cólon e do Recto. 18º Congresso Nacional de MGF/12º Encontro Nacional de Internos de MGF e Jovens MF. September 2013.
- Pereira AP, Neves A, Bonifacio E, Neto MV, Maricoto T. Obesidade e Excesso de Peso: Estão os nossos utentes bem codificados?. 30º Encontro Nacional MGF. February 2013.
- Silva E, Maricoto T, Girão MJ. Um caso típico de Síndroma Metabólico nos Cuidados Primários. IV Jornadas de Endocrinologia, Diabetes e Nutrição de Aveiro. May 2012.

Poster Presentations:

- Maricoto T. Marques-Gomes J. Correia-de-Sousa J. Taborda-Barata L. Intervenções educativas com revisão da técnica inalatória em idosos com Asma ou DPOC - Uma análise custo-efetividade com uma perspetiva aos cuidados de saúde em Portugal. 1as Jornadas de Investigação Clínica do CACB. November 2018.
- Maricoto T. Monteiro L. Gama JMR. Correia-de-Sousa J. Taborda-Barata L. Ensino da técnica inalatória em idosos com Asma ou DPOC: impacto no controlo da doença e exacerbações: uma revisão sistemática e meta-análise. 1as Jornadas de Investigação Clínica do CACB. November 2018.

- Maricoto T. Santos D. Carvalho C. Telles I. Correia-de-Sousa J. Taborda-Barata L. Técnica inalatória em idosos com Asma ou DPOC – uma ferramenta preditiva de risco clinico. 1as Jornadas de Investigação Clínica do CACB. November 2018.
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- Maricoto T. Monteiro L. Gama JMR. Correia-de-Sousa J. Taborda-Barata L. Ensino da técnica inalatória em idosos com Asma ou DPOC: impacto no controlo da doença e exacerbações: uma revisão sistemática e meta-análise. 39ª Reunião Anual da SPAIC. September 2018.
- Maricoto T. Santos D. Carvalho C. Telles I. Correia-de-Sousa J. Taborda-Barata L. Técnica inalatória em idosos com Asma ou DPOC – uma ferramenta preditiva de performance. 39ª Reunião Anual da SPAIC. September 2018.
- RESPIRA - Environmental Risk Factors for the Development and Progression of Pulmonary Diseases: Study Rationale. XI Annual CICS-UBI Symposium. 30 June - 1 July 2016.
- Inhalation technique education and its impact in asthma and COPD. 25th European Respiratory Society International Congress. September 2015.
- Approach To Diabetic Nephropathy In Children – Evidence-based Review. 47th Annual Scientific Meeting of the European Society for Paediatric Nephrology. September 2014.
- Scientific Activity in a Portuguese post-graduation group. 19th WONCA Europe Conference. July 2014.
- Referral to secondary care in Gynecologic Pathology. 19th WONCA Europe Conference. July 2014.
- viALERT – Characterization of the referral to Rheumatology consultation. 19th WONCA Europe Conference. July 2014.
- Quality improvement in colorectal cancer screening - a General Practitioner file study. 19th WONCA Europe Conference. July 2014.
- Review of inhaler technique in Asthma and COPD- Quality Assessment. 19th WONCA Europe Conference. July 2014.
- Projecto Mexer com a Diabetes. IV Congresso Nacional de Saúde Pública. October 2014.
- Diabetes Mellitus de tipo 2 no Adolescente. 7º Congresso Nacional de Medicina do Adolescente. May 2014.
- Rastreio Oportunista de DPOC na População Geral. XXX Congresso de Pneumologia. November 2014.
- Avaliação da Técnica Inalatória e Controlo Clínico e Funcional da Asma e DPOC. XXX Congresso de Pneumologia. November 2014.
- Da Gota à Incapacidade. Simpósio Inflamação & Dor. May 2013.
- Obesidade e Satisfação Sexual. 18º Congresso Nacional de MGF/12º Encontro Nacional de Internos de MGF e Jovens MF. September 2013.
- From vomits to antidepressant. A somatization case. 22nd World Congress on Psychosomatic Medicine. September 2013.
- Dos vómitos ao Antidepressivo. 17º Congresso Nacional de MGF/11º Encontro Nacional de Internos e Jovens MF. September 2012.
- Uso profilático de anti-histamínicos na dermatite atópica. Qual a evidência? 17º Congresso Nacional de MGF/11º Encontro Nacional de Internos de MGF e Jovens MF. September 2012.

- Alimentação no 1º ano de vida, um tema controverso/ Consenso da UCF de Aveiro, vertente materno-infantil. 17º Congresso Nacional de MGF/11º Encontro Nacional de Internos de MGF e Jovens MF. September 2012.

Activity as a speaker and moderator in scientific events:

- Speaker in 36º Encontro Nacional de MGF. "Nova metrica da lista de utentes: evoluções e projectos". March 2019.
- Session Moderator in 36º Encontro Nacional de MGF. "Conversas com o colégio-Idoneidade Formativa: um novo discurso ou um novo paradigma?". March 2019.
- Session Moderator in 36º Encontro Nacional de MGF. "Oral Comunications in Original Research". March 2019.
- Session Moderator in 22º Congresso Nacional de MGF. "Gestão da Lista para totós". September 2018.
- Session Moderator in 22º Congresso Nacional de MGF. "Poster comunications in Original research". September 2018.
- Session Moderator in 5ª Academia Médica. "As Bombas da Medicina - Avaliação nas USF e melhoria contínua da qualidade". June 2018.
- Speaker in 35º Encontro Nacional de MGF. "Lista de utentes - A evolução inevitável". March 2018.
- Session Moderator in 21º Congresso Nacional de MGF e 16º Encontro Nacional de Internos de MGF e Jovens MF. "Poster Comunications in Case Report". September 2017.
- Session Moderator in 34º Encontro Nacional de MGF. "Oral Comunications in Original Research". March 2017.
- Session Moderator in 34º Encontro Nacional de MGF. "Debate de Encerramento". March 2017.
- Session Moderator in 34º Encontro Nacional de MGF. "Fibrilhação auricular e síncope". March 2017.
- Session Moderator in 34º Encontro Nacional de MGF. "Acolher o Futuro". March 2017.
- Speaker in 34º Encontro Nacional de MGF. "Nova Métrica da Lista de Utentes". March 2017.
- Session Moderator in 20º Congresso Nacional de MGF e 15º Encontro Nacional de Internos de MGF e Jovens MF. "Poster Comunications in Practice". September 2016.
- Session Moderator in 20º Congresso Nacional de MGF e 15º Encontro Nacional de Internos de MGF e Jovens MF. "Apresentação dos resultados do estudo EspiroPed". September 2016.
- Session Moderator in 20º Congresso Nacional de MGF e 15º Encontro Nacional de Internos de MGF e Jovens MF. "Diversidade nacional na Estrutura e organização do Internato". September 2016.
- Session Moderator in 20º Congresso Nacional de MGF e 15º Encontro Nacional de Internos de MGF e Jovens MF. "Sr. Doutor. Esqueço-me de tudo.". September 2016.
- Session Moderator in 33º Encontro Nacional de MGF. "Pneumonia da Comunidade. Para além das bactérias...". March 2016.
- Speaker in 33º Encontro Nacional de MGF. "Lista de Utentes - que limite?". March 2016.
- Speaker in 19º CN de MGF/14º Encontro Nacional de Internos de MGF e Jovens MF. "Apneia do sono e o controlo da HTA. O que nos falta?" presenting the results of the OxiMAPA study. September 2015.
- Session Moderator in 19º CN de MGF/14º Encontro Nacional de Internos de MGF e Jovens MF. "Avaliação Final do Internato". September 2015.
- Session Moderator 19º CN de MGF/14º Encontro Nacional de Internos de MGF e Jovens MF. "Oral Comunications in Case Report". September 2015.

- Session Moderator in 9º Congresso Português de HTA e Risco CV Global. "Sessão Magna SPH-APMGF". March 2015.
- Session Moderator in 32º Encontro Nacional de MGF. "DPOC". March 2015.
- Session Moderator in 19th WONCA Europe Conference. "Research Information Technology". July 2014.
- Session Moderator in the Opening Cerimony in 1ª Academia Médica. June 2014.
- Session Moderator in 1ª Academia Médica. "As Bombas da Medicina". June 2014.
- Speaker in Jornadas do Internato Médico de Santa Maria da Feira. "O Doente Incontinente na Consulta de Rotina". May 2014.
- Speaker in 2ª Jornadas GRESP. "Como fazer uma consulta de asma em equipa de saúde?". February 2014.

Activity as an editor, reviewer and scientific jury:

2019: selected jury of scientific communications in Academia Médica 2019. July.
2019: Selected jury of scientific communications in the category "research" in 36º Encontro Nacional de MGF. March.
2019 – Now: Reviewer of the journal: World Allegry Organization Journal.
2018 – Now: Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF).
2018 – Now: Reviewer of the journal: Respiratory Medicine.
2018: Selected jury of scientific communications in the category "Research" in 22º Congresso Nacional de MGF. September.
2018: Selected jury of scientific communications in the category "Practice" in 35º Encontro Nacional de MGF. March.
2018: Selected jury of scientific communications in the 23rd WONCA Europe Conference. January.
2017 – Now: Assitant Editor of the Portuguese Journal of General and Family Medicine.
2015 - 2017: Reviewer of the journal: Revista da Associação de Internos de MGF da Zona Norte.
2017: Selected jury of scientific communications in the category "Clinical Reports" in 21º Congresso Nacional de MGF. September.
2017: Selected jury of scientific communications in the category "Clinical Reports" in 34º Encontro Nacional de MGF. March.
2016: Selected jury of scientific communications in the category "Practice" in 20º Congresso Nacional de MGF. September.
2016: Selected jury of scientific communications in the 21st WONCA Europe Conference. June.
2016: Selected jury of scientific communications in the category "Practice" in 33º Encontro Nacional de MGF. March.
2015: Jury element in the research grant APMGF/Tecnifar 2015, intended to grant 5.000€ to the project "Rastreio da Neuropatia Diabética – Exame do pé vs eletromiografia".
2015: Jury element in the scientific grant APMGF "WONCA Europa 2015", intended to grant with allowance fees the best Portuguese communications held in the event.
2015: Jury of scientific communications in the category "Practice" in 19º Congresso Nacional de MGF e 14º Encontro Nacional de Internos de MGF e Jovens MF. September.
2015: Reviewer of Acta Médica Portuguesa.

ACTIVITY AS A TEACHER

Teacher of academic students of medicine:

- Teacher of medicine student in traineeship from University of Lisbon. May 2018.
- Teacher of medicine student in traineeship from University of Porto. June-July 2017.
- Teacher of master`s degree students at University of Beira Interior of a "research methods" discipline. March-May 2017.
- Teacher of master`s degree students at University of Beira Interior of a "research methods" discipline. February-June 2018.

Teacher of doctors in post-graduate medical career:

- Teacher of resident in post-graduate training of the first stage of the general clinical career. April-July 2018.
- Teacher of resident in post-graduate training of the first stage of the general clinical career. September 2017.
- Teacher of resident in post-graduate training of the first stage of the general clinical career. January-March 2017.
- Teacher in respiratory diseases post-graduation course. Pós-Graduação em Doenças Respiratórias da Faculdade de Ciências da Saúde da Universidade do Minho. November 2015.
- Teacher in anticoagulation and antiplatelet therapy course. Agrupamento de Centros de Saúde do Baixo Vouga. June 2015.
- Teacher in respiratory diseases intensive course. Escola de Outono da APMGF. October 2014.
- Workshop: Interpretation of Spirometry. 5ª Academia Médica. June. 2018.
- Workshop of Inhalation technique in the events:
  - IPCRG 9th World Conference and 1st Ibero-American Conference. June 2018.
  - 20º Congresso Nacional de Medicina Geral e Familiar. September 2016.
  - 4ª Reunião da Imunoalergologia Hospital Dona Estefânia. May 2015.
  - 1ª Academia Médica – Oficina de Habilidades. June 2014.
  - 6º Encontro Nacional das USF. May 2014.
  - XX Encontro do Internato de MGF da Zona Norte. October 2013.
  - General and Family Medicine regional Residency Group of Aveiro. October 2013.
  - 2ª Jornadas GRESP. February 2014.
- Workshop: Environmental contaminants and respiratory diseases. IV Encontro Nacional de Pós-Graduação em Ciências Biológicas. April. 2015
- Workshop of Asthma dificult to control in the events:
  - 32º Encontro Nacional de MGF. March 2015.
  - 31º Encontro Nacional de MGF. February 2014.
  - 2ª Jornadas GRESP. February 2013.

INSTITUTIONAL AND ORGANIZATIONAL ACTIVITY

2015-Now: Member of the National Board of the Portuguese Association of General and Family Medicine (APMGF). In this organization I was a member of the organizing committee of the events:

- 32º Encontro Nacional de MGF. March 2015.

- 19º Congresso Nacional de MGF e 14º Encontro Nacional de Internos de MGF e Jovens MF. September 2015.
- 33º Encontro Nacional de MGF. March 2016.
- 20º Congresso Nacional de MGF e 15º Encontro Nacional de Internos de MGF e Jovens MF. September 2016
- 34º Encontro Nacional de MGF. March 2017.
- 21º Congresso Nacional de MGF e 16º Encontro Nacional de Internos de MGF e Jovens MF. September 2017
- 35º Encontro Nacional de MGF. March 2018.
- 22º Congresso Nacional de MGF e 17º Encontro Nacional de Internos de MGF e Jovens MF. September 2018
- 36º Encontro Nacional de MGF. March 2019.
- Scheduled: 23º Congresso Nacional de MGF e 18º Encontro Nacional de Internos de MGF e Jovens MF. September 2019

2012-Now: Member of the Respiratory Group of APMGF (GRESP). In this organization I was a member of the organizing committee of the event:

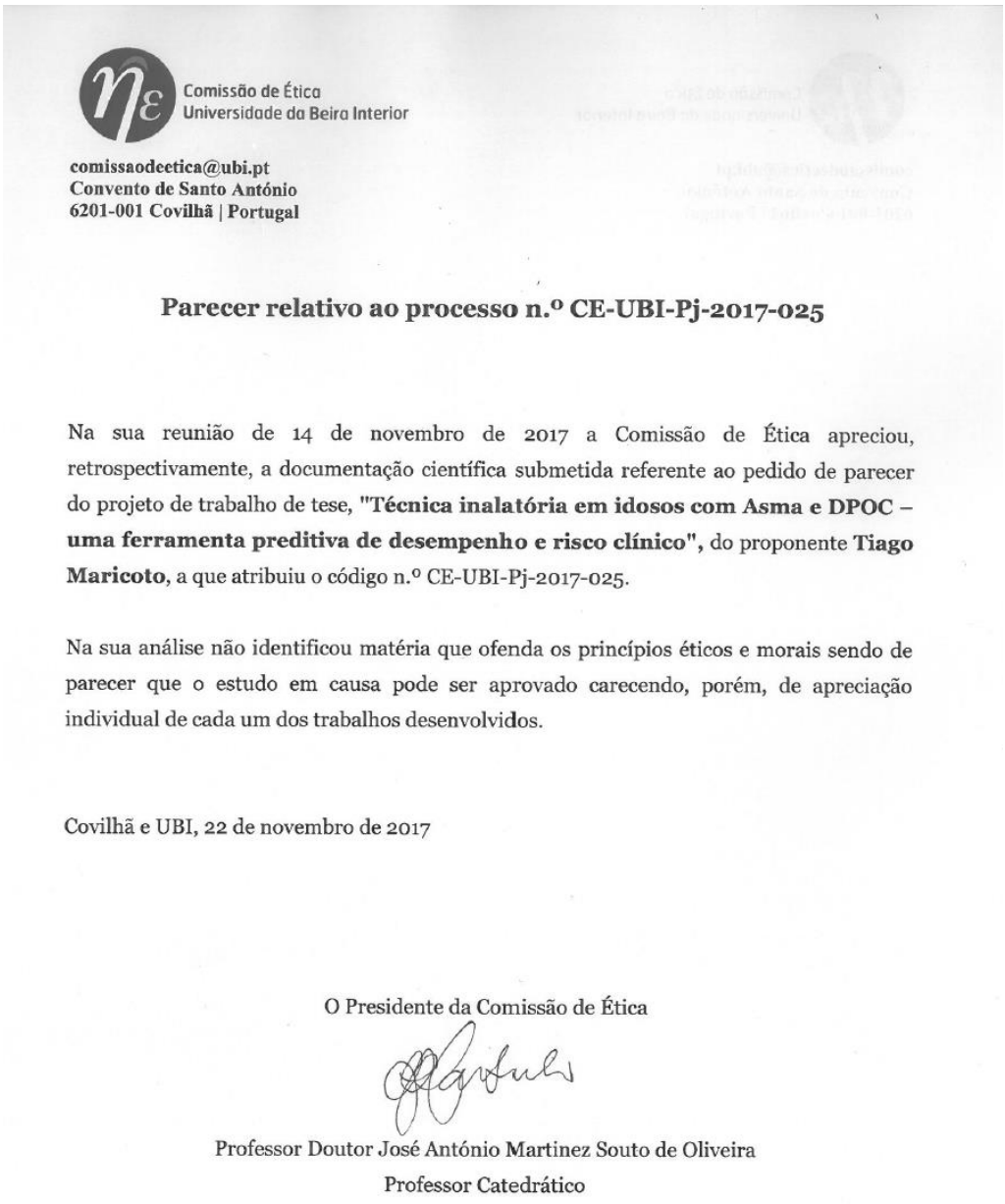
- 2ª Jornadas GRESP. February 2014.
- 4ª Jornadas GRESP. April 2017.

2012-2016: Member of *Centro Dinamizador de Conteúdos em Medicina geral e familiar* (CDC.MGF). In this organization I was a member of the events:

- 1ª Academia Médica. June 2014.
- 2ª Academia Médica e 1ª Academia Pública. July 2015.
- 3ª Academia Médica e 2ª Academia Pública. July 2016.

Appendix II - Approvals from Ethics Committee, Local Health Administrations; Data Protection Authority; and permissions for the use of questionnaires.

University of Beira Interior ethics committee:



Comissão de Ética
Universidade da Beira Interior

comissaodeetica@ubi.pt
Convento de Santo António
6201-001 Covilhã | Portugal

Parecer relativo ao processo n.º CE-UBI-Pj-2017-025

Na sua reunião de 14 de novembro de 2017 a Comissão de Ética apreciou, retrospectivamente, a documentação científica submetida referente ao pedido de parecer do projeto de trabalho de tese, **"Técnica inalatória em idosos com Asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico"**, do proponente **Tiago Maricoto**, a que atribuiu o código n.º CE-UBI-Pj-2017-025.

Na sua análise não identificou matéria que ofenda os princípios éticos e morais sendo de parecer que o estudo em causa pode ser aprovado carecendo, porém, de apreciação individual de cada um dos trabalhos desenvolvidos.

Covilhã e UBI, 22 de novembro de 2017

O Presidente da Comissão de Ética

Professor Doutor José António Martinez Souto de Oliveira
Professor Catedrático

Centro regional administration ethics committee:

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

ARSC ADMINISTRAÇÃO REGIONAL DE SAÚDE DO CENTRO, I.P.

COMISSÃO DE ÉTICA PARA A SAÚDE

PARECER FINAL:	DESPACHO:
Parecer Favorável.	Homologado 30/10/2017

ASSUNTO: **73/2017 - "Técnica inalatória em idosos com Asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico."**

Estudo com objectivos louváveis e bem desenhado.

Esta Comissão de Ética deverá receber cópia do relatório final.

Coimbra, 25 de outubro de 2017

Carlos Fontes Ribeiro

Presidente da Comissão de Ética

Luiz Miguel Santiago

Relator

North regional administration ethics committee:

ARS NORTE
Administração Regional
de Saúde do Norte, I.P.

☐ ☐ ☐ DATA : 7.dezembro.2017

INFORMAÇÃO Nº 153/2017 Nº <Processo> <Registo>

PARA: Conselho Diretivo da ARS Norte

DE: Comissão de Ética para a Saúde da ARS Norte

ASSUNTO: Parecer nº 142/2017

Levo ao conhecimento do Conselho Diretivo o Parecer nº 145/2017 sobre o Estudo "Técnica inalatória em idosos com asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico", aprovado na reunião de 5 de dezembro de 2017, por unanimidade.

À consideração superior

Ana Paula Capela
Ana Paula Capela
(Assessoria CES/UIC)

DELIBERADO CONCORDAR
2017.12.13

Dr. Pimenta Marinho
Presidente do C.D.

Paula Duarte
Vogal do CD

Rita Moreira
Vice-Presidente do CD

Dr. Ponciano Oliveira
Vogal C.D.

ADMINISTRAÇÃO REGIONAL DE SAÚDE DO NORTE, IP
EXARADO NA ACTA N.º 55
REUNIÃO DE 13.12.2017

Rua Santa Catarina, 1288 Tel 220 411 000 arsn@arsnorte.min-saude.pt
4000-447 Porto Fax 220 411 005 www.arsnorte.min-saude.pt

GOVERNO DE PORTUGAL | MINISTÉRIO DA SAÚDE

ARS NORTE
Administração Regional
de Saúde do Norte, I.P.

Comissão de Ética para a Saúde
Administração Regional de Saúde do Norte, IP

PARECER Nº 145/2017

Sobre o estudo T800 - "Técnica inalatória em idosos com asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico"

A – RELATÓRIO

A.1. A Comissão de Ética para a Saúde (CES) da Administração Regional de Saúde do Norte, I.P. (ARSN) iniciou a apreciação do estudo "Técnica inalatória em idosos com asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico", a pedido do Dr Tiago Maricoto, estudante de Doutoramento da Universidade da Beira Interior, sob a orientação do Doutor Luís Taborda Barata, da UBI, e do Doutor Jaime Correia de Sousa, com o objetivo de identificar os factores preditivos de mau desempenho na técnica inalatória, bem como dos seus outcomes adversos, nomeadamente o mau controlo dos sintomas e o maior risco de exacerbações.
A.2. Trata-se de um estudo observacional transversal, multicêntrico, em que a técnica inalatória é avaliada por observação do doente na execução do seu próprio inalador e registo do número de erros detetados de acordo com a descrição de cada aparelho. Paralelamente será analisado um conjunto de variáveis que poderão estar associadas ao desempenho da técnica inalatória. Todos os participantes realizarão uma espirometria com prova de broncodilatação de base para confirmação diagnostica e classificação funcional.
A.3. Prevê-se a inclusão de 174 participantes, após consentimento informado, entre os doentes diagnosticados com Asma ou DPOC, medicados com qualquer tipo de dispositivo inalatório, com idade ≥65 anos, e sendo utilizadores regulares dos Cuidados de Saúde Primários.
A.4. Os dados serão recolhidos pelos investigadores por entrevista direta ao participante e vertidos em base de dados anonimizada por um sistema de codificação alfanumérica.

B – Identificação das questões com eventuais implicações éticas

B.1. Reconhece-se relevância ao estudo e interesse nos resultados esperados.
B.2. Os dados recolhidos são adequados à dimensão em estudo.
B.3. Não há intervenção direta significativa sobre doentes, não se prevendo alteração da regular prestação de cuidados assistenciais.
B.4. Os dados serão tratados de forma lícita, preservando a confidencialidade e a anonimização dos participantes.
B.5. O formulário de consentimento informado está de acordo com o protocolo do estudo, respeitando a autonomia dos participantes.
B.6. Os dados serão recolhidos por profissionais de saúde competentes e mantidos anónimos para efeitos de investigação.
B.7. Os recursos orçamentados são adequados aos objetivos da investigação.

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C – Conclusões

C.1. Face ao exposto, a CES delibera que o estudo de investigação em causa pode ser aprovado sem restrições de natureza ética.
C.2. Não obstante, devem os investigadores obter as autorizações das unidades de saúde envolvidas e dos respetivos ACeS previamente a inclusão de participantes.

Aprovado em reunião do dia 5 de dezembro de 2017, por unanimidade

O relator,

Professor Doutor Paulo Santos

O Presidente da Comissão de Ética para a Saúde da ARS Norte IP

Professor Doutor Alberto Pinto Hespanhol

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Lisbon and Tagus Valley regional administration ethics committee:

Parecer Intermédio

Proc. 066/CES/INV/2017

Título: Técnica inalatória em idosos com Asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico.

Âmbito do estudo: doutoramento

Enquadramento institucional do proponente Universidade da Beira Interior (UBI)

Investigador (es): Tiago Maricoto

Orientador(es): Luís Taborda Barata; Jaime Correia de Sousa

Financiamento : sem financiamento externo;

Fundamentação do estudo:

Em Portugal, estima-se que a Asma afecte até 10% da população, mas apenas 57% destes doentes apresentarem os seus sintomas controlados(1-4); e em relação à Doença Pulmonar Obstructiva Crónica (DPOC), a sua prevalência atinge até 14.2% na população com 40 ou mais anos(2, 5).Os idosos são particularmente vulneráveis às doenças respiratórias e apresentam algumas particularidades de difícil abordagem, como o frequente atraso no diagnóstico e tratamento, pelo início tardio dos sintomas, ou mesmo o maior risco de interacções medicamentosas, que requerem monitorização regular (6, 7).

As taxas de hospitalização por Asma e DPOC em Portugal estão reportadas em 2,8% dos doentes em cada ano. Este valor pode estar subestimado, pois frequentemente apenas os episódios graves são codificados, escapando a maioria das exacerbações abordadas em cuidados de saúde primários (8). No entanto em estudos controlados, as taxas de exacerbação atingem 27% entre os doentes de baixa adesão ao tratamento, podendo chegar a 53% entre os casos tratados na comunidade primária.

A terapia inalatória é a mais usada para tratar a Asma e a DPOC (9), mas cerca de 90% dos doentes não usam os dispositivos inalatórios correctamente, mostrando erros na técnica em diversos estudos(10, 11).Diversos dispositivos estão disponíveis no mercado, alguns deles surgindo nos últimos anos, e quer as diferenças entre eles, bem como as diferentes características dos doentes aparentam ter um significativo efeito no desempenho da técnica. Não é contudo claro se estas diferenças surgem porque alguns dispositivos são "melhores" ou se é devido a outros factores relacionados com os doentes (12-15). Entre os diferentes factores identificados, coloca-se a idade, sexo, nº de anos de diagnóstico, escolaridade e estado emocional (16, 17).

Apesar disto, todos os dispositivos quando usados correctamente apresentam eficácia semelhante no tratamento ??? (18, 19). Está bem estabelecido que a má técnica inalatória está associada a menor deposição pulmonar do fármaco (20), bem como a mau controlo da Asma e DPOC(21-25) e conduzindo a mais custos e consumo de recursos de saúde(26).

Evidencia significativa mostra que o desempenho da técnica inalatória é particularmente complexa em idosos com Asma e DPOC, estando associada a diversos factores, como a própria idade (27-30). Alem disso, os idosos também apresentam menores índices de adesão (10)e são

mais resistentes a correcções no desempenho da inalação (31-33). Contudo, a significância destas observações deve ser estudada de forma mais detalhada e aprofundada, pois os doentes idosos são frequentemente excluídos dos principais estudos e apresentam diversas variáveis de confundimento. ***Este estudo irá focar-se no subgrupo particular de doentes****, e tem com objectivo* ***identificar os factores preditivos de mau desempenho na técnica inalatória****, bem como dos* ***seus outcomes adversos****, como o mau controlo dos sintomas e maior risco de exacerbações.*

Parecer

Trata-se de uma proposta de estudo que pretende identificar os factores preditivos do mau desempenho da técnica inalatória em doentes idosos com ASMA e DPOC bem como os resultados adversos (incluindo o descontrolo de sintomas e o maior risco de exarcebações) seguidos em consulta de MGF em algumas unidades de saúde.

Trata-se de um projecto que aparenta ter um delineamento sistemático e que procura um conhecimento não generalizável

Trata-se assim de um estudo com as seguintes características:
1.- Envolve profissionais de Saúde da ARSLVT
2.- que ainda não foi realizado
3.- é uma investigação sistemática e pretende gerar um conhecimento de âmbito local;
4.- É um estudo que envolve dados de seres humanos;
5.- Implica a interacção com utentes do SNS e com profissionais de saúde;
6.- Tendo em conta os pressupostos anteriores cumpre critérios de apreciação por esta Comissão de Ética

No que concerne aos aspectos metodológicos interessar-nos-ia que fossem esclarecidos alguns dos seus aspectos, a saber:

1.- A fundamentação do estudo mereceria uma melhor referenciação bibliográfica nomeadamente no que concerne aos estudos realizados nesta área em Portugal e seus resultados;

2.- Na fundamentação do estudo não é possível descortinar e compreender a justificação para a selecção de cada um das variáveis propostas para o estudo e muito menos a sua racionalidade. Interessaria que a fundamentação justificasse e integrasse circunstanciadamente, uma por uma, o interesse e justificação de cada variável e, no contexto do estudo, o que se pretenderá medir e avaliar com cada uma delas. Sem esta informação, sem esta justificação não tem a Comissão condições para avaliar da bondade do estudo e do cumprimento da dimensão beneficência e não maleficência deste estudo. Saliente-se que uma parte significativa das escalas propostas não está enunciada nos objectivos do estudo.

3.- Não é possível percepcionar se as escalas que irão ser utilizadas no estudo foram anteriormente validadas para a população portuguesa e se, para uma delas, o investigador solicitou aos seus autores autorização para a sua utilização no contexto deste estudo.

4.- São-nos apresentados, nos anexos, os diversos e múltiplos métodos de aplicação dos dispositivos inalatórios. Ora, não é perceptível qual o seu interesse e como pretende o investigador utiliza-los e para quê?

5.- Não é perceptível a forma como pretende o investigador medir o "mau desempenho na técnica inalatória" – avaliação da técnica inalatória. Qual o procedimento que o investigador irá utilizar para medir esta significativa diversidade de métodos? Dispõe o investigador de critérios específicos para a valorização destas técnicas que permitam uma leitura transversal dos resultados, independentemente do método utilizado?

6. A metodologia para o recrutamento de médicos não é perceptível nos documentos que nos foram referenciados.

5.- Interessaria explicitar a quem caberá a responsabilidade por contactar os doentes por telefone e quais serão os critérios de selecção dos doentes?

7.- A metodologia para a análise dos resultados não se encontra disponível nos documentos que nos foram enviados.seria de explicitar

Custos, Financiamento e Recursos Humanos

A estimativa de custos é um passo importante para a valorização de uma investigação.
Não é possível realizar um trabalho de investigação sem que se dispendam recursos humanos e materiais que representam um valor não só financeiro mas também um valor de investimento dos próprios investigadores e da sociedade, em geral. Estimar é, neste contexto, valorizar.
Estimar e explicitar custos na investigação clínica é portanto um imperativo ético e representa uma forma de dignificar o trabalho desenvolvido pelos investigadores.

Apreciação Ética

Respeito pela dignidade da pessoa humana
Autonomia
Modalidade de obtenção do consentimento informado
Não explicita
Salienta-se que a obtenção de um consentimento é um processo, não uma assinatura. Um processo em que se informam os potenciais participantes, oralmente ou através de um folheto informativo. Se permite que o participante potencial possa dispor de tempo para consultar os seus amigos, o seu médico de família, a sua família, sobre o estudo e as suas implicações. Findo este período de reflexão prevê-se então um novo encontro com o investigador para que esta possa esclarecer eventuais dúvidas do potencial participante e se assegure que o participante compreendeu na íntegra o interesse e as finalidades dos estudo e é capaz de deliberar sobre a sua participação de uma forma livre e esclarecida. É, exactamente após terem sido cumpridos todos estes passos que se considera que estarão reunidas todas as condições para que o potencial participante possa participar livre e esclarecidamente no estudo e confimar essa vontade através da sua assinatura no formulário de consentimento.
Nesta circunstância a folha de informação pelas razões que atrás expusemos não pode ser idêntica para o investigador e para o potencial participante.
Da folha de informação ao participante e do formulário de consentimento
A Folha de informação ao participante deve conter:
Um convite à participação
√ - As informações relativas aos objectivos do estudo;
√ - À sua metodologia,
√ - Duração Expectável do ensaio;
√ - à voluntariedade da participação e que a recusa ou a retirada do consentimento não terá prejuízo ou perda de benefícios;

√ - Ao tempo para decisão e à possibilidade de aconselhamento por outras pessoas;

√ -Aos procedimentos a serem seguidos, incluindo os procedimentos invasivos, consultas e seus detalhes;
√ - Aos benefícios expectáveis, ou se tais benefícios não são expectáveis;
√- Ao acesso aos dados pessoais e garantia de preservar a confidencialidade e a protecção dos dados pessoais mediante procedimento específico e afirmação de cumprimento da norma legal aplicável.
√ - Aos contactos para informação e emergência;
√ - Às circunstâncias em que um ensaio pode terminar;
√ - Número aproximado de indivíduos a serem envolvidos;
√ - O procedimento de consentimento deve ser obtido pelo investigador ou co-investigador;

Privacidade e Confidencialidade de Dados
Não é imediatamente perceptível a forma como será garantida a anonimização dos dados, o seu arquivo, armazenamento e destruição. Seria de clarificar.
Beneficência
Os potenciais benefícios do estudo face aos seus riscos permitem-nos afirmar que os potenciais benefícios poderão superar os riscos que este estudo desde que clarificadas as objecções propostas pela Comissão.
Justiça
No presente projecto de investigação não foram identificados problemas associados ao cumprimento do princípio da justiça nas suas duas dimensões, discriminação e exploração.
Não maleficência
Os riscos previsíveis de um estudo desta natureza poderão ser menores que os mínimos.

Cronograma: *presente (descrito)*

CV dos Investigadores: não presentes (unidades de saúde da ARSLVT)
Declaração dos Orientadores Pedagógicos : em falta
Declaração dos responsáveis das Unidades de saúde: em falta
Caderno de Recolha de Dados : em falta
Comissão Nacional de Protecção de Dados : em falta
Monitorização da investigação : Não prevista
Previsão de custos financeiros para os ACES: Não estimados
Divulgação dos resultados: Não explícitos
Propriedade dos dados: não explicita
Compromisso de entrega de relatório final : não explicito

Conclusão:
Trata-se de um estudo com potencial mérito científico e valor social.
Propomos o envio do presente parecer ao investigador.

3.11.2017
Relatores: João Ramires/ António Faria Vaz
Declaração de conflito de interesses: **Nada a declarar**

Data Protection Authority:

Autorização n.º 14256/ 2017

Tiago João Pais Maricoto notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de realizar um Estudo Clínico sem Intervenção, denominado Técnica inalatória em idosos com Asma e DPOC uma ferramenta preditiva de desempenho e risco clínico. .

A investigação é multicêntrica, decorrendo, em Portugal, nos centros de investigação identificados na notificação.

Existe justificação específica para o tratamento de dados comportamentais, psicológicos ou volitivos, os quais estão diretamente relacionados com a investigação.

O participante é identificado por um código especificamente criado para este estudo, constituído de modo a não permitir a imediata identificação do titular dos dados; designadamente, não são utilizados códigos que coincidam com os números de identificação, iniciais do nome, data de nascimento, número de telefone, ou resultem de uma composição simples desse tipo de dados. A chave da codificação só é conhecida do(s) investigador(es).

É recolhido o consentimento expresso do participante ou do seu representante legal.

A informação é recolhida diretamente do titular e indiretamente do processo clínico.

As eventuais transmissões de informação são efetuadas por referência ao código do participante, sendo, nessa medida, anónimas para o destinatário.

A CNPD já se pronunciou na Deliberação n.º 1704/2015 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios aplicáveis para o correto cumprimento da Lei n.º 67/98, de 26 de outubro, alterada pela Lei n.º 103/2015, de 24 de agosto, doravante LPD, bem como sobre as condições e limites aplicáveis ao tratamento de dados efetuados para a finalidade de investigação clínica.

No caso em apreço, o tratamento objeto da notificação enquadra-se no âmbito daquela deliberação e o responsável declara expressamente que cumpre os limites e condições aplicáveis por força da LPD e da Lei n.º 21/2014, de 16 de abril, alterada

pela Lei n.º 73/2015, de 27 de junho – Lei da Investigação Clínica –, explicitados na Deliberação n.º 1704/2015.

O fundamento de legitimidade é o consentimento do titular.

A informação tratada é recolhida de forma lícita, para finalidade determinada, explícita e legitima e não é excessiva – cf. alíneas a), b) e c) do n.º 1 do artigo 5.º da LPD.

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, da alínea a) do n.º 1 do artigo 28.º e do artigo 30.º da LPD, bem como do n.º 3 do artigo 1.º e do n.º 9 do artigo 16.º ambos da Lei de Investigação Clínica, com as condições e limites explicitados na Deliberação da CNPD n.º 1704/2015, que aqui se dão por reproduzidos, autoriza-se o presente tratamento de dados pessoais nos seguintes termos:

Responsável – Tiago João Pais Maricoto

Finalidade – Estudo Clínico sem Intervenção, denominado Técnica inalatória em idosos com Asma e DPOC uma ferramenta preditiva de desempenho e risco clínico.

Categoria de dados pessoais tratados – Código do participante; idade/data de nascimento; género; dados antropométricos; composição do agregado familiar sem identificação dos membros; dados da história clínica; dados de meios complementares de diagnóstico; medicação prévia concomitante; dados de qualidade de vida/efeitos psicológicos; relativos à atividade profissional com conexão com a Investigação; comportamentais, psicológicos ou volitivos com conexão com a Investigação; eventos adversos

Exercício do direito de acesso – Através dos investigadores, presencialmente/ por escrito

Comunicações, interconexões e fluxos transfronteiriços de dados pessoais identificáveis no destinatário – Não existem

Prazo máximo de conservação dos dados – A chave que produziu o código que permite a identificação indireta do titular dos dados deve ser eliminada 5 anos após o fim do estudo.

Da LPD e da Lei de Investigação Clínica, nos termos e condições fixados na presente Autorização e desenvolvidos na Deliberação da CNPD n.º 1704/2015, resultam obrigações que o responsável tem de cumprir. Destas deve dar conhecimento a todos os que intervenham no tratamento de dados pessoais.

Lisboa, 21-12-2017

A Presidente

Filipa Calvão

Permissions for the use of questionnaires:

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Pedido de autorização para uso de questionário validado para língua Portuguesa

Tiago Maricoto <tiago.maricoto@gmail.com> 5 de dezembro de 2017 às 15:02
Para: jaque_pfaria@hotmail.com

Exma. Dr. Jaqueline Petroni Faria Roxo

O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro em Portugal, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC. Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.

Uma dessas escalas é o questionário Asthma Control Test, cuja validação para a língua portuguesa foi elaborada por si.

Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.

Os melhores cumprimentos,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
Member of the Respiratory Group of APMGF (GRESP)
Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Re: Permission request to use a clinical control questionnaire in a PhD research

Paul Jones <pjones@sgul.ac.uk> 13 de dezembro de 2017 às 08:44
Para: Tiago Maricoto <tiago.maricoto@gmail.com>

Dear Tiago

You have my permission to use the SGRQ.

Kind regards

Paul

Paul Jones

Emeritus Professor of Respiratory Medicine

+44 20 8725 5372

St George's University of London

INSTITUTE FOR INFECTION & IMMUNITY

From: Tiago Maricoto <tiago.maricoto@gmail.com>
Date: Wednesday, 13 December 2017 at 08:06
To: Paul Jones <pjones@sgul.ac.uk>
Subject: Re: Permission request to use a clinical control questionnaire in a PhD research

> Hi Dr. Paul Jones,
>
> My name is Tiago Maricoto, I am a Family Doctor at USF Aveiro-Aradas, in the Aveiro Health Center, Portugal, and I am currently attending my PhD at the University of Beira Interior, Covilhã, Portugal.
>
> My thesis will focus the performance of inhaler technique in elderly patients with Asthma and COPD, and for the development of my main research, I will need to apply several questionnaires and scales of clinical control.
>
> One of these scales is the St. George's Respiratory Questionnaire for COPD control, whose validation for the Portuguese language was elaborated by you.

So, I came to ask you for permission to use it in my work.

Best regards,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
Member of the Respiratory Group of APMGF (GRESP)
Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Fwd: Pedido de autorização para uso do Moca versão portuguesa

Sandra Freitas <sandrafreitas0209@gmail.com> 19 de dezembro de 2017 às 18:22
Para: tiago.maricoto@gmail.com

Caro Tiago,

Em resposta ao seu pedido, junto envio a versão portuguesa da prova e do respetivo manual de administração e cotação.
Envio, ainda o estudo normativo que poderá ser útil no âmbito do seu projeto.
Ao dispor para qualquer esclarecimento necessário.
Votos de uma excelente investigação.

Com os melhores cumprimentos,

Sandra Freitas

Neuropsychology, PhD
Centre for Neuroscience and Cell Biology (CNC)
Centro de Investigação do Núcleo de Estudos e Intervenção Cognitivo Comportamental (CINEICC)
Psychological Assessment Lab., Faculty of Psychology and Educational Sciences
University of Coimbra, Portugal
E-mail: sandrafreitas0209@gmail.com

3 anexos

MoCA - Version 1.pdf
178K

Manual MoCA - Version 1.pdf
215K

2011_Freitas et al_MoCA - Normative study for the Portuguese population.pdf
167K

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Pedido de autorização para uso de questionário validado para língua Portuguesa

Tiago Maricoto <tiago.maricoto@gmail.com> 5 de dezembro de 2017 às 15:08
Para: cristinaneumann@via-rs.net

Exma Dra. Cristina Rolim Neumann

O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC. Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.

Uma dessas escalas é o questionário de Adesão terapêutica de Morisky-Green, cuja validação para a língua portuguesa foi elaborada por si.

Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.

Os melhores cumprimentos,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
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PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Pedido de autorização para uso de questionário validado para língua Portuguesa

Tiago Maricoto <tiago.maricoto@gmail.com> 5 de dezembro de 2017 às 15:05
Para: marquesa@med.up.pt

Exmo Prof. Agostinho Marques

O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC. Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.

Uma dessas escalas é o questionário Asthma Quality of Life, cuja validação para a língua portuguesa foi elaborada por si.

Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.

Os melhores cumprimentos,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
Member of the Respiratory Group of APMGF (GRESP)
Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Gmail Tiago Maricoto <tiago.maricoto@gmail.com>

Re: Permission request to use a clinical control questionnaire in a PhD research

João A Fonseca <fonseca.ja@gmail.com> 5 de dezembro de 2017 às 16:33
Para: Tiago Maricoto <tiago.maricoto@gmail.com>
Cc: CARAT network <info@caratnetwork.org>

Caro Tiago Maricoto,
Temos muito gosto que utilize o questionário CARAT nos seus trabalhos de Doutoramento. Conforme os termos de licenciamento do CARAT pedimos apenas que nos informe de publicações em que resultados do CARAT sejam apresentados.
Pessoalmente desejo-lhe que os seus trabalhos corram com o maior sucesso e estou ao dispor para algum esclarecimento ou opinião que entenda útil.
Cumprimentos,
Joao A Fonseca

CINTESIS - Centro de Investigação em Tecnologias e Sistemas de Informação em Saúde
MEDCIDS - Departamento Medicina da Comunidade, Informação e Decisão em Saúde da Faculdade de Medicina da Universidade do Porto
MEDIDA - Medicina, EDucação, I&D e Avaliação, Lda
http://orcid.org/0000-0002-0887-8796

On 5 December 2017 at 15:16, Tiago Maricoto <tiago.maricoto@gmail.com> wrote:
> Good morning,
>
> My name is Tiago Maricoto, I am a Family Doctor at USF Aveiro-Aradas, in the
> Aveiro Health Center, Portugal, and I am currently attending my PhD at the
> University of Beira Interior, Covilhã, Portugal.
> My thesis will focus the performance of inhaler technique in elderly
> patients with Asthma and COPD.
> For the development of my main research, I will need to apply several
> questionnaires and scales of clinical control.
>
> One of these scales is the CARAT for asthma control, whose validation for
> the Portuguese language was elaborated by your institution.
>
> So, I came to ask you for permission to use it in my work.
>
> Yours sincerely,
>
> Tiago Maricoto
> ---
> Tiago Maricoto M.D.
>
> Family Doctor
> USF Aveiro/Aradas, Aveiro Health Center - Portugal
> Tel: +351 234 891 213
> Member of Executive Board of the Portuguese Association of General and
> Family Medicine (APMGF)
> Member of the Respiratory Group of APMGF (GRESP)
> Assistant-Editor of the Portuguese Journal of General and Family Medicine
> (RPMGF)
> PhD Student in Faculty of Health Sciences - University of Beira Interior
> e-mail: tiago.maricoto@gmail.com
>
>
>
>
>

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

RES: Pedido de autorização para uso de questionário validado para língua Portuguesa

eanes@fortalnet.com.br <eanes@fortalnet.com.br> 5 de dezembro de 2017 às 17:53
Para: Tiago Maricoto <tiago.maricoto@gmail.com>

Caro Tiago Maricoto,

Uma vez que o CAT já teve sua tradução e validação publicados para o português , este pode ser utilizado em qualquer pesquisa na língua portuguesa.

Atenciosmante

Eanes Pereira

De: Tiago Maricoto [mailto:tiago.maricoto@gmail.com]
Enviada em: terça-feira, 5 de dezembro de 2017 12:04
Para: eanes@fortalnet.com.br
Assunto: Pedido de autorização para uso de questionário validado para língua Portuguesa

Exmo Dr. Eanes Delgado Barros Pereira

O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro em Portugal, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.

A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC.

Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.

Uma dessas escalas é o questionário COPD Assessment Tool, cuja validação para a língua portuguesa foi elaborada por si.

Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.

Os melhores cumprimentos,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
Member of the Respiratory Group of APMGF (GRESP)
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PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Re: Pedido de autorização para uso de questionário validado para língua Portuguesa

João Apostolo <apostolo@esenfc.pt> 5 de dezembro de 2017 às 16:12
Para: Tiago Maricoto <tiago.maricoto@gmail.com>

Caro DR Tiago Maricoto
Pode usar a GDS
Bom trabalho

João Apóstolo

Enviado do meu iPhone

No dia 05/12/2017, às 15:06, Tiago Maricoto <tiago.maricoto@gmail.com> escreveu:

> Exmo Dr. João Luís Alves Apóstolo
>
> O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
> A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC.
> Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.
>
> Uma dessas escalas é o questionário de Depressão Geriátrica, cuja validação para a língua portuguesa foi elaborada por si.
>
> Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.
>
> Os melhores cumprimentos,
>
> Tiago Maricoto
> ---
> Tiago Maricoto M.D.
>
> Family Doctor
> USF Aveiro/Aradas, Aveiro Health Center - Portugal
> Tel: +351 234 891 213
> Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
> Member of the Respiratory Group of APMGF (GRESP)
> Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
> PhD Student in Faculty of Health Sciences - University of Beira Interior
> e-mail: tiago.maricoto@gmail.com

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

Assunto: Pedido de autorização para uso de questionário validado para língua Portuguesa

Daniella Pires Nunes <dpiresnunes@yahoo.com.br> 7 de dezembro de 2017 às 12:40
Responder a: "dpiresnunes@yahoo.com.br" <dpiresnunes@yahoo.com.br>
Para: "tiago.maricoto@gmail.com" <tiago.maricoto@gmail.com>

Prezado Tiago,
Agradeço pelo contato e pelo interesse em utilizar a escala validada por nós.
Autorizo a utilização da escala e coloco-me a disposição para esclarecer quaisquer dúvidas.
Atenciosamente,

Enviado do Yahoo Mail no Android

Em Ter, 5 5e dez 5e 2017 às 12:11, Tiago Maricoto
<tiago.maricoto@gmail.com> escreveu:

> Exma Dra. Daniela Pires Nunes
>
> O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
> A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC.
> Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.
>
> Uma dessas escalas é a avaliação de Fragilidade do Idoso, cuja validação para a língua portuguesa foi elaborada por si.
>
> Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.
>
> Os melhores cumprimentos,
>
> Tiago Maricoto
> ---------- ----------
> Tiago Maricoto M.D.
>
> Family Doctor
> USF Aveiro/Aradas, Aveiro Health Center - Portugal
> Tel: +351 234 891 213
> Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
> Member of the Respiratory Group of APMGF (GRESP)
> Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
> PhD Student in Faculty of Health Sciences - University of Beira Interior
> e-mail: tiago.maricoto@gmail.c om

Gmail

Tiago Maricoto <tiago.maricoto@gmail.com>

RE: Pedido de autorização para uso de questionário validado para língua Portuguesa

Fabio Pitta <fabiopitta@uol.com.br> 13 de dezembro de 2017 às 13:15
Para: Tiago Maricoto <tiago.maricoto@gmail.com>

Prezado Thiago,

O periódico (que é quem de fato detem os direitos autorais do artigo) não tem imposto nenhuma limitação ao seu uso para fins "científicos". Portanto, para esse fim, pode seguir em frente.

Atenciosamente,

Fabio

De: "Tiago Maricoto" <tiago.maricoto@gmail.com>
Enviada: 2017/12/13 06:07:14
Para: fabiopitta@uol.com.br
Assunto: Re: Pedido de autorização para uso de questionário validado para língua Portuguesa

Exmo Dr. Fábio Pitta

O meu nome é Tiago Maricoto, sou Médico de Família na USF Aveiro-Aradas, no Centro de Saúde de Aveiro em Portugal, e estou de momento a realizar o meu doutoramento na Universidade da Beira Interior, na Covilhã.
A minha tese será sobre a performance do uso dos dispositivos inalatórios em doentes idosos com Asma e DPOC. Nesse sentido, para o desenvolvimento do meu estudo principal, irei necessitar de aplicar aos participantes diversas escalas de controlo clínico e avaliação.

Uma dessas escalas é o questionário mMRC, cuja validação para a língua portuguesa foi elaborada por si.

Venho assim solicitar-lhe autorização para poder usar o respectivo questionário no meu trabalho.

Os melhores cumprimentos,

Tiago Maricoto

Tiago Maricoto M.D.

Family Doctor
USF Aveiro/Aradas, Aveiro Health Center - Portugal
Tel: +351 234 891 213
Member of Executive Board of the Portuguese Association of General and Family Medicine (APMGF)
Member of the Respiratory Group of APMGF (GRESP)
Assistant-Editor of the Portuguese Journal of General and Family Medicine (RPMGF)
PhD Student in Faculty of Health Sciences - University of Beira Interior
e-mail: tiago.maricoto@gmail.com

Appendix III – Material used throughout the study on objectives three and four (informed consent form, questionnaires applied to participants and checklists for inhaler performance evaluation)

Informed consent form:

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Técnica inalatória em idosos com Asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico"

A sua unidade de saúde convidou-o a participar no estudo "Técnica inalatória em idosos com Asma e DPOC – uma ferramenta preditiva de desempenho e risco clínico.". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.
Os objectivos deste estudo são:

- Verificar se utiliza correctamente o seu dispositivo inalatório.
- Identificar os factores e características que estão associados à forma como usa o seu dispositivo e à forma como a sua doença está controlada.

Aceita fornecer os seus dados pessoais aos investigadores conforme solicitados nos questionários apresentados, e que pretendem comparar as diferentes características dos participantes entre si. O potencial benefício que vai gerar ao nos fornecer os seus dados é ajudar a investigação científica a melhorar o controlo clínico das doença respiratórias, melhorar a capacidade respiratória dos doentes e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde.
O estudo será conduzido na sua Unidade de Saúde com o investigador responsável abaixo-assinado e este será a única pessoa a ter acesso aos seus dados identificativos, ficando salvaguardado o anonimato dos seus dados para futuras publicações científicas.
Este estudo é isento de qualquer fonte de financiamento ou remuneração aos investigadores e é coordenado por uma equipa de investigadores, sendo o Dr. Tiago Maricoto (USF Aveiro-Aradas, Aveiro) o investigador principal e os restantes elementos o Dr. Luís Taborda Barata (Hospital Universitário Cova da Beira, Covilhã) e o Dr. Jaime Correia de Sousa (USF Horizonte, Matosinhos).

[Parte declarativa do profissional**]**
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante

Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente**]**

Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME:

|_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE

(se o menor tiver discernimento deve também assinar em cima)

NOME: .....

DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /...… /…....

GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....

ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio na Unidade Presente.

Questionnaires applied to participants:

ACT – asthma control test

1. Nas últimas **4 semanas**, por quanto tempo sua **asma** te atrapalhou na escola ou em casa?

O tempo todo	1	Muito tempo	2	Algumas vezes	3	Só um pouco	4	Nada	5

2. Nas últimas **4 semanas**, com que frequência você teve falta de ar ?

Mais de 1x por dia	1	1x p/ dia	2	3 a 6 vezes p/ semana	3	1 a 2 vezes p/ semana	4	Nada	5

3. Nas últimas **4 semanas**, quantas vezes sua **asma** te acordou à noite ?

4 ou mais p/ semana	1	2 ou 3 vezes p/ semana	2	1x por semana	3	1 ou 2 x por mês	4	Nada	5

4. Nas últimas **4 semanas**, quantas vezes você usou a "bombinha" para sair da crise ?

3 ou mais por dia	1	1 ou 2 vezes por dia	2	2 a 3 vezes p/ semana	3	1x p/ semana ou menos	4	Nada	5

5. Como você classificaria o controle da sua **asma** na últimas **4 semanas** ?

Fora de controle	1	Mal controlada	2	Parcialmente controlada	3	Bem controlada	4	Completamente sob controle	5

TOTAL

CARAT – control of allergic rhinitis and asthma test

CARAT

Teste de Controlo da Asma e Rinite Alérgica

Nas últimas 4 semanas, por causa da sua asma/rinite/alergia, em média, quantas vezes teve:

	Nunca	Até 1 ou 2 dias por semana	Mais de 2 dias por semana	Quase todos ou todos os dias
1. Nariz entupido ?	3	2	1	0
2. Espirros?	3	2	1	0
3. Comichão no nariz?	3	2	1	0
4. Corrimento/pingo do nariz?	3	2	1	0
5. Falta de ar/dispneia?	3	2	1	0
6. Chiadeira no peito/pieira?	3	2	1	0
7. Aperto no peito com esforço físico?	3	2	1	0
8. Cansaço/dificuldade em fazer as suas actividades ou tarefas do dia-a-dia?	3	2	1	0
9. Acordou durante a noite por causa da sua asma/rinite/alergia?	3	2	1	0

Nas últimas 4 semanas, por causa da sua asma/rinite/alergia, quantas vezes teve que:

	Não estou a tomar medicamentos	Nunca	Menos de 7 dias	7 ou mais dias
10. Aumentar a utilização dos seus medicamentos?	3	2	2	0

Pontuação total Pontuações superiores a 24 indicam bom controlo da doença.

Pontuação vias aéreas superiores (item 1-4): Controlado se pontuação for >8

Pontuação vias aéreas inferiores (item 5-10): Controlado se pontuação for >15

mMRC – dyspnea scale on COPD

Questionário para avaliação do grau de dispneia, adaptado da versão modificada do Medical Research Council Dyspnoea Questionnaire (mMRC)

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". ☐

CAT – COPD assessment tool

O seu nome: Data de hoje:

COPD Assessment Test™

Como está a sua DPOC (Doença Pulmonar Obstrutiva Crónica)? Faça o Teste de Avaliação da DPOC (COPD Assessment Test – CAT)

Este questionário irá ajudá-lo a si e ao seu profissional de saúde a medir o impacto que a DPOC (Doença Pulmonar Obstrutiva Crónica) está a ter no seu bem estar e no seu quotidiano. As suas respostas e a pontuação do teste podem ser utilizadas por si e pelo seu profissional de saúde para ajudar a melhorar a gestão da sua DPOC e a obter o máximo benefício do tratamento.

Por exemplo: Estou muito feliz	0 X 2 3 4 5	Estou muito triste	
Nunca tenho tosse	0 1 2 3 4 5	**Estou sempre a tossir**	PONTUAÇÃO
Não tenho nenhuma expectoração (catarro) no peito	0 1 2 3 4 5	**O meu peito está cheio de expectoração (catarro)**	
Não sinto nenhum aperto no peito	0 1 2 3 4 5	**Sinto um grande aperto no peito**	
Não sinto falta de ar ao subir uma ladeira ou um lance de escadas	0 1 2 3 4 5	**Quando subo uma ladeira ou um lance de escadas sinto bastante falta de ar**	
Não sinto nenhuma limitação nas minhas actividades em casa	0 1 2 3 4 5	**Sinto-me muito limitado nas minhas actividades em casa**	
Sinto-me confiante para sair de casa, apesar da minha doença pulmonar	0 1 2 3 4 5	**Não me sinto nada confiante para sair de casa, por causa da minha doença pulmonar**	
Durmo profundamente	0 1 2 3 4 5	**Não durmo profundamente devido à minha doença pulmonar**	
Tenho muita energia	0 1 2 3 4 5	**Não tenho nenhuma energia**	
		pontuação total	

AQLQ – quality of life on Asthma

QUESTIONÁRIO DE QUALIDADE DE VIDA NA ASMA-VERSÃO REDUZIDA (PORTUGUESE VERSION) PREENCHIDO PELO DOENTE

Por favor responda a todas as perguntas pondo um círculo à volta do número que melhor descreve como se tem sentido durante as duas úitimas semanas, por ter asma.

EM GERAL, QUANTO TEMPO, DURANTE AS 2 ÚLTIMAS SEMANAS:

	Sempre	Quase sempre	Bastante tempo	Algum tempo	Pouco tempo	Quase nunca	Nunca
1. Sentiu FALTA DE AR por causa da asma?	1	2	3	4	5	6	7
2. Se sentiu incomodado/a por, ou teve de evitar um ambiente com PÓ?	1	2	3	4	5	6	7
3. Teve um sentimento de FRUSTRAÇÃO, TRISTEZA OU REVOLTA por causa da asma?	1	2	3	4	5	6	7
4. Se sentiu incomodado/a por ter TOSSE?	1	2	3	4	5	6	7
5. Teve MEDO OU RECEIO DE NÃO TER À MÃO A MEDICAÇÃO PARA A ASMA?	1	2	3	4	5	6	7
6. Teve uma sensação de APERTO NO PEITO ou de PESO NO PEITO?	1	2	3	4	5	6	7
7. Se sentiu incomodado/a por, ou teve de evitar um ambiente com FUMO DE TABACO?	1	2	3	4	5	6	7
8. Teve DIFICULDADE EM DORMIR BEM DE NOITE por ter asma?	1	2	3	4	5	6	7
9. Se sentiu PREOCUPADO/A POR TER ASMA?	1	2	3	4	5	6	7
10. Sentiu PIEIRA ("GATINHOS") no peito?	1	2	3	4	5	6	7
11. Se sentiu incomodado/a por, ou teve de evitar sair por causa do TEMPO, DO CLIMA OU DA POLUIÇÃO DO AR?	1	2	3	4	5	6	7

ATÉ QUE PONTO É QUE SE SENTIU LIMITADO/A DURANTE AS 2 ÚLTIMAS SEMANAS AO DESEMPENHAR ESTAS ACTIVIDADES, POR TER ASMA?

	Completamente limitado/a	Extremamente limitado/a	Muito limitado/a	Moderadamente limitado/a	Pouco limitado/a	Muito pouco limitado/a	Nada limitado/a
12. ACTIVIDADES EXTENUANTES (tais como ter de se apressar, fazer ginástica, correr pela escada acima, praticar desporto)	1	2	3	4	5	6	7
13. ACTIVIDADES MODERADAS (tais como andar a pé, fazer o trabalho doméstico, tratar do jardim ou do quintal, ir às compras, subir escadas)	1	2	3	4	5	6	7
14. ACTIVIDADES SOCIAIS (tais como falar, brincar com crianças ou pegá-las ao colo, visitar amigos ou família)	1	2	3	4	5	6	7
15. ACTIVIDADES RELACIONADAS COM A SUA PROFISSÃO (tarefas que tem de desempenhar no seu trabalho*)	1	2	3	4	5	6	7

**Se não está empregado/a nem trabalha por conta própria, estas serão as tarefas que tem de desempenhar a maior parte dos dias*

CODIFICAÇÃO DE DOMÍNIOS:
Sintomas: 1, 4, 6, 8, 10
Limitação de actividade: 12, 13, 14, 15
Função emocional: 3, 5, 9
Estímulos do ambiente: 2, 7, 11

St. George – quality of life on COPD

PARTE 1

Estas perguntas exploram quais problemas respiratórios você teve ***durante os últimos 3 meses.***

Marque com um X somente uma resposta em cada pergunta.	Quase todos os dias da semana	Vários dias da semana	Poucos dias no mês	Só em caso de infecções respiratórias	Nunca
1. Durante os últimos 3 meses, tem tossido:	☐ (4)	☐ (3)	☐ (2)	☐ (1)	☐ (0)
2. Durante os últimos 3 meses, houve expectoração:	☐	☐	☐	☐	☐
3. Durante os últimos 3 meses, teve falta de ar:	☐	☐	☐	☐	☐
4. Durante os últimos 3 meses, teve crises de sibilos (chiados) no peito:	☐	☐	☐	☐	☐
5. Durante os últimos 3 meses, quantas vezes teve problemas respiratórios que foram graves ou muito desagradáveis?	Mais de 3 vezes ☐ (4)	3 vezes ☐ (3)	2 vezes ☐ (2)	1 vez ☐ (1)	Nenhuma vez ☐ (0)
6. Quanto tempo durou a pior das suas crises respiratórias? *(Passe à pergunta 7 caso i não tenha havido nenhuma crise grave)*	Uma semana ou mais ☐ (3)	3 dias ou mais ☐ (2)	1 ou 2 dias ☐ (1)	Menos de um dia ☐ (0)	
7. Durante os últimos 3 meses, em uma semana normal, quantos dias tem passado bem (com pouco problema respiratório)?	Nenhum dia bem ☐ (4)	1 ou 2 dias bem ☐ (3)	3 ou 4 dias bem ☐ (2)	Quase todos os dias estive bem ☐ (1)	Todos os dias estive bem ☐ (0)
8. Se seu peito chia, é pior pela manhã quando se levanta?	Não ☐ (0)	Sim ☐ (1)			

PARTE 2

Seção 1	*Como descreveria sua enfermidade respiratória? Marque com um X somente uma resposta*	É meu problema mais importante ☐ (3)	Causa muitos problemas ☐ (2)	Causa poucos problemas ☐ (1)	No me causa problema nenhum ☐ (0)
	Se alguma vez houve um trabalho remunerado, marque com um X uma das seguintes opções:	Meu problema respiratório me obrigou a deixar de trabalhar por completo ☐ (2)	Meu problema respiratório interfere (ou interferiu) no meu trabalho ou me fez trocar de emprego ☐ (1)	Meu problema respiratório não afeta (ou não afetou) meu trabalho ☐ (0)	

Seção 2 *Estas perguntas se relacionam com as atividades que atualmente lhe causam falta de ar. Para cada opção marque com um x verdadeiro ou falso, segundo seu caso.*

	Verdadeiro	Falso
Sentar-se quieto/a ou encostar-se quieto/a na cama	☐ (1)	☐ (0)
Durante higiene pessoal ou vestir-se	☐	☐
Caminhar pela casa	☐	☐
Caminhar fora da casa, em um terreno plano	☐	☐
Subir um lance de escadas	☐	☐
Subir por uma rampa	☐	☐
Fazer exercício ou praticar algum esporte	☐	☐

Seção 3 *Estas perguntas também têm a ver com sua tosse e a falta de ar que atualmente sofre. Para cada opção marque com um X verdadeiro o falso, segundo seu caso.*

	Verdadeiro	Falso
Dói ao tossir	☐ (1)	☐ (0)
Canso ao tossir	☐	☐
Falta o ar ao falar	☐	☐
Falta o ar ao me agachar	☐	☐
Minha tosse ou minha respiração me incomodam quando durmo	☐	☐
Canso facilmente	☐	☐

Seção 4 *Estas perguntas se relacionam com outros efeitos que seu problema respiratório pode estar lhe causando atualmente. Para cada opção marque com um X verdadeiro ou falso, segundo seja o caso:*

	Verdadeiro	Falso
Tenho vergonha de tossir ou da minha respiração quando estou com outras pessoas	☐ (1)	☐ (0)
Meu problema respiratório é um incomodo para minha família, amigos ou vizinhos	☐	☐
Assusto ou sinto pânico quando não posso respirar	☐	☐
Sinto que não posso controlar meu problema respiratório	☐	☐
Não creio que meus problemas respiratórios vão melhorar	☐	☐
Por causa de meu problema respiratório, me tornei uma pessoa frágil ou inválida.	☐	☐
Fazer exercícios é arriscado pra mim	☐	☐
Tudo o que faço me custa muito trabalho	☐	☐

Seção 5 *Estas perguntas se referem a sua medicação. Se você não toma nenhuma , passe diretamente à Seção 6.*
Para cada opção marque com um X verdadeiro o falso, segundo seu caso

	Verdadeiro	Falso
A medicação que tomo não me ajuda muito	☐ (1)	☐ (0)
Tenho vergonha tomar meus remédios diante de outras pessoas	☐	☐
Tenho efeitos secundários desagradáveis provocados pela medicação	☐	☐
A medicação que tomo interfere muito em minha vida	☐	☐

Seção 6 *Estas são perguntas sobre como suas atividades podem ser afetadas por sua respiração. Em cada pergunta marque com um X verdadeiro a opção de verdadeiro, se uma ou mais partes da pergunta se aplicam a você devido a seu problema respiratório, do contrário, marque-a como falsa.*

	Verdadeiro	Falso
	☐ (1)	☐ (0)
Levo muito tempo para higiene pessoal e para me vestir		
Não posso tomar banho ou levo muito tempo para faze-lo	☐	☐
Caminho mais lentamente que outras pessoas ou preciso parar para descansar	☐	☐
Levo muito tempo para terminar os afazeres domésticos ou preciso parar para descansar	☐	☐
Caso queira subir um andar pelas escadas, tenho que ir lentamente o parar para descansar	☐	☐
Se me apresso ou caminho mais rápido, tenho que diminuir a velocidade ou parar para descansar	☐	☐
Minha respiração, torna mais difícil subir ladeiras, escadas carregando coisas, regar as plantas, jogar bola, dançar com meus filhos.	☐	☐
Minha respiração, torna mais difícil carregar coisas pesadas, trabalhar no campo, caminhar rápido (8 km/h) ou jogar futebol	☐	☐
Minha respiração, torna difícil fazer trabalho manual muito pesado, correr, andar de bicicleta ou praticar esportes dinâmicos	☐	☐

Seção 7

Gostaríamos de saber de que forma seu problema respiratório afeta sua vida diária.
Por favor, marque com um X a opção de verdadeiro ou falso. (Lembre-se que deve marcar a opção verdadeiro somente nos casos em que sua respiração lhe impedir de realizar essa atividade)

	Verdadeiro	Falso
Não posso praticar esportes ou fazer exercícios	☐ (1)	☐ (0)
Não posso sair para me distrair ou para me divertir	☐	☐
Não posso sair de casa para fazer compras	☐	☐
Não posso fazer os serviços domésticos	☐	☐
Não posso me mover para longe da minha cama	☐	☐

Por último, marque com um X a opção que melhor descreve em que seu problema respiratório o afeta:	Não me impede de fazer nada do que eu gostaria de fazer	Impede-me de fazer uma ou duas coisas que gostaria de fazer	Impede-me de fazer a maioria das coisas que gostaria de fazer	Impede-me de fazer tudo que gostaria de fazer
	☐ (0)	☐ (1)	☐ (2)	☐ (3)

Adherence evaluation

ANEXO. Versão em português do instrumento Brief Medication Questionnaire.

1) Quais medicações que você usou na ÚLTIMA SEMANA?
Entrevistador: Para cada medicação anote as respostas no quadro abaixo:
Se o entrevistado não souber responder ou se recusar a responder coloque NR

NA ÚLTIMA SEMANA					
a) Nome da medicação e dosagem	b) Quantos dias você tomou esse remédio	c) Quantas vezes por dia você tomou esse remédio	d) Quantos comprimidos você tomou em cada vez	e) Quantas vezes você esqueceu de tomar algum comprimido	f) Como essa medicação funciona para você 1 = Funciona Bem 2 = Funciona Regular 3 = Não funciona bem

2) Alguma das suas medicações causa problemas para você? (0) Não (1) Sim
a) Se o entrevistado respondeu SIM, por favor, liste os nomes das medicações e quanto elas o incomodam

	Quanto essa medicação incomodou você?				
Medicação	Muito	Um pouco	Muito pouco	Nunca	De que forma você é incomodado por ela?

3) Agora, citarei uma lista de problemas que as pessoas, às vezes, têm com seus medicamentos.

Quanto é difícil para você:	Muito difícil	Um pouco difícil	Não muito difícil	Comentário (Qual medicamento)
Abrir ou fechar a embalagem				
Ler o que está escrito na embalagem				
Lembrar de tomar todo remédio				
Conseguir o medicamento				
Tomar tantos comprimidos ao mesmo tempo				

Escore de problemas encontrados pelo BMQ

DR – REGIME (questões 1a-1e)	1 = sim	0 = não
DR1. O R falhou em listar (espontaneamente) os medicamentos prescritos no relato inicial?	1	0
DR2. O R interrompeu a terapia devido ao atraso na dispensação da medicação ou outro motivo?	1	0
DR3. O R relatou alguma falha de dias ou de doses?	1	0
DR4. O R reduziu ou omitiu doses de algum medicamento?	1	0
DR5. O R tomou alguma dose extra ou medicação a mais do que o prescrito?	1	0
DR6. O R respondeu que "não sabia" a alguma das perguntas?	1	0
DR7. O R se recusou a responder a alguma das questões?	1	0
NOTA: ESCORE ≥ 1 INDICA POTENCIAL NÃO ADESÃO soma:		*Tregime*
CRENÇAS		
DC1. O R relatou "não funciona bem" ou "não sei" na resposta 1g?	1	0
DC2. O R nomeou as medicações que o incomodam?	1	0
NOTA: ESCORE ≥ 1 INDICA RASTREAMENTO POSITIVO PARA BARREIRAS DE CRENÇAS soma:		*Tcrencas*
RECORDAÇÃO		
DRE1. O R recebe um esquema de múltiplas doses de medicamentos (2 ou mais vezes/dia)?	1	0
DRE2. O R relata "muita dificuldade" ou "alguma dificuldade"em responder a 3c?	1	0
NOTA: ESCORE ≥ 1 INDICA ESCORE POSITIVO PARA BARREIRAS DE RECORDAÇÃO soma:		*Trecord*

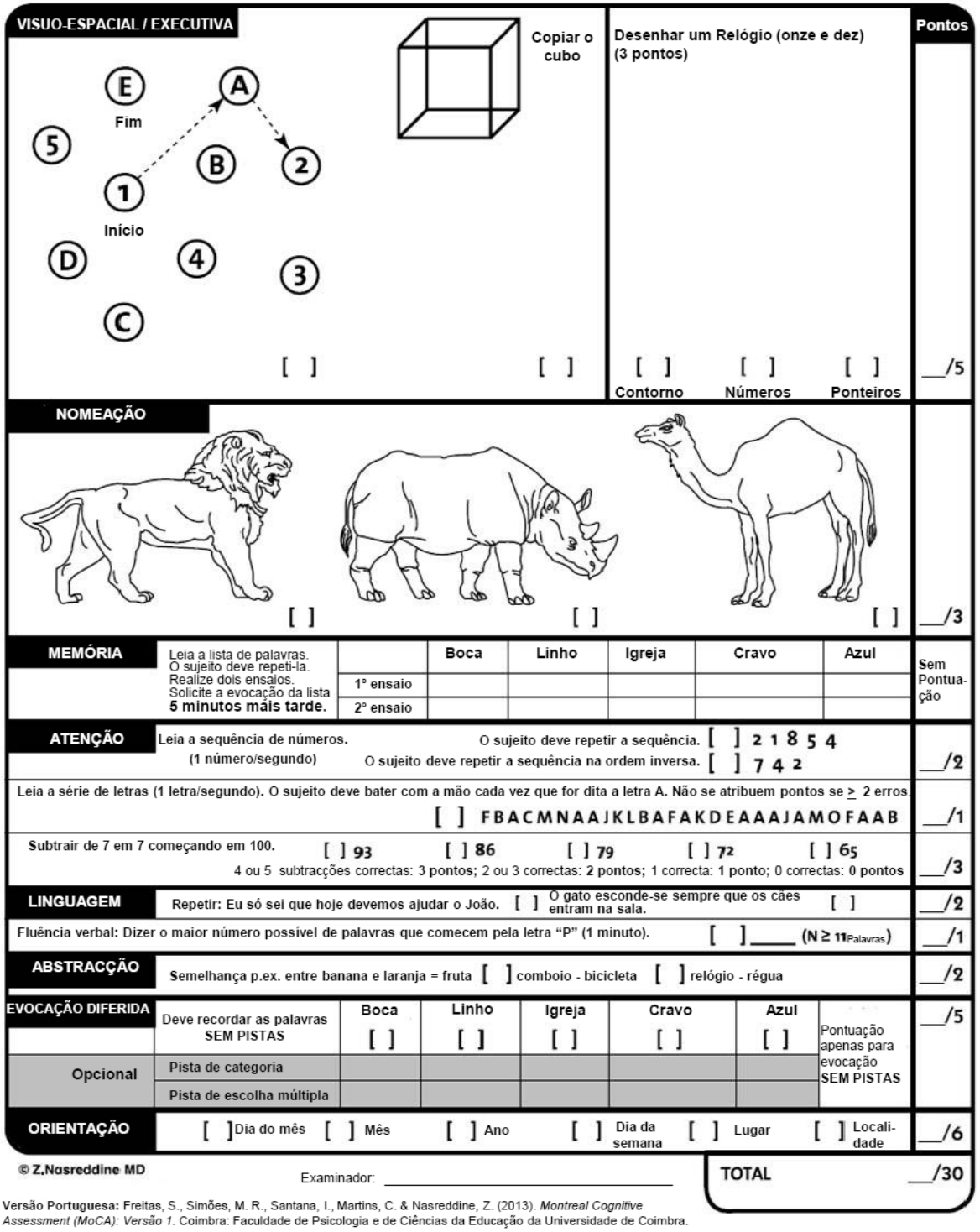
R = respondente NR = não respondente

MoCA cognitive assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)

VERSÃO PORTUGUESA – 7.1 VERSÃO ORIGINAL

Nome: _____ Idade: _____
Género: _____ Data de Nascimento: _____
Escolaridade: _____ Data de Avaliação: _____



Versão Portuguesa: Freitas, S., Simões, M. R., Santana, I., Martins, C. & Nasreddine, Z. (2013). *Montreal Cognitive Assessment (MoCA): Versão 1.* Coimbra: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra.

Geriatric depression scale

ESCALA DE DEPRESSÃO GERIÁTRICA - GDS

1. Está satisfeito (a) com sua vida? (não =1) (sim = 0)
2. Diminuiu a maior parte de suas atividades e interesses? (sim = 1) (não = 0)
3. Sente que a vida está vazia? (sim=1) (não = 0)
4. Aborrece-se com freqüência? (sim=1) (não = 0)
5. Sente-se de bem com a vida na maior parte do tempo? (não=1) (sim = 0)
6. Teme que algo ruim possa lhe acontecer? (sim=1) (não = 0)
7. Sente-se feliz a maior parte do tempo? (não=1) (sim = 0)
8. Sente-se freqüentemente desamparado (a)? (sim=1) (não = 0)
9. Prefere ficar em casa a sair e fazer coisas novas? (sim=1) (não = 0)
10. Acha que tem mais problemas de memória que a maioria? (sim=1) (não = 0)
11. Acha que é maravilhoso estar vivo agora? (não=1) (sim = 0)
12. Vale a pena viver como vive agora? (não=1) (sim = 0)
13. Sente-se cheio(a) de energia? (não=1) (sim = 0)
14. Acha que sua situação tem solução? (não=1) (sim = 0)
15. Acha que tem muita gente em situação melhor? (sim=1) (não = 0)

Avaliação:

0 = Quando a resposta for diferente do exemplo entre parênteses.
1= Quando a resposta for igual ao exemplo entre parênteses.
Total > 5 = suspeita de depressão

Yesavage JA, Brink TL Rose TL et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiat Res 1983;17:37-49.

Almeida OP, Almeida SA. Confiabilidade da versão brasileira da Escala de Depressão Geriátrica (GDS) versão reduzida. Arquivos de Neuro-Psiquiatria, 1999, 57(2)-B:421-426.

Paradela EMP, Lourenço RA, Veras RP. Validação da escala de depressão geriátria em um ambulatório geral. Revista de Saúde Pública, 2005, 39(6):918-923.

Tabela para apresentação dos resultados do GDS

DATA	RESPOSTA SIM	RESPOSTA NÃO	PONTUAÇÃO TOTAL	CLASSIFICAÇÃO

Fraily syndrome scale

Escala de rastreio de Fragilidade do Idoso

Componente da fragilidade	Perguntas e respostas
Perda de peso (Pontuava-se neste componente o idoso que referisse mais de 3 kg)	*Nos últimos 12 meses, o(a) sr.(a) perdeu peso sem fazer nenhuma dieta?* Sim, quantos quilos? Entre 1 kg e 3 kg Mais de 3 kg Não
Redução da força	*Nos últimos 12 meses (último ano), o(a) sr.(a) sente mais enfraquecido, acha que sua força diminuiu?* Sim Não
Redução da velocidade de caminhada	*O(A) sr.(a) acha que hoje está caminhando mais devagar do que caminhava há 12 meses (há um ano)?* Sim Não
Baixa atividade física	*O(A) sr.(a) acha que faz menos atividades físicas do que fazia há 12 meses (há um ano)?* Sim Não
Fadiga relatada (Pontuava-se neste componente o idoso que referisse "algumas vezes" ou "a maior parte do tempo" em pelo menos uma das perguntas)	*Com que frequência, na última semana, o(a) sr.(a) sentiu que não conseguiria levar adiante suas coisas (iniciava alguma coisa mas não conseguia terminar):* Nunca ou raramente (menos de 1 dia) Poucas vezes (1 - 2 dias) Algumas vezes (3 - 4 dias) A maior parte do tempo *Com que frequência, na última semana, a realização de suas atividades rotineiras exigiram do(a) sr.(a) um grande esforço para serem realizadas:* Nunca ou raramente (menos de 1 dia) Poucas vezes (1 - 2 dias) Algumas vezes (3 - 4 dias) A maior parte do tempo

Frágeis	Se pontuam para ≥3 componentes
Pré-Frágeis	Se pontuaram para 1 a 2 componentes
Não-Frágeis	Se não apresentaram nenhum dos componentes

Checklists for inhaler performance evaluation:

DISPOSITIVO PRESSURIZADO DE DOSE CALIBRADA (PMDI) SEM CÂMARA EXPANSORA (CE)

1. Retirar a tampa	
2. Agitar o inalador	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação lenta	
6. Ativar o inalador após iniciar a inalação	
7. Manter a inalação durante 5 segundos até encher os pulmões	
8. Manter a respiração suspensa o máximo tempo possível e confortável	
9. Recolocar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Não agitar o inalador	
• Inalar demasiado rápido	
• Ativar o inalador antes de iniciar a inalação (má coordenação)	
• Parar a inalação logo após a ativação do inalador (por efeito *coldfreon*)	

PMDI + CE EM INALAÇÃO ÚNICA

1. Retirar a tampa	
2. Agitar o inalador	
3. Inserir o dispositivo na câmara, na vertical e virado para cima	
4. Esvaziar completamente os pulmões com a boca fora do bucal	
5. Colocar os lábios em torno do bucal com os dentes afastados	
6. Ativar o inalador e iniciar uma inalação lenta	
7. Manter a inalação durante 5 segundos até encher os pulmões	
8. Manter a respiração suspensa o máximo tempo possível e confortável	
9. Retirar o inalador da câmara e recolocar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Não agitar o inalador	
• Inalar demasiado rápido	

pMDI + CE EM INALAÇÃO MÚLTIPLA

1. Retirar a tampa	
2. Agitar o inalador	
3. Inserir o dispositivo na câmara, na vertical e virado para cima	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar respiração em volume corrente	
6. Ativar o inalador	
7. Manter a respiração em volume corrente durante 10 segundos (2 a 3 ciclos)	
8. Retirar o inalador da câmara e recolocar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Não agitar o inalador	
• Inalar demasiado rápido	

QVAR AUTOHALER

1. Retirar a tampa	
2. Agitar o inalador	
3. Ativar o inalador, levantando a patilha superior	
4. Esvaziar completamente os pulmões com a boca fora do bucal	
5. Colocar os lábios em torno do bucal com os dentes afastados	
6. Iniciar uma inalação lenta e continuar após ouvir um "*click*"	
7. Manter a inalação durante 5 segundos até encher os pulmões	
8. Manter a respiração suspensa o máximo tempo possível e confortável	
9. Recolocar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Não agitar o inalador	
• Inalar demasiado rápido	
• Parar a inalação logo após ouvir o "*click*"	
• Parar a inalação logo após a libertação do fármaco (efeito *coldfreon*)	

RESPIMAT- SMI (NÉVOA SUAVE)

1. Segurar o inalador na vertical com a tampa fechada	
2. Rodar a base até ouvir um "*click*" para activar a dose	
3. Abrir a tampa	
4. Esvaziar completamente os pulmões com a boca fora do bucal	
5. Colocar os lábios em torno do bucal com os dentes afastados	
6. Iniciar uma inalação lenta	
7. Ativar o inalador após iniciar a inalação	
8. Manter a inalação durante 5 segundos até encher os pulmões	
9. Manter a respiração suspensa o máximo tempo possível e confortável	
10. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Não ativar o inalador (rodando a base)	
• Inalar demasiado rápido	
• Ativar o inalador antes de iniciar a inalação (má coordenação)	
• Parar a inalação logo após a ativação do inalador (por efeito similar ao *coldfreon*)	

TURBOHALER

1. Abrir a tampa	
2. Ativar o inalador na vertical rodando a base para a frente e para trás	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Ativar o inalador na posição horizontal	
• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	

DISKUS / ACCUHALER

1. Abrir a tampa	
2. Ativar o inalador clicando na patilha até ao fim	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	
• Clicar na patilha de ativação para a frente e para trás varias vezes seguidas	
• Parar a inalação ao sentir o fármaco ser libertado	

AEROLIZER / HANDIHALER / BREEZHALER

1. Abrir a tampa	
2. Colocar a cápsula no compartimento interno	
3. Perfurar a cápsula clicando no botão, com o inalador na posição vertical	
4. Esvaziar completamente os pulmões com a boca fora do bucal	
5. Colocar os lábios em torno do bucal com os dentes afastados	
6. Iniciar uma inalação rápida e profunda até encher os pulmões	
7. Manter a respiração suspensa o máximo tempo possível e confortável	
8. Verificar se a cápsula está vazia. Se não estiver, repetir 4 a 7.	
9. Retirar a cápsula e fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Ingerir a cápsula	
• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	
• Premir o botão que perfura a cápsula durante a inalação (a cápsula fica imóvel)	
• Parar a inalação ao sentir o fármaco ser libertado	

SPIROMAX

1. Segure o inalador na vertical com a tampa para baixo	
2. Abrir a tampa até ouvir um "*click*"	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Retirar a cápsula e fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	
• Parar a inalação ao sentir o fármaco ser libertado	

TWISTHALER

1. Abrir a tampa com o inalador na vertical	
2. Esvaziar completamente os pulmões com a boca fora do bucal	
3. Colocar os lábios em torno do bucal com os dentes afastados	
4. Iniciar uma inalação rápida e profunda até encher os pulmões	
5. Manter a respiração suspensa o máximo tempo possível e confortável	
6. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	

EASYHALER

1. Abrir a tampa	
2. Ativar o inalador pressionando o botão superior, na posição vertical	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	
• Agitar ou virar o inalador ao contrário depois de ativar a dose	

NOVOLIZER / GENUAIR

1. Abrir a tampa	
2. Pressionar e libertar o botão superior até ouvir "*click*" par activar o inalador (a janela deve ficar verde)	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Confirmar que a janela passa da cor verde para vermelho	
8. Fechar a tampa	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	
• Parar de inalar ao ouvir o "*click*" inicial da libertação do fármaco	

BUDESONIDO DA *FARMOZ*®

1. Retirar a tampa branca do inalador.	
2. Pressionar a tampa castanha para ativar, com o bocal virado para baixo	
3. Esvaziar completamente os pulmões com a boca fora do bucal	
4. Colocar os lábios em torno do bucal com os dentes afastados	
5. Iniciar uma inalação rápida e profunda até encher os pulmões	
6. Manter a respiração suspensa o máximo tempo possível e confortável	
7. Fechar a tampa rodando-a no sentido dos ponteiros do relógio	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	

ELLIPTA

1. Abrir a tampa do inalador deslizando-a até ouvir um "*click*".	
2. Esvaziar completamente os pulmões com a boca fora do bucal	
3. Colocar os lábios em torno do bucal com os dentes afastados	
4. Iniciar uma inalação rápida e profunda até encher os pulmões	
5. Manter a respiração suspensa o máximo tempo possível e confortável	
6. Fechar a tampa deslizando-a no sentido oposto.	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	

FORSPIRO

1. Abrir a tampa do inalador	
2. Ativar a dose levantando a extremidade da alavanca branca e rodando-a até ouvir um "*click*"	
3. Feche a alavanca branca, rodando-a para a sua posição original, até se ouvir novamente outro "*click*"	
4. Esvaziar completamente os pulmões com a boca fora do bucal	
5. Colocar os lábios em torno do bucal com os dentes afastados	
6. Iniciar uma inalação rápida e profunda até encher os pulmões	
7. Manter a respiração suspensa o máximo tempo possível e confortável	
8. Fechar a tampa do inalador.	

Erros mais frequentes (assinalar se estiverem presentes):

• Soprar para dentro do inalador	

Appendix IV – Published article and supplementary material of objective one:

"Inhaler technique education and exacerbation risk in older adults with Asthma or COPD: a Meta-analysis":

CLINICAL INVESTIGATIONS

Inhaler Technique Education and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease: A Meta-Analysis

Tiago Maricoto, MD,[*†] *Luís Monteiro, MD,*[†‡] *Jorge M.R. Gama, PhD,*[§] *Jaime Correia-de-Sousa, MD,*[¶‖] *and Luís Taborda-Barata, MD*[**†††‡‡]

OBJECTIVES: To evaluate the effect of inhaler education programs on clinical outcomes and exacerbation rates in older adults with asthma or chronic obstructive pulmonary disease (COPD).

DESIGN: Systematic review and meta-analysis.

SETTING AND PARTICIPANTS: Older adults with asthma or COPD, either in primary or secondary health care and pharmacy setting.

MEASUREMENTS: We searched the Medline, Embase, and Central databases according to the main eligibility criteria for inclusion: systematic reviews, meta-analysis, clinical trials and quasi-experimental studies; participants aged 65 and older; education on inhaler technique and reporting of disease control and exacerbation rates. We used the Grading of Recommendations, Assessment, Development and Evaluations scale for quality assessment and used a random-effect model with Mantel–Haenszel adjustment to perform a meta-analysis.

RESULTS: We included 8 studies (4 randomized, 4 quasi-experimental) with a total of 1,812 participants. The most frequent type of intervention was physical demonstration of inhaler technique, training with placebo devices. Five studies showed significant reduction in exacerbation rates (pooled risk ratio=0.71, 95% confidence interval=0.59–0.86; $p < .001$), although effect on disease control and quality of life showed high discrepancy in the reported results, and all randomized studies revealed uncertainty in their risk of bias assessment.

CONCLUSION: All interventions seemed to improve inhaler performance and clinically relevant outcomes, but a placebo device could be the most effective. There is evidence that interventions reduce exacerbation risk in older adults, although to an overall moderate degree. **J Am Geriatr Soc 00:1–10, 2018.**

Key words: asthma; chronic obstructive pulmonary disease; inhalers

Asthma and chronic obstructive pulmonary disease (COPD) affect up to 10% of the population, and many individuals with these conditions have uncontrolled symptoms.[1] They experience frequent exacerbations, some of which can be life threatening. Up to 53% of community-treated individuals may experience exacerbations, and good adherence to therapy is associated with reductions in exacerbations in half of cases.[2–4] Inhaled therapy is the most widely used treatment, but up to 90% of individuals used incorrect technique in clinical studies,[5] partly because the extensive variety of inhalers and their technical specifications create significant barriers to understanding of proper use.[6] Although all available inhalers may be equally efficient when properly used,[7] there are various device- and person-related factors that may significantly influence performance.[8–11] Poor inhaler technique is associated with worse symptom control[12,13] and leads to greater healthcare resource consumption and costs.[14]

Some studies have showed that teaching inhaler technique may lower the risk of exacerbations and death in these individuals,[2,3,15–17] but the effect of teaching decreases with time, indicating the importance of regular reassessment.[9,18,19] There are many tools for teaching inhaler technique,[20] and two systematic reviews have addressed this. One concluded

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0002-8614/18/$15.00

that there is lack of evidence about which is the best education method to improve inhaler technique.[21] The other concluded that there is sufficient evidence of the efficacy of different inhaler educational strategies, but the authors did not quantify this effect with precision because it did not include a meta-analysis.[22] In addition, neither review focused on older adults.

Inhaler technique performance is regarded as particularly complex in older adults with asthma or COPD, who also tend to have lower inhaler adherence rates.[19,23,24] These individuals find it more difficult than younger adults to use the devices correctly, with several characteristics seeming to hamper them, such as cognitive impairment, low education level, osteoarthritis, and global frailty.[23,25–28] For such reasons, and because these conditions are frequently underdiagnosed, elderly adults are more susceptible to disease consequences and exacerbations[29,30] and are frequently excluded from clinical trials of education programs. Thus, there is a lack of evidence regarding the real effect that educational interventions have in these individuals. Our systematic review and meta-analysis assessed whether there is evidence that inhaler technique education in older adults with asthma or COPD improves clinical control and reduces disease exacerbations. We also analyzed which is the best method for teaching inhaler technique and how often it should be taught.

METHODS

Eligibility Criteria

Search Criteria Following a Population, Intervention, Comparator, Outcomes Format

Participants

We selected studies that included (not exclusively) participants aged 65 and older with asthma or COPD. In studies aggregating adults and older adults, we used the average age to decide on inclusion. Studies with mean age between 60 and 65 were included in preliminary analyses to assess their magnitude of influence on our major results and conclusions and were included in detailed analysis if considered highly relevant.

Intervention

We defined as the main criteria interventions that focus on teaching inhalation technique and, provided by health professionals and directed to patients or their caregivers, whatever method used (e.g., oral instructions and physical demonstration with placebo device, text-based print resources, media, educational tools (e.g., turbutest, InCheckDial), e-health interventions, combinations thereof). We included studies involving hospital staff (e.g., clinicians, nurses), pharmacists, general practitioners, community health workers, and others as providers.

Comparator

Different methods were compared with one another or placebo or usual care (treatment provided in a real-world scenario, according to local guidelines or healthcare provider judgments).

Outcomes

We included studies that addressed any of the following outcomes: inhaler performance evaluation (change from baseline scores preferred); all-cause hospitalization or all-cause mortality; exacerbation rate or loss of control; clinical control (preferably measured on a validated scale); quality of life (preferably measured on a validated scale); functional control (e.g., as change from baseline scores in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow (PEF))

Types of studies

We searched systematic reviews, meta-analyses, randomized controlled trials (RCTs), nonrandomized clinical trials, and quasi-experimental studies. We included quasi-randomized studies because of the lack of RCTs to reinforce the quality of our review and confidence in our findings.

Search Methods

We used the EMBASE, CENTRAL, and MEDLINE databases as primary sources and reference lists from studies included in primary sources and those found by author review and expert opinion as secondary sources. We also screened the main trial registry databases, such as the U.S. National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trial search).

We used the Medical Subject Heading terms "nebulizers and vaporizers," "asthma," and "pulmonary disease, chronic obstructive," with a time limit for publication of March 2017.

Overall, we intended to reproduce the same search strategy of previous systematic reviews that addressed the same questions (see detailed search strategies in Supplementary Appendix S1).

Selection Process

Two independent, blinded authors (TM, LM) selected the articles according to the defined criteria and applied the following filter stages: cleaning of duplicated articles, selection of articles according to eligibility criteria and by reading the title and abstract, and selection of articles according to full-text reading.

Reasons for article rejection are expressed in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram[31] (Figure 1). All disagreements, at every stage, including selection of studies, quality assessment, and data extraction, were resolved through discussion or by a third review author (LT-B).

Data Collection Process

Two authors (TM, LM) collected data from selected articles in their original presentation and noted them in a spreadsheet. We also collected indirect data from figures and

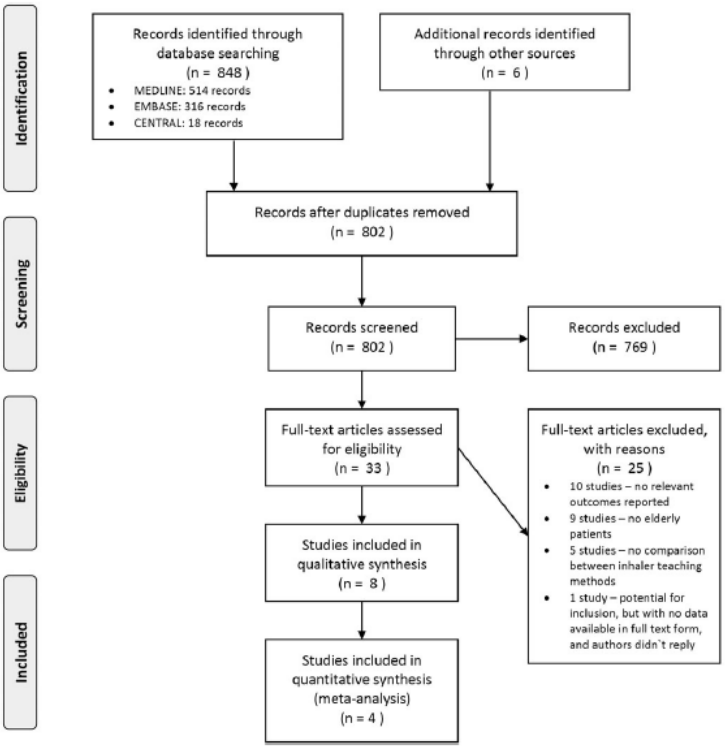

Figure 1. Flow diagram on search and article inclusion, according to Preferred Reporting Items for Systematic Reviews and Meta-Analysesstatement.[31]

charts, adapting their interpretation by consensus, and authors of original articles were contacted for further information and data.

Type of Data Collected

Two authors (TM, LM) collected the following information.

General data: Year, study type, number of participants, age, sex, follow-up time, withdrawals, diagnosis, disease severity, type of intervention, study location, time between interventions, type of intervention provider, adverse events and outcomes reported.

Outcomes: Inhaler performance, adherence rate, clinical control, quality of life (in any type of validated scale) and functional control (FEV_1%; FVC%, PEF%, FEV_1/FVC ratio) (in median, range, 95% confidence interval (CI), standard deviation, standard error, or any index of percentage of change) and exacerbation rate, hospitalization, and mortality (in odds ratio, risk ratio (RR), hazard rate, number needed to treat, and their respective 95% CIs).

One author (TM) inserted data into software for preparing and maintaining Cochrane Reviews (Review Manager (RevMan), http://community.cochrane.org), and data were double-checked for correct entry.

Analysis of Results and Assessment of the Risk of Bias

Two authors (TM, LM) analyzed the data according to risk of bias using a qualitative approach. Quality of evidence for the collected outcomes of interest and recommendation for the interventions were assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system, as reported in the Cochrane Handbook for Systematic Reviews of Interventions.[32] Two other authors (LT-B or JCS) confirmed this assessment.

Risk of bias was assessed in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases.

Risk of bias in each study was graded as high, low, or uncertain and justifications for such judgment were reported in the "Risk of bias" table [Supplementary Appendix S2].

Publication bias was analyzed using a funnel plot.

Measures of Treatment Effect

Two authors (TM, JG) quantitatively analyzed RCTs to determine effect estimations, heterogeneity, and consistency

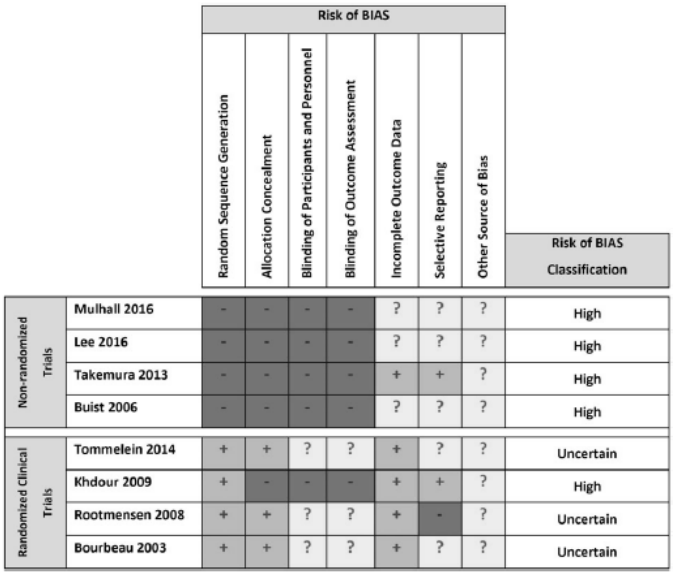

Figure 2. Risk of bias assessment in included studies according to Grading of Recommendations, Assessment, Development and Evaluations tool and recommended by Cochrane.[32]

tests. We used Mantel-Haenzsel RRs with 95% CIs using a random-effects model for dichotomous data. Continuous outcomes were analyzed as standardized mean differences with 95% CIs using a random-effects model, because the included studies used different measurement instruments. We used meta-analysis only for RCTs. Heterogeneity between effect sizes of included studies was assessed using visual inspection of forest plots and the chi-square test for heterogeneity (with P<.10), and inconsistency between trials was described according to percentage of variability in effect estimates due to heterogeneity rather than chance (I^2). We also performed sensitivity analyses of the included studies and their effect on the meta-analysis. Results of the primary outcome, exacerbation risk reduction, with trial sequential analysis were also presented using the O'Brien Fleming monitoring boundaries approach. This was performed considering the results pooled in meta-analysis to exclude false-positive or false-negative results from our review.[33]

No subgroup analysis was planned because of the small number of studies. Quantitative analyses were not performed in quasirandomized studies because of their high risk of bias.

All statistical procedures were performed using RevMan, GRADEPro online (https://gradepro.org/), and trial sequential analysis software provided by the Copenhagen Trial Unit (http://www.ctu.dk).

RESULTS

Description of Studies

Our search yielded 854 articles (Figure 1). From the 802 unique articles, eight studies met the inclusion criteria and were analyzed. Most studies were excluded because they did not address inhaler education in elderly adults or because no relevant outcomes were used. One study presented potential criteria for inclusion in its abstract, but no data from outcomes were available in full-text format, so it was excluded.[34] One included study evaluated quality of life, but those results were not published in the article.[35] Authors of these publications were contacted but did not reply.

Of the eight studies included, four had a randomized design,[16,35–37] and the remaining four had a quasi-randomized pre- and post-intervention design[17,38–40] (details in Supplementary Appendix S3).

1812 participants were evaluated. Five studies addressed only COPD, one addressed asthma, and two addressed both. Five studies were performed in secondary health care facilities, two at community pharmacies and one at primary health care centers. A pharmacist performed the educational intervention in half of the studies and a nurse or a doctor in the other half. Follow-up varied from 1 month to 2 years, and half of the studies had at least 1 year of follow-up. The mean age of participants was slightly greater than 65 in six of the studies and younger than 65 in the other two. We decided to include them to reinforce the quality of our review and confidence in our findings because the search strategy yielded few studies. Also, these two studies had large sample sizes[39] and reported exacerbation risk as an outcome.[35]

Educational interventions varied between studies. Three studies examined a physical demonstration with placebo devices, which was the most frequent type of intervention, covering more than half of the total amount of participants. Two studies used video demonstration, and another two

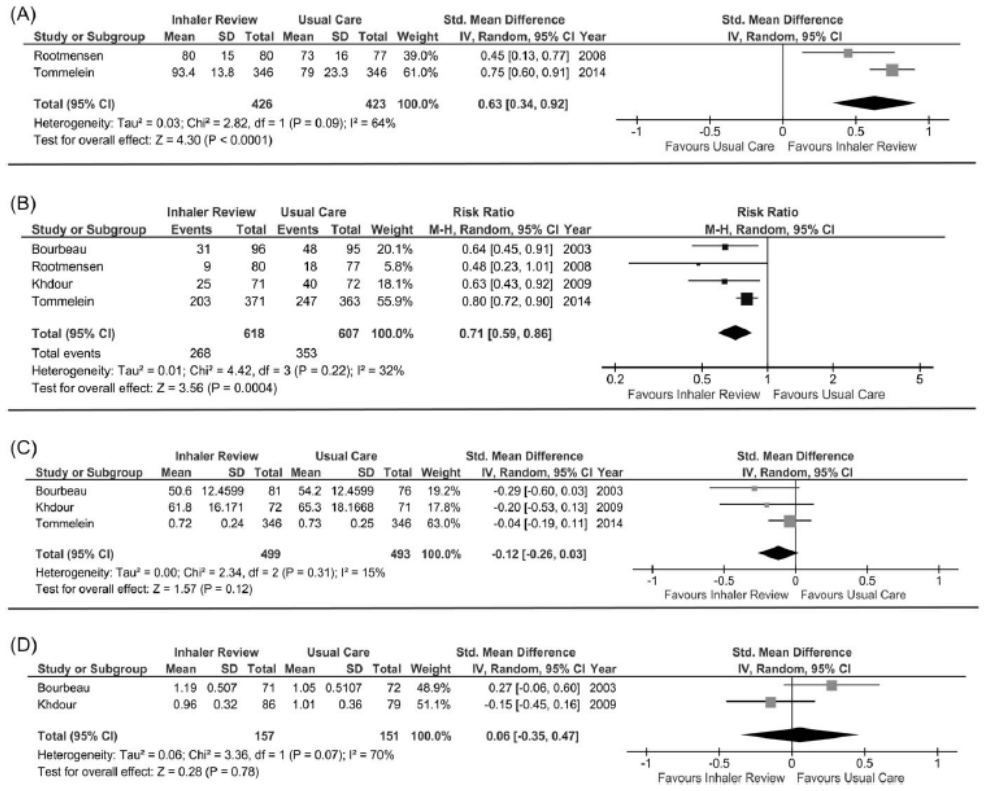

Figure 3. Meta-analysis. (a) Inhaler performance. Tommelein et al.[ref. 16] measured the global % of correct steps. Rootmensen et al.[ref. 35] measured the global score of correct performance; (b) Exacerbation Rate. (c) Quality of Life. Tommelein et al.[ref. 16] used ED-5D scale. Khdour et al.[ref. 36] and Bourbeau et al.[ref. 37] used St. George questionaire. (d) Respiratory function (change in forced expiratory volume in 1 second).

studies delivered written information. One study did not specify inhaler education type,[35] and another one was unclear.[17]

Quality of life and exacerbations were the most commonly reported main outcomes (six studies), but different instruments and scales were used.[16,17,35–37,40] Similar limitations occurred with clinical and functional control, adherence rate, and inhaler performance evaluation. Cost-effectiveness was never reported.

Most studies examined several aspects of intervention in addition to inhaler technique education: self-management plans, disease knowledge, and management of exacerbations and their triggers. Only two studies included a repeated education program, providing intervention every 6 months.[17,40] All the other studies provided the intervention only at baseline.

Risk of Bias in Included Studies

Two independent reviewers (TM, LM) evaluated risk of bias of the included studies, reaching consensus in all evaluations (Figure 2). Nonrandomized trials were classified as being at high risk of bias in the main parameters, such as random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. In our review, RCTs showed an overal uncertainty in their risk assessment, although most of them had good blinding on random sequence generation and allocation concealment. The main limitation of RCTs was lack of blinding of the intervention and outcome assessment (detailed evaluation in Supplementary Appendix S2).

Logistic regression tests were used to determine whether there was a statistically significant relationship between lower risk of bias and magnitude of effect in the main reported outcomes. To build the model, we set all variables as binary: risk of bias (0 = high, 1 = uncertain) and inhaler performance, adherence rate, symptom control, respiratory function, quality of life, and exacerbation rate (0 = negative outcome, 1 = positive outcome). None of these outcome variables was statistically associated with risk of bias of included studies.

Table 1. Summary of Findings of Intervention Effect on Clinical and Relevant Outcomes: Inhaler Technique Education Programs on Clinical Control and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease (COPD)

Outcome	Participants, n	Randomized Controlled Trials, n	Risk Ratio (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty	Comments
				Without Inhaler Education Programs	With Inhaler Education Programs	Difference		
Exacerbation rate	1,225	4	0.71 (0.59–0.86)	58.2%	41.3% (34.3–50.0)	16.9% fewer (23.8 fewer to 8.1 fewer)	⊕⊕⊕◯ Moderate[1,2,3]	
Quality of life	992	3	-	-	-	SMD 0.12 SD lower (0.26 lower to 0.03 higher)	⊕⊕◯◯ Low[1,2,3,4]	Longer follow-up seems to be associated with positive effect
Functional control (FEV1)	308	2	-	-	-	SMD 0.06 SD higher (0.35 lower to 0.47 higher)	⊕⊕◯◯ Low[1,2,3,4]	
Inhaler technique performance	849	2	-	-	-	SMD 0.63 SD higher (0.34 higher to 0.92 higher)	⊕⊕⊕◯ Moderate[2,3]	Different tools to teach inhaler performance used; one study did not specify the tool used

Population: older adults with asthma or COPD. Setting: pharmacy and secondary health care. Intervention: inhaler education programs. Comparison: usual care. The risk in the intervention group (and its 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

SMD=standardized mean difference; SD=standard deviation.

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]Most studies did not blind participants to interventions, exposing them to the Hawthorn effect.

[2]None of the included studies addressed inhaler technique education alone.

[3]Studies with smaller sample sizes had wide CIs on the estimated parameter.

[4]Included studies with divergent results on the estimated parameter.

Effects of Interventions

Table 1 shows the main findings of clinical and relevant outcomes from selected studies, and Figure 3 shows the results of the meta-analysis.

Inhaler Performance

Only half of the studies measured the effect of the intervention on inhaler performance, and all[16,38,40] except one[35] showed improvement. That one study did not specify the type of tool used to teach inhaler technique, and it may not have been the primary objective of the intervention. Authors were contacted but did not reply. Although significant differences were not found after the intervention, when results were pooled in a meta-analysis together with a RCT,[16] they showed a significant effect on inhaler performance. Nevertheless, heterogeneity was high, probably because different measures of inhaler performance were used. Also, the one study[35] found a significant reduction in exacerbation rate at the end of follow up, which could be due to the additional topics covered in the intervention, especially disease self-management skills.

Exacerbation Rate

All RCTs resulted in a significant reduction in exacerbation rates, in the intervention group, and comparing with usual care group.[16,35–37] The reported mean RR on these studies varied from 0.45 to 0.82, with wide CIs and favouring the intervention group. Pooling these results in a meta-analysis, we found a significant mean reduction of almost 30% in exacerbation rates favouring the intervention. (RR=0.71, 95% CI=0.59–0.86) and a significant low heterogeneity index. In addition, sensitivity analysis showed that removing any of the included studies did not affect the outcome. Also, trial sequential analysis (Supplementary Appendix S4) confirmed our confidence in these findings, excluding the risk of a false-positive result, because significant boundaries and the necessary sample size were achieved.

One quasirandomized study had the same results, with relative reduction in exacerbation rates of almost 50%.[17] One study did not show any differences.[40] This was a randomized study, comparing the use of a peak flow meter with symptom monitoring as a basis for disease control, and used physical demonstration with placebo devices in all participants, repeated every 6 months and provided by a clinician. It had a large sample size (396 participants) and 24 months of follow-up and participants had predominantly moderate to severe asthma. The authors did not find a reduction in global exacerbation rate, which could be because this study included only individuals with asthma, whereas participants in the other studies had COPD or both.

Disease Control

All studies evaluated the effect of intervention on several aspects of disease control, mainly on quality of life and symptoms. A although the results were highly discrepant because half of the studies found improvement in these outcomes[36,37,39,40], whereas the other half did not[16,17,35,38]. Meta-analysis including only RCTs did not find significant improvement in quality of life, although a sensitivity analysis including only the two studies that used the St. George's Respiratory Questionnaire[36,38] showed an improvement of 3.57 points in mean score (95% CI=0.36–6.78). No relevant characteristics seemed to differentiate the studies with regard to these findings, but detailed analysis of the RCTs showed that longer follow-up was associated with a more significant positive effect on quality of life.[36,38] Nevertheless, the magnitude of these effects was small, and with wide CIs, and was associated with overall moderate strength of evidence.

Respiratory Function

Half of the studies evaluated effect on FEV_1, but only one showed a significant benefit of the intervention.[40] In this study, inhaler education was not the primary objective, and all participants received a thorough disease self-management program, with several intervention aspects in addition to inhaler education. The magnitude of the observed effect was small, with a wide CI. Quantitative analysis did not show any significant benefit either.

Adherence

Three studies evaluated the effect on adherence to inhaled medication, and all showed significant improvement after the intervention.[16,17,36] This effect may also be due to the Hawthorne effect. Only two of the RCTs evaluated this outcome, but they used different scales, and one did not report useful results for quantitative analysis.

Education Frequency

Only two studies included a repeated education program, which was mainly on a biannual basis.[17,40] Both were nonrandomized and reported divergent results in the main outcomes. Thus, we could not perform a quantitative or sensitivity analysis on them, which limits any kind of conclusion about how often inhaler review and education should be recommended.

DISCUSSION

Summary of Main Results

The main finding of our review is that inhaler technique education can significantly reduce exacerbation risk; this is reinforced by a significant pooled result with a low index of statistical heterogeneity in the meta-analysis. This is the first study to find such results in older adults with asthma or COPD.

Interventions can also improve quality of life and clinical control, but results are still divergent. Also, by enhancing self-management education, adherence also increases, but this was difficult to quantify. These findings should be interpreted with caution because most studies lack sufficient quality of the evidence on their results, and this is due to several limitations in design and methods that introduce a high risk of bias.

Most studies addressed complex intervention aspects beyond inhaler technique education alone, and this is particularly relevant to the outcomes of interest because it makes it harder to determine the true effect of an inhaler education approach alone. Thus, this review failed to uncover any important information about the role of inhaler technique education alone.

Although many guidelines recommend regular inhaler review, it is unclear how often that should be performed with older adults.

Only one RCT included individuals with asthma,[35] and the others only had participants with COPD. Thus, individuals with asthma accounted for only 6% of total analyzed individuals, which skews the available evidence toward COPD.

We could not perform additional subgroup analysis, namely according to age strata (such as in patients below or above 75 years old), or even according to important comorbidities (e.g., osteoarthritis, frailty, cognitive disorders). All studies had a mean age of younger than 70 and none reported such data. Such subgroup analysis would be clinically relevant because there is increasing evidence suggesting that such characteristics seem to be determinant to inhaler performance and to disease outcomes in these individuals.[23,25,27,28]

Overall Applicability and Quality of Evidence

Using the GRADE approach to rate the quality of the evidence, our analysis showed a significant overall risk of bias in studies. Half did not have a randomized design, and even RCTs were not blinded to the intervention because of its intrinsic nature. This introduces a potential Hawthorne effect, which could overestimate the main outcomes. Although this could compromise the internal validity of trials, globally, all showed a regular and similar trend in the results, indicating their external validity and applicability.

Although the included studies did not perform any cost-effective analysis or report adverse effects of the interventions, the potential benefits may outweigh the risks, which also favors regular inhaler education. Several studies have highlighted these aspects.[2,14,15]

It is difficult, with the existing evidence, to determine the true potential of inhaler education alone or what the most efficient education method is. Some studies suggested that placebo device demonstration may be the best,[41–43] but this was not clear in our review. It is possible that older adults have some resistance to this method because of problems such as cognitive impairment.[23,26] We found only one RCT that used placebo device training for the intervention, and it showed improvement in exacerbation risk only for severe episodes.[16] More randomized and blinded studies are needed to test different types of interventions, clarify which factors may influence inhaler performance, and assess the effect of performance on clinically relevant outcomes in older adults.

Well-trained staff with adequate time dedicated to instruction performed these studies. This does not usually happen in the real world, where health professionals are on tight schedules and do not have proper training on handling all available devices. This could undermine generalizability of study findings.

Potential Biases in the Review Process

Our review process was based on Cochrane recommendations[32] and is in accordance with the PRISMA statement,[31] which makes it less susceptible to major biases and errors. The search method was based on main databases (CENTRAL, MEDLINE, EMBASE) and covered important secondary sources. Criteria used were broad, yielding a representative selection of studies. Previous systematic reviews[21,22] on the same topic were also screened for secondary sources of important studies, which minimizes the risk of bias in this process. During the selection process, in addition to RCTs, we included nonrandomized studies to avoid underestimation of true effects of inhaler education programs. Although the quality of evidence from nonrandomized studies is poor, we believe that all four studies included helped reinforce the strength of recommendation regarding some of the outcomes, namely exacerbation risk reductions. In addition, by including quasirandomized studies, we highlight the need for further, adequately designed research in this population.

Two independent reviewers assessed quality of evidence using the GRADE approach, and agreement was obtained in all studies. Two other authors confirmed the process. In addition, the main results of this analysis are similar to those reported in previous systematic reviews.[21,22]

Performing a meta-analysis of such different and complex interventions could lead to false interpretation of results, because these studies are not truly comparable. To overcome this, we confirmed the main meta-analysis findings using trial sequential analysis (Supplementary Appendix S4), which strongly reinforced the finding of a significant reduction of exacerbations, increasing confidence in the results and excluding risk of a false-positive result.

Comparison with Other Studies and Reviews

To our knowledge, this is the first systematic review of inhaler education in older adults with asthma or COPD that obtained such clinically relevant results on disease control, namely the reduction of exacerbation risk. Given the aging of the population and the complex characteristics of these individuals, we find this work relevant and timely.

This systematic review stands out from previous ones for several reasons.[21,22] First, it focuses on older adults, who often have poor clinical control, are more susceptible to exacerbations, and often have poor inhaler technique.[25,26] In addition, we included randomized and nonrandomized studies, which allowed us to make realistic conclusions about the effect of inhaler technique education. Also, our review included recent studies that were not included in previous work. Finally, our systematic review highlights that most studies showed a positive effect of training on exacerbation risk reduction.

In a systematic review,[21] the authors included only individuals with asthma and included adults and older adults together, without performing a subgroup analysis of the latter. This spread of age ranges may have introduced some bias, mainly derived from endotypic and phenotypic disease differences, which could lead to different clinical responses to education on inhaler performance. Another systematic review[22] focused on postintervention inhaler performance as the main outcome but did not fully analyze the clinically relevant outcomes. Also, it included a wide age range, did not perform a subgroup analysis of older adults, and did not include a meta-analysis. In any case, previous work and our review indicate that inhaler technique education improves performance and has a potential benefit for clinical outcomes, although the strength of the evidence is low to moderate.

We found inconsistent results in clinical control and quality of life, but overall, interventions seem to significantly reduce exacerbation rates. This is particularly relevant for health economics, and several studies have shown positive, cost-effective associations in this field.[2,14,15]

CONCLUSIONS

Inhaler technique education is a critical aspect of self-management programs, and different types of interventions seem to improve inhaler performance and clinically relevant outcomes. Review of inhaler technique is recommended, and there is evidence that interventions that promote improvement in inhaler technique ameliorate disease control. In addition, these interventions significantly reduce exacerbation risk in older adults, although the strength of evidence for these outcomes is moderate. Further studies are warranted to compare education methods and target populations and to define the best regular follow-up.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this systematic review was registered in PROSPERO with the number CRD42017063847, available at: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017063847.

The study protocol differs from the final work only in the age criteria. In the protocol, we intended to include only studies with a mean age of participants aged 65 and older but included two studies with a mean age slightly below that because we found them very relevant to our objective, and both reported important outcomes.

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Conflict of Interest: The authors declare no conflict of interests.

Author Contributions: Study design: TM, LT-B. Data extraction: TM, LM. Data review and analysis: all authors. Statistical tests in first approach: TM, JG. First draft: TM, LM. Comments on first draft: all authors. LT-B and JCS are the guarantors of the study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1: Search Strategy Used

Appendix S2: Quality assessment and Risk of bias table.

Appendix S3: Complete data of selected studies.

Appendix S4: Trial sequential analysis on the primary outcome, exacerbation risk reduction, with a two-sided graph. The required information size to demonstrate or reject a 25% relative risk reduction in benefit on inhaler technique review with a usual care group proportion of 58.2%, an alpha of 5% and a beta of 80% is 527 patients (vertical etched line), and according to heterogeneity index found in meta-analysis. The curved etched lines represent the trial sequential monitoring boundaries and the futility boundaries. The solid curved line is the cumulative Z-curve.

Sub-appendix S1 – Search strategy used:

- In MEDLINE:
  - MeSH terms approach: ("Nebulizers and Vaporizers"[Mesh]) AND ("Asthma"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh])
  - Article Types: Clinical Trial, Comparative Study, Controlled Clinical Trial,
  - Pragmatic Clinical Trial, Randomized Controlled Trial
  - Trial; Systematic Reviews
  - Species: Humans
  - Age: Aged: 65+ years

- In CENTRAL:
  - #1 : MeSH descriptor: [Nebulizers and Vaporizers] explode all trees
  - #2 : Nebulizers and Vaporizers
  - #3 : Inhaler
  - #4 : MeSH descriptor: [Asthma] explode all trees
  - #5 : Asthma
  - #6 : MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
  - #7 : Pulmonary Disease, Chronic Obstructive
  - #8 : #1 or #2 or #3
  - #9 : #4 or #5 or #6 or #7
  - #10: MeSH descriptor: [Aged] explode all trees
  - #11: Elderly
  - #12: #8 and #9 and (#10 or #11)
  - Article Types filter: Trials

- In EMBASE:
  - 'nebulizer'/exp AND ('asthma'/exp OR 'chronic obstructive lung disease'/exp) AND ([english]/lim OR [portuguese]/lim) AND ([aged]/lim OR [very elderly]/lim)

Sub-appendix S2 - Quality asessment and risk of bias table:

	Initial Classification (evidence; risk)	Weaknesses		Strenghts	Risk of Bias in GRADE							Final Classification (evidence; risk)
		Limitations	Risk of Bias		1	2	3	4	5	6	7	
Mulhall 2016	High evidence; High risk	High risk for one or more key domains. Not a RCT. Not blinded. Low sample size.	High	None	-	-	-	-	?	?	?	Low evidence; High Risk
Lee 2016	High evidence; High risk	High risk for one or more key domains. Not a RCT. Not blinded.	High	Good sample size.	-	-	-	-	?	?	?	Low evidence; High Risk
Takemura 2013	High evidence; High risk	High risk for one or more key domains. Not a RCT. Not blinded. Low sample size. Inhaler education method not well defined (Placebo device + booklet?).	High	Good follow-up length.	-	-	-	-	+	+	?	Low evidence; High Risk
Buist 2006	High evidence; High risk	High risk for one or more key domains. Although it is a RCT, data was collected as a quasi-RCT, so it lacks randomization and blinding to intervention.	High	Good sample size and good follow-up length.	-	-	-	-	?	?	?	Low evidence; High Risk
Tommelein 2014	High Evidence; Low risk	Uncertain risk for one or more key domains. Short follow-up. Potential bias on data collection. No Intention-to-treat (ITT) and Per-protocol (PP) comparisons in results.	Uncertain	Good sample size. Few losses of follow-up. Randomization and allocation well conducted. Outcomes of interest well defined.	+	+	?	?	+	?	?	Moderate evidence; Uncertain risk.
Khdour 2009	High Evidence; Low risk	High risk for one or more key domains. No blinding in allocation. Only reports PP analysis.	High	Randomization well conducted and good follow-up length. Outcomes of interest well defined.	+	-	-	-	+	+	?	Low evidence; High Risk
Rootmensen 2008	High Evidence; Low risk	Uncertain risk for one or more key domains. Inhaler education method not well defined. No blinding on personnel. Incomplete data. Short follow-up.	Uncertain	Randomization and allocation well conducted. ITT analysis well performed with consistent results.	+	+	?	?	+	-	?	Moderate evidence; Uncertain risk.
Bourbeau 2003	High Evidence; Low risk	Uncertain risk for one or more key domains. Potential bias on data collection.	High	Good sample size. Few losses of follow-up. Randomization and allocation well conducted. Outcomes of interest well defined. Good follow-up length. ITT analysis well performed.	+	+	?	?	+	?	?	Moderate evidence; Uncertain risk.

1 - Random Sequence Generation
2 - Allocation Concealment
3 - Blinding of Participants and Personnel
4 - Blinding of Outcome Assessment
5 - Incomplete Outcome Data
6 - Selective Reporting
7 - Other Source of Bias

Sub-appendix S3 – Complete data of selected studies:

Study				Sample Size (nº)			AGE (mean±SD or median+range)			GENDER (%M, %F)		
Author	Year	Type	Blinding	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)
Mulhall	2016	Quasi	none	50			67.7±9.4			98;2		
Lee	2016	Quasi	none	285			62.2±14.7			60.7;29.3		
Takemura	2013	Quasi	none	51			69±8			93;7		
Buist	2006	Quasi*	none	296			66±9.4			48;52		
Tommelein	2014	RCT	single		346	346		68.9±9.7	68.4±9.6		69;31	64;36
Khdour	2009	RCT	none		72	71		67.3±9.2	65.6±10.1		43.7; 56.3	44.2;55.8
Rootmensen	2008	RCT	single		77	80		61±15	60±15		63;37	54;46
Bourbeau	2003	RCT	single		79	86		69.6±7.4	69.4±6.5		59;41	52;48
NOTES:	*RCT design, but all participants recieved inhaler teaching. Data collected as quasi-RCT design with all sample size in pre and post intervention. NA - Not Available; ND - Not Defined.											

Study				DIAGNOSIS				FOLLOW_UP (months)	FREEQUENCY of outcome evaluation (months)	INTERVENTION (Flyer, Placebo device, Video, etc..)			FREEQUENCY of intervention	INTERVENTION PROVIDER (doctor, nurse, pharm.)	SETTING (PHC, SHC, Pharmacy)
Author	Year	Type	Blinding	Asthma &/or COPD	% Asthma	% COPD	Stage/ Severity			Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)			
Mulhall	2016	Quasi	none	COPD	0	100	Mod/Severe	4,7	Baseline-End	Videos			baseline	Pharmaceutical	SHC
Lee	2016	Quasi	none	COPD+ Asthma	55,4	44,6	ND	1	Baseline-End	Videos			baseline	Doctor	PHC
Takemura	2013	Quasi	none	COPD	0	100	Mild/Mod	48	Baseline-End	Booklet/ Placebo device?			Every 6M	Pharmaceutical	Pharmacy
Buist	2006	Quasi*	none	Asthma	100	0	Mod/Severe	24	Every 6M	Placebo Device			Every 6M	Doctor	SHC
Tommelein	2014	RCT	single	COPD	0	100	Moderate	3	0-1-3M		Usual Care	Placebo Device	baseline + 1M	Pharmaceutical	Pharmacy
Khdour	2009	RCT	none	COPD	0	100	Mod/Severe	12	0-6-12M		Usual Care	Written Info	baseline	Pharmaceutical	SHC
Rootmensen	2008	RCT	single	COPD+ Asthma	42	58	Mild/Mod	6	Baseline-End		Usual Care	ND	baseline	Nurse	SHC
Bourbeau	2003	RCT	single	COPD	100	0	Severe	24	Every month		Usual Care	Written Info	baseline	Nurse	SHC

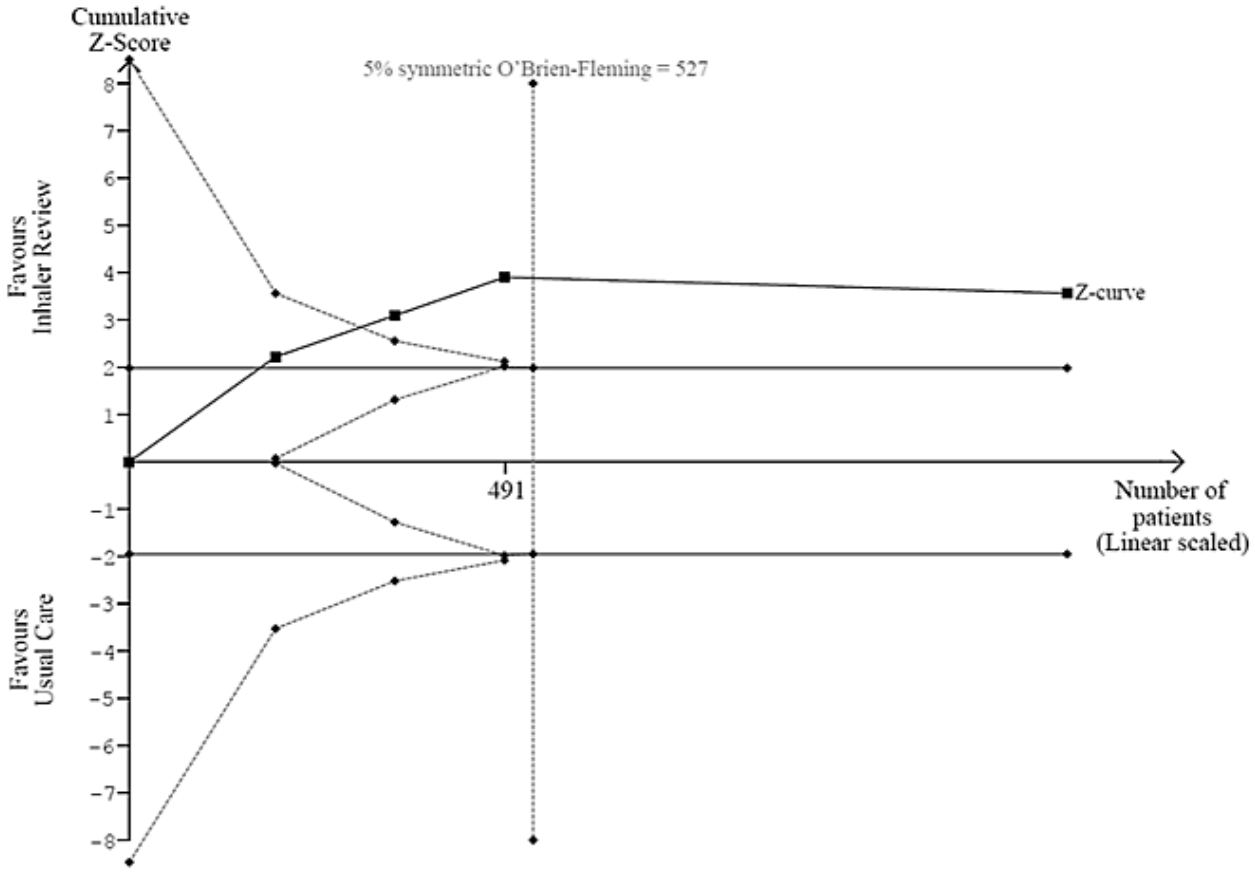
Study				INHALER PERFORMANCE (% of mistakes, index/score at: mean±SD or median+range) (pre and post intervention)			MEDICATION ADHERENCE (any type of questionnaire: mean±SD or median+range; variation in %) (pre and post intervention)		
Author	Year	Type	Blinding	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)
Mulhall	2016	Quasi	none	%errors (pMDI|pMDI+Chamber|DPI): 68.8 ; 91.6 | 72.5 ; 95.4 | 83.4 ; 96.2			NA		
Lee	2016	Quasi	none	NA			NA		
Takemura	2013	Quasi	none	NA			Likert scale: 4.1±0.7 ; 4.4±0.8		
Buist	2006	Quasi*	none	score (0-8): 4.0±2.0 ; 7.3±0.8			NA		
Tommelein	2014	RCT	single		%correct steps: 68.8±28.8 ; 79±23.3	%correct steps: 67.7±32.5 ; 93.4±13.8		MRA scale: 82.7±23.9 ; 85.7±26.6	MRA scale: 84±23.5 ; 93.9±21.5
Khdour	2009	RCT	none		ND	ND		% Morisky<2: 60	% Morisky<2: 77.8
Rootmensen	2008	RCT	single		score (0-100): 71±14 ; 73±16	score (0-100): 78±13 ; 80±15		ND	ND
Bourbeau	2003	RCT	single		ND	ND		ND	ND

Study				SYMPTOMS CONTROL (any type of questionnaire: mean±SD or median+range; variation in %) (pre and post intervention)			FUNCTIONAL TESTS (any of: FEV1%; FVC%, PEF%, MEF25-75%, ratio FEV1/FVC) (pre and post intervention)		
Author	Year	Type	Blinding	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)
Mulhall	2016	Quasi	none	CAT score: 17.4±8.3 ; 17±8.3			NA		
Lee	2016	Quasi	none	CAT score: 19.9±9.7 ; 15.4±9.2 ACT score: 16.6±4.6 ; 19.8±4.1			NA		
Takemura	2013	Quasi	none	NA			%FEV1: 68.1±16.0 ; 61.0±18.4		
Buist	2006	Quasi*	none	NA			%FEV1: 58.9 (±21.8) ; 62.9		
Tommelein	2014	RCT	single		CAT score: 16.4±7.6 ; 15.9±7.7 % mMRC≥2: 38.1 ; 36.1	CAT score: 16.7±7.8 ; 15.9±7.8 % mMRC≥2: 40.9 ; 37.6		ND	ND
Khdour	2009	RCT	none		ND	ND		Value FEV1: 1.12 (0.98-1.21) ; 1.05 (0.94-1.17)	Value FEV1: 1.15 (0.99-1.23) ; 1.19 (1.05-1.31)
Rootmensen	2008	RCT	single		ND	ND		ND	ND
Bourbeau	2003	RCT	single		ND	ND		Value FEV1: 0.98±0.31 ; 1.01±0.36	Value FEV1: 1.0±0.33 ; 0.96±0.32

Study				QUALITY OF LIFE (any type of questionnaire: mean±SD or median+range; variation in %) (pre and post intervention)			EVENTS (exacerbaions, ER/hospitalizations or mortality, at: mean n°±SD or RR, HR, OR with IC95%) (pre and post intervention; relation beteween groups)		
Author	Year	Type	Blinding	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)	Total Sample (if quasi-RCT)	Usual Care (if RCT)	Intervention (if RCT)
Mulhall	2016	Quasi	none	NA			NA		
Lee	2016	Quasi	none	NA			NA		
Takemura	2013	Quasi	none	St.George score: 40.4±20.1 ; 40.8±20.8			Person-year 1.5±1.6 ; 0.8±1.4		
Buist	2006	Quasi*	none	AQLQ scale (0-7): 5.05 ; 5.45 [increased 0.4 (0.3-0.5)]			Person-year: 0.16 ; 0.15		
Tommelein	2014	RCT	single		EQ-5D scale: 0.71±0.25 ; 0.73±0.25	EQ-5D scale: 0.68±0.25 ; 0.72±0.24		RR moderate events: 0.82 (0.64–1.06) RR severe events: 0.45 (0.25–0.80)	
Khdour	2009	RCT	none		St. George scale: 64.2 (60.5-67.9) ; 65.3 (61.0-69.6)	St. George scale: 63.6 (59.8-66.6) ; 61.8 (57.9-65.6)		RR: 0.63 (0.43-0.92)	
Rootmensen	2008	RCT	single		St. George scale: NA (authors unable to be contacted)	St. George scale: NA (authors unable to be contacted)		RR: 0.48 (0.23-1.0)	
Bourbeau	2003	RCT	single		St. George scale: 55.7±15.7 ; 54.2	St. George scale: 54.1±16.6 ; 50.6		RR: 0.64 (0.48-0.86)	

Sub-appendix S4 – Trial Sequential Analysis:

Trial sequential analysis on the primary outcome, exacerbation risk reduction, with a two-sided graph. The required information size to demonstrate or reject a 25% relative risk reduction in benefit on inhaler technique review with a usual care group proportion of 58,2%, an alpha of 5% and a beta of 80% is 527 patients (vertical etched line), and according to heterogeneity index found in meta-analysis. The curved etched lines represent the trial sequential monitoring boundaries and the futility boundaries. The solid curved line is the cumulative Z-score.



Appendix V – Published article of objective two:

"Inhaler review in elderly with Asthma or COPD – a cost-effectiveness study and a perspective in Portugal":

CLINICAL INVESTIGATION

Inhaler Review in Older Adults with Asthma or COPD: A Cost-Effectiveness Study and a Perspective in Portugal

Tiago Maricoto, MD,[*†] *João Marques-Gomes, PhD,*[‡] *Jaime Correia-de-Sousa, PhD,*[§¶] *and Luís Taborda-Barata, PhD*[‖**]

OBJECTIVES: Older patients with asthma or chronic obstructive pulmonary disease are particularly susceptible to exacerbations that may be associated with incorrect use of inhalers. Educational programs with inhaler technique review seem to be effective, but no studies have addressed their cost-effectiveness in older adult patients.

The objective was to perform a cost-effectiveness analysis of education programs in older patients and estimate the cost benefit of applying such a program in Portugal.

DESIGN: We developed a decision tree analysis from a healthcare perspective, according to intervention costs and the exacerbation rates and costs described in a previous meta-analysis. A sensitivity analysis of worst and best case scenarios was performed to estimate thresholds for intervention affordable limits, as well as cost-saving estimations and incremental cost-effectiveness ratios (ICERs) for a Portuguese scenario.

SETTING AND PARTICIPANTS: We estimated cost-effectiveness thresholds applicable in all settings and performed a sensitivity analysis of a theoretical intervention model in all patients including an inhaler technique review at an annual appointment with a doctor and a nurse.

RESULTS: In the best case scenario, the intervention affordable budget could be up to almost 1800€ (US $1585.24) per patient per year. Mean intervention-associated savings in Portugal would be 311.88€ (US $274.68) per patient per year, representing annual savings up to €131 million (US $150 million) for the whole health system, already including intervention costs. ICERs for Portugal vary between 93.73€ (US $82.55) and 437.43€ (US $385.25) per exacerbation avoided.

CONCLUSION: A model of an intervention program with an inhaler technique review in older adult patients suggests that this intervention is cost-effective and can generate significant savings. J Am Geriatr Soc 00:1–7, 2019.

Key words: cost-effectiveness; inhaler; asthma; chronic obstructive pulmonary disease; older adults

Respiratory diseases are one of the main causes of death worldwide. Asthma and chronic obstructive pulmonary disease (COPD) affect up to 10% of the population.[1] Inhaled therapy is the main treatment pathway used, but most patients use devices incorrectly, frequently with critical errors, thereby contributing to poor clinical control and increased risk of exacerbations.[2–5] In addition, many studies showed that poor clinical control also leads to increased costs in health services.[6–9] However, true estimates of the burden due to asthma and COPD are unavailable because direct and indirect costs are difficult to quantify, and different parts of the world report different estimations.

Significant evidence shows that educational programs for asthma and COPD may be effective in terms of clinical improvement,[10–14] but few have addressed inhaler technique review alone. In addition, strong evidence supports the cost-effectiveness of those programs, although the reported results show a broad range of annual cost savings with interventions, ranging from 200€ (US $176.17) to 2000€ (US $1761.70) per patient.[15–20] In Portugal, acute care and exacerbations-associated annual costs are estimated between 330€ (US $290.69) and 8000€ (US $7047.30) per patient,[7,21] but no study has yet evaluated the cost-effectiveness

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of a conceptualized national education program for asthma and COPD.

Portugal has one of the oldest populations in Europe, and older adult patients tend to have a poor quality of life.[22] Also, respiratory diseases represent the second leading cause of death in these patients.[23] Older patients with asthma or COPD are particularly susceptible to poor disease control and exacerbations,[24,25] due to particular characteristics such as increased comorbidities, poor adherence to treatment, and inadequate inhaler technique.[26–28] Nevertheless, a recent meta-analysis showed that educational interventions of inhaler technique review in older patients significantly reduced the risk of exacerbations, with a pooled risk reduction of 29%.[29] These are patients who may benefit most from educational interventions. This reported effectiveness was not previously described in younger patients.[30,31]

However, as far as we know, no cost-effectiveness study has been published that has analyzed educational interventions in older patients. Decision analysis and cost-effectiveness analysis are useful tools that integrate evidence in specific context conditions to address a specific decision problem.[32] Developed countries face the need to reduce health costs and maximize clinical benefits from interventions. Thus one major strategy is to identify the most cost-effective subgroups of patients.

We hypothesized that a simple intervention (review of inhaler technique) would result in a slight increase in intervention costs but also in a decrease in direct costs of exacerbations, resulting in overall healthcare costs savings in a model for older patients with asthma or COPD. Thus our study aims to determine, in accordance with the main results reported in the previous meta-analysis, the cost-effectiveness of educational interventions including inhaler technique review in older patients with asthma or COPD.

METHODS

Study Design and Framework

We developed a standard cost-effectiveness analysis, based on a decision tree approach[33] and in accordance with CHEERS recommendations (Supplementary Appendix S1).[34] Our aims were to perform estimations of treatment-affordable thresholds and according to exacerbation costs in older patients. In addition, we performed estimations of cost savings and incremental cost-effectiveness ratios (ICERs) for a Portuguese scenario, according to local costs of a theoretical intervention program.

Sources of Data

We used data from previously published studies on exacerbation costs, exacerbation rates, and local costs for intervention on inhaler technique review to determine cost-effectiveness ratios. According to a previously published meta-analysis, interventions that include inhaler technique review in older patients with asthma or COPD reduce exacerbation rates from 0.58 to 0.43 (number of exacerbations per patient per year). Absolute mean reductions of exacerbation rates range from 0.07 to 0.22, in worst and best case scenarios and according to 95% confidence interval (CI) limits.[29] In addition, exacerbations and acute medical care, alone, represent annual costs between 330€ (US $290.69) and 8000€ (US $7047.30) per patient.[7,21] A more recent estimation for COPD in Portugal points out annual costs of 2250€ (US $1982.04) per patient.[35] Due to the wide range of values, we used all these references to estimate scenarios for the best case, worst case, and mean estimation.

Base-Case Definition

The base-case population of our analysis were older patients with asthma or COPD because these patients are more susceptible to poor clinical control and exacerbation risks. This is a healthcare payer's perspective study in which only direct costs were considered because indirect costs and each patient's own costs were not reliably available. We did not consider medication costs in the different stages of disease management either. Two types of costs were calculated, the intervention costs and the exacerbation costs, which were assigned to the decision tree analysis. This model assumes the previously reported exacerbation risk reduction, as well as the costs associated with each exacerbation. We also performed sensitivity analysis to assess uncertainty regarding thresholds of intervention cost-effectiveness, using reported 95% CI limits to estimate worst and best case scenarios.

Intervention

Different intervention programs were tested in these patients in previous studies, with a wide variety of aspects addressed. Most interventions addressed inhaler technique review, self-management tools, and functional control, and almost all studies performed it only at baseline of the follow-up period. In addition, interventions were delivered by different health professionals such as doctors, nurses, and pharmacists.[29] For that reason, we developed a conceptual intervention program with annual control appointments by a doctor and a nurse. Each appointment would require a 20-minute evaluation to perform inhaler technique review and to assess clinical control and lung function through spirometry.

Setting

Due to inherent difficulties in specifying different aspects of interventions (inhaler technique review, self-management strategies, lung function evaluation, etc), the costs of such programs were calculated as a whole, considering health professionals' salaries in 2017 based on the official values defined by the Portuguese Central Administration of Health System, as well as spirometry costs.[7] All costs and outcomes were expressed as additional factors to the main comparator, which was Usual Care. We used Usual Care as the main comparator because it was the reference control reported in most studies that was included in the previous meta-analysis.[29] The time frame in the base-case analysis was 1 year because exacerbation rates were reported that way. No discount rates were considered in cost estimation.

Outcome Measures

We used a synthesis-based estimate to define outcome measures that included exacerbation rates, cost per exacerbation,

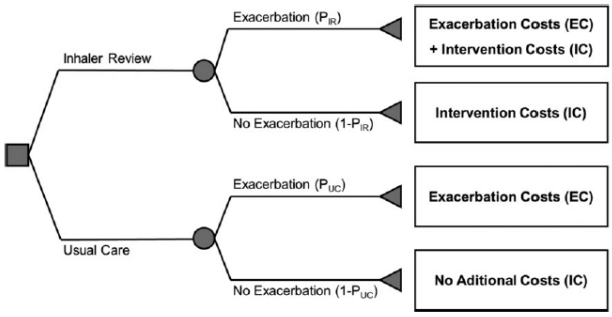

Figure 1. Decision tree model to compare Usual Care vs Inhaler technique review intervention. EC, Exacerbation costs; IC, Intervention costs; P_{IR}, Probability of exacerbation under inhaler technique review; P_{UC}, Probability of exacerbation under Usual Care.

and thresholds of cost-effectiveness for the designed intervention program. All cost estimations were used according to 2017 references, in euros (€). Exacerbation costs were considered as a whole in mean estimations, regardless of the type of treatment or management that is usually provided to patients. For that reason, some types of clinical interventions provided for the management of exacerbations could be the same as those provided in our theoretical intervention program. However, that would not hamper the ability to compare them as a conceptual framework for the cost-effectiveness analysis.

Figure 1 shows the decision tree used in the model. The resulting equation for cost-effectivity balance is the following one (where EC = Exacerbation costs; IC = Intervention Costs; PIR = Probability of exacerbation under Inhaler Technique Review; and PUC = Probability of exacerbation under Usual Care):

$$Expected\ Value\,(InhalerReview) = Expected\ Value\,(Usual\ Care)$$
$$[(EC+IC)\times P_{IR}] + [IC\times(1-P_{IR})] = (EC\times P_{UC}) + [0\times(1-P_{UC})]$$
$$IC = EC\times(P_{UC}-P_{IR})$$

Table 1 summarizes all data considered in parameters assigned to cost estimations. Using the model assumptions presented in Figure 1, we estimated the affordable limits for intervention costs at mean values and at worst and best case scenarios. Worst case scenario was estimated using the 95% CI lower limit of probability of exacerbation under Usual Care and 95% CI upper limit of probability of exacerbation under Inhaler Technique Review intervention. Best case scenario was estimated using the 95% CI upper limit of Probability of exacerbation under Usual Care, and 95% CI lower limit of Probability of exacerbation under Inhaler Technique Review intervention. Mean estimation was obtained with the respective mean values.

Cost-saving estimation for Portugal was also obtained according to worst and best case scenarios. In the worst case scenario, we used the lower limit of reported exacerbation cost, the worst case estimation of intervention cost and worst case estimation of risk difference (the difference between exacerbation risk of Inhaler Technique Review group and Usual Care group). In the best case scenario, we used the upper limit of reported exacerbation cost, the best case estimation of intervention cost, and the best case estimation of risk difference.

Table 1. Input parameters used in the model

Parameter	Value	95% CI lower limit	95% CI upper limit	Reference source
Annual exacerbation rate				
• Usual care	0.58	0.54	0.62	29
• Inhaler technique review	0.43	0.40	0.47	29

Parameter	Mean estimation	Best case estimation	Worst case estimation	Reference source
Intervention costs, € (US $)				
• Doctor (20-min intervention once/year)[a]	7.25€ (US $6.39)	4.10€ (US $3.61)	10.40€ (US $9.16)	[c]
• Nurse (20-min intervention once/year)[b]	4.45€ (US $3.92)	2.60€ (US $2.29)	6.30€ (US $5.55)	[c]
• Control spirometry	13.92€ (US $12.26)	13.92€ (US $12.26)	13.92€ (US $12.26)	7
TOTAL	25.62€ (US $22.56)	20.62€ (US $18.16)	30.62€ (US $26.96)	
Exacerbation costs, € (US$)				
Cost per patient	2250€ (US $1982.04)	330€ (US $290.69)	8000€ (US $7047.30)	7, 21, 35

CI = confidence interval; € = 2017 Portuguese euro; $ = US dollar.
[a]Mean salary of a doctor for each hour ranges from 12,22€ (US $10.76) to 31,13€ (US $27.41).
[b]Mean salary of a nurse for each hour ranges from 7,90€ (US $6.96) to 18,80€ (US $16.55).
[c]Based on official values defined by the Portuguese Central Administration of Health System.

RESULTS

Cost-Effectiveness Estimation and Sensitivity Analysis

Our analysis estimated the cost-effectiveness thresholds for intervention costs affordable limits per patient per year. Figure 2 presents these results in the range of exacerbation costs between 0€ (US $0) and 8000€ (US $7047.30). The respective estimation equations are as follows: (where EC = Exacerbation costs; IC = Intervention Costs; PIR = Probability of exacerbation under Inhaler Technique Review; and PUC = Probability of exacerbation under Usual Care):

Worst case scenario: [95% CI lower limit of P_{UC} and upper limit of P_{IR}].

$$IC = EC \times (0.54 - 0.47) < = > IC = 0.07 \times EC.$$

Mean estimation scenario: [mean P_{UC} and mean P_{IR}]

$$IC = EC \times (0.58 - 0.43) < = > IC = 0.15 \times EC$$

Best case scenario: [95% CI upper limit of P_{UC} and lower limit of P_{IR}]

$$IC = EC \times (0.62 - 0.40) < = > IC = 0.22 \times EC$$

In the best case scenario of intervention effectiveness and with exacerbation costs at the reported upper limit, the intervention affordable budget could be up to almost 1800€ (US $1585.24) per patient per year. The more exacerbation costs increase, the higher the affordable limit rises to develop an intervention program.

Cost-Effectiveness Estimations for a Portuguese Scenario

Cost-saving estimations for Portugal were obtained considering mean values, worst and best case scenarios, and according to variations between exacerbation annual costs that range from 330.95€ (US $291.54) to 8000€ (US $7047.30) per patient. These reported costs concern the global population but were used here to estimate savings for older patients. The main equations used to estimate cost savings were as follows (where EC = Exacerbation costs; IC = Intervention costs; and RD = risk difference between Inhaler Technique Review and Usual Care):

Worst case scenario:

$$Estimation\ Savings_{worst-case} = (EC_{best-case} \times RD_{worst-case}) - IC_{worst-case}$$
$$Estimation\ Savings_{worst-case} = (330.95 \times 0.07) - 30,62$$
$$Estimation\ Savings_{worst-case} = (-)7,45$$

Mean estimation:

$$Estimation\ Savings_{mean} = (EC_{mean} \times \mathrm{RD}_{mean}) - IC_{mean}$$
$$Estimation\ Savings_{mean} = (4165.48 \times 0.15) - 25,62$$
$$Estimation\ Savings_{mean} = 599.20$$

Best case scenario:

$$Estimation\ Savings_{best-case} = (EC_{worst-case} \times RD_{best-case}) - IC_{best-case}$$
$$Estimation\ Savings_{worst-case} = (8000 \times 0.22) - 20,62$$
$$Estimation\ Savings_{worst-case} = 1739,38$$

Considering data from exacerbation risk difference reported for older patients, we estimated mean annual savings of 311.88€ (US $274.68) per patient for an intervention program in Portugal. We found a wide interval between worst and best case scenarios, ranging from an annual negative balance of minus 7.45€ (US $6.56) and a positive budget of 1739,38€ (US $1532.09) per patient. However, considering the reported difference in annual costs associated with clinically well-controlled patients and clinically uncontrolled patients, which is about 469.42€ (US $413.47),[7] the worst case scenario increases to a positive balance of 2.24€ (US $2.13) per patient/year.

Approximately 2,2 million older adults live in Portugal. Thus considering an overall 10% combined prevalence of asthma or COPD,[1] the mean estimation for effectively implemented interventions in this age group could theoretically

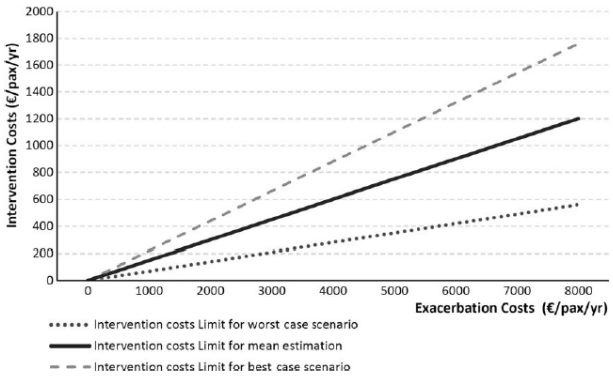

Figure 2. Cost-effectivity thresholds according to exacerbation costs. Lines represent the intervention costs affordable limit scenarios according to exacerbation proportions of 95% confidence interval (CI) lower limit, mean estimation, and 95% CI upper limit.

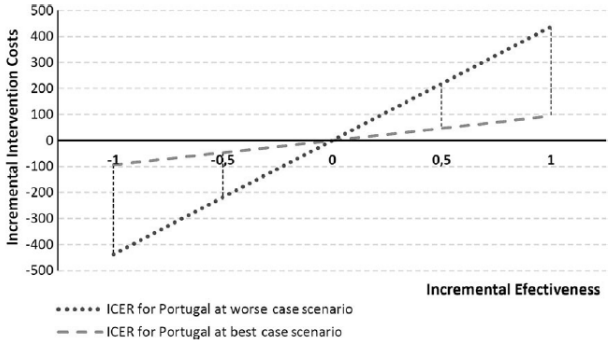

Figure 3. Incremental cost-effectiveness ratio (ICER) for Portugal at worst case and best case scenarios according to lower and upper limits of Intervention Costs and Risk Difference. Incremental effectiveness was estimated according to number of prevented exacerbations.

represent a total annual savings of €131 million (US $150 million) for the Portuguese national health system, and this estimation already includes all the intervention costs.

Incremental Cost-Effectiveness Ratio Estimations for a Portuguese Scenario

ICER was estimated for worst and best case scenarios, and according to upper and lower limits of intervention costs and risk difference. Incremental effectiveness was estimated according to the number of prevented exacerbations. Figure 3[31] represents ICER for Portugal at worst case and best case scenarios that vary between 93.73€ (US $82.55) and 437.43€ (US $385.25) per exacerbation avoided. The min equations used were as follows (where IC = Intervention costs; and RD = risk difference between Inhaler Technique Review and Usual Care):

At worst case scenario:

$$ICER_{worst\ case} = \frac{IC_{worst\ case}}{RD_{worst\ case}} = \frac{30.62}{0.07} = 437.43$$

At best case scenario:

$$ICER_{best\ case} = \frac{IC_{best\ case}}{RD_{best\ case}} = \frac{20.62}{0.22} = 93.73$$

DISCUSSION

Our results show that interventions that include inhaler technique review to improve clinical control in older patients with asthma or COPD may be cost-effective and may generate significant savings from the perspective of the healthcare provider.

This is the first study showing that these interventions could save up to several hundreds of million euros in Portugal. Also, this is the first study establishing thresholds for affordable budget interventions that can be adopted worldwide according to exacerbations costs. Moreover, as exacerbations costs get higher, affordable limits for intervention budget also increase. These thresholds may apply to other healthcare systems because they are based on worldwide data of exacerbation rate variations and are unaffected by local health costs. In a simple approach, healthcare systems may invest in interventional programs up to 22% of total exacerbation costs to be cost-effective.

The intervention costs and exacerbation costs used were based on data from Portugal and might differ from costs in other countries that might lead to different cost-saving estimations. However, when actually compared with reports from other countries, our study found similar mean savings with interventions in the Portuguese scenario, which reinforces the generalizability of our findings. In addition, most previous reports used a standard cost-effectiveness model, which was also our approach.[15–19] However, similarly to these reports, we also found a very wide range of plausible values, which could be due to uncertainty of estimation of exacerbation costs and difficulty in establishing the true costs of intervention programs.

More recent studies have estimated less savings with interventions,[15,16] which could be due to various reasons. First, because these studies mostly included adult patients in the base-case analysis, without focusing on older patients. Second, they mostly included COPD patients, who have irreversible airway obstruction and an increased risk of exacerbations. In asthma patients, inhaled medication, such as inhaled corticosteroids, is more effective. Finally, the observed discrepancy may also be due to different country settings and their respective costs. In contrast, we focused our analysis mainly on older patients because they tend to have higher exacerbation rates and are probably more susceptible to the benefits of interventions.[24,25,29] This approach may have improved our findings. These patients also have more comorbidities and drug interactions that can increase costs of exacerbations and worsen disease control. Moreover, exacerbations may not only lead to direct costs of additional treatment and/or hospitalizations, but there is also evidence that they result in significant lung function decline and thus in a tremendous loss in overall functions, such as increased frailty and cognitive impairment.[36,37]

Our study has some limitations. First, we were not able to estimate and obtain indirect costs, mainly those regarding the patients' perspective, because exacerbation costs

were uncertain in the available literature. In addition, exacerbation rates in these older patients may also be imprecise because the meta-analysis we used as the basis for our work included relatively few studies.[29] Lastly, we could not perform a cost-utility analysis based on quality-adjusted life years, due to the scarcity of available data. We accept that such analysis would probably reinforce the clinical relevance of our findings.

We found that the worst case scenario for cost savings could represent a slight negative balance, but that could be underestimated. In fact, for that estimation we used data from a Portuguese study on asthma,[7] but we only considered acute medical care costs that represent about 40% of patients included. However, the real prevalence of exacerbations in older patients is slightly higher. In addition, using the real difference in annual costs between controlled and uncontrolled patients (about a 469.42€ increase [US $413.47]), our worst case scenario turns to a positive balance.

Another important aspect to consider is the intervention conceptual program itself. In fact, the mean follow-up period of previous interventional studies is wide, varying from 3[12] up to 24 months,[14] and none of those studies tested a regular inhaler technique review. Further studies should be designed to test how often and for how long the intervention is needed to maintain effectiveness because evidence indicates that inhaler technique review is lost after some time.[38,39] Other features may also affect exacerbation risk and progressive lung function decline, such as the choice of the type of inhaler, the use of multiple devices,[40] or even the choice of drugs or the combination of drugs because newer combination inhalers may make a difference in outcome.[24,25]

Finally, it is notable that interventions in these patients should include several aspects of disease control, such as self-management plans and inhaler technique review. This is particularly relevant because most interventional studies included in a previous meta-analysis covered other features in addition to inhaler technique review.[29] In addition, most of those studies measured adherence as an outcome, rather than inhaler technique performance, an important aspect to be taken into account, because it may bias the result of intervention effectiveness. Better adherence to inhaler therapy does not necessarily mean better inhaler technique performance, which should be clarified in future studies. Also, improving adherence seems to be related to decreased exacerbation risk[12,13] that may be independent of inhaler technique performance.[3,41,42] Adherence may also be an important aspect to consider in terms of cost estimation because it also affects medication costs.[43] Here, medication costs were not considered as a subset, although cost estimations included them in the main source. Medication costs may decrease due to better inhaler technique because as clinical control improves, other concurrent therapies are needed less often (such as oral corticosteroids or antibiotics), and the optimal inhaled dosing may also be reduced. Those aspects were not considered in our analysis.

However, it is difficult to ascertain the cost-effectiveness of such aspects alone, mainly the impact of inhaler technique review, which was noted as a key point in previous work by others.[15]

In conclusion, intervention programs in older patients with asthma or COPD seem to be cost-effective and may generate significant savings in Portugal. Also, the affordable limits for intervention costs are wide and augmented as exacerbation costs increase.

Intervention programs should embrace different dimensions such as self-management tools and inhaler technique review, which should be considered before changing or adding new treatment options.

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Authors Contributions: *Study design and data extraction:* Maricoto and Taborda-Barata. *Data review and analysis*: All authors (sensitivity analysis rechecked by Marques-Gomes and Correia-de-Sousa). *First draft:* Maricoto. All authors commented on the first draft and agreed with the final version. *Guarantors of the study:* Taborda-Barata and Correia-de-Sousa.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Appendix S1. CHEERS recommendations checklist

Supplementary Appendix S1 - CHEERS recommendations checklist:

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	5-6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	7
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	9-10
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	9-10
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	8
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	8
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	9-10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	9-10
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	7
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	9
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	8
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	9
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	8
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9-10
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11-13
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11-13
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-13
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	14-17
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	19
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

Appendix VI – Published article of objective five:

"Inhaler technique education in elderly patients with Asthma or COPD: impact on disease exacerbations – a protocol for a single-blinded randomised controlled trial":

Open access Protocol

BMJ Open

Inhaler technique education in elderly patients with asthma or COPD: impact on disease exacerbations—a protocol for a single-blinded randomised controlled trial

Tiago Maricoto,[1,2] Jaime Correia-de-Sousa,[3,4] Luís Taborda-Barata[5,6]

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ABSTRACT

Introduction Chronic Obstructive Pulmonary Disease (COPD)and asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients.

Methods and analysis A multicentre single-blinded Randomised Controlled Trial (RCT) will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care, with a 1-year follow-up, in patients above 65 years of age with asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions χ^2 test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics.

Ethics and dissemination Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on 22 November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017–025. Results will be presented in scientific meetings and published in peer-reviewed journals.

Trial registration number NCT03449316; Pre-Results.

Strengths and limitations of this study

- ► This study is innovative because it includes exclusively elderly patients with asthma or COPD, addressing, in a 1-year follow-up, a specific placebo device education programme, alone, without any other aspects.
- ► No previous study has addressed this teaching method in these patients, as it seems to be the most efficient one.
- ► Our study has a randomised design, which has been a major limitation in previous studies.
- ► The 1-year follow-up period, with one interim evaluation, allows this study to comprehensively address the real impact of a regular education programme.
- ► The main limitation of this study is the single blinded design, due to the nature of intervention itself, which may introduce some performance bias.

INTRODUCTION

Epidemiology

Asthma and COPD affect about 10% of the population, but many patients have uncontrolled symptoms.[1] In asthma, in particular, it should be highlighted that only 57% of all patients were shown to have their symptoms controlled,[2 3] and the elderly population is particularly vulnerable to this condition.[3] In fact, late onset asthma may be frequently misdiagnosed and mistreated, and the risk of drug interactions also requires close monitoring.[4] Hospitalisation rates due to asthma and COPD are reported to reach 27% among non-adherent patients and could be up to 53% in community treated cases, and this may be even more apparent in elderly patients. It should also be stressed that good adherence to inhaler treatment may, in contrast, be associated with a lower rate of severe exacerbations, with reductions observed in up to half of the cases.[5–7]

Inhaler technique

Inhaled therapy is the most widely used way to treat patients with asthma and COPD,[8] but up to 90% of them do not use their inhalers correctly.[9 10] Performance errors have been

described with almost every type of device, and over the past decades this problem has not improved, which highlights the need to better understand the specificities of different inhaler use as well as the impact of different inhaler teaching methods.[11] Several inhaler devices are available on the market and it seems that differences either in device type or in patient characteristics may significantly influence performance.[12] However, all inhalers, when properly used, show no significant differences in terms of treatment efficacy,[13 14] but it is well established that poor inhaler technique leads to poor clinical control[15 16] and also to increased health costs.[17] In addition, some type of specific errors seem to have a higher impact on clinical control, but there is no consensus yet on which errors are critical and non-critical.[18 19]

Patients in controlled trials receive more training in inhaler performance and more counselling on adherence than patients who are seen as part of routine clinical practice, but few studies have addressed these variables as separate outcomes.[20] Some studies show that teaching inhaler technique may lower the risk of exacerbations and death.[6 21 22] However, its impact is quickly lost as time elapses, suggesting this is a practice that should be rechecked and regularly applied to patients.[23 24] Nevertheless, how often the review should be carried out has not been established yet, since most studies have not addressed this issue in an isolated manner.

Significant evidence has shown that inhaler technique performance is regarded as particularly complex by older patients.[25 26] These patients also present lower adherence rates[9] and are more resistant to correct performance.[27 28] Furthermore, other major characteristics may influence inhaler use, such as educational level, previous teaching or even age itself (ie, age above 75 years).[29] However, the significance of these observations still has to be fully ascertained since elderly patients are frequently excluded from major clinical trials. Randomised studies with elderly patients are scarce, and most of them did not address these aspects. Some of these studies have shown significant reductions in exacerbation risk, but most of them addressed several aspects of intervention besides inhaler technique education itself, namely self-management plans, disease knowledge, management of exacerbations and their triggers. None has yet addressed inhaler review alone or in a regular education programme.[21 30–33]

Inhaler technique may be taught using many tools, such as step-by-step flyer schemes, video demonstrations, videoconferencing and face-to-face demonstrations or even using web-based platforms, but there is insufficient evidence about which is the best education method to improve inhaler performance or its impact on major outcomes.[34–37] Nevertheless, some studies including adult patients as well suggest that the most efficient method seems to be using a teach-to-goal approach with placebo device demonstration and training provided in person.[38–42] In addition, manufacturers' recommendations often differ from clinical guidelines, which makes it difficult for patients to fully understand all the necessary steps of inhaler use.[43] This highlights the importance of watching patients using their inhalers, which can be achieved with a placebo device training set.

This study will focus on elderly patients and aims at testing the effect of a structured and regular placebo device training approach on disease exacerbation rates.

SPECIFIC AIMS AND HYPOTHESES

Our objective is to test the impact of an inhaler technique education programme on the risk of exacerbations in elderly patients with asthma or COPD.

The main hypothesis is that, among elderly patients with asthma or COPD, regular education of inhaler technique using a teach-to-goal placebo device-based approach, and delivered by family doctors at baseline, 3 and 6 months, can reduce the exacerbation risk by 50% after a 1 year follow-up, when compared with usual care.

RESEARCH DESIGN AND METHODOLOGY

Study design

Two arms single blinded randomised controlled trial with a 1-year follow-up (figure 1). Participants will be allocated to each group on a random basis, which is defined by a computerised generator and is independent of the control of the principal investigator. The allocation sequence of the 146 participants will be defined through a computer generator prior to the start of the study. After the generation of this sequence, 146 envelopes will be created, numbered in the appropriate order and will contain the result of the allocation. The order of the envelopes' number will define the order of participants' enrolment. The principal investigator will not be aware of the information contained within the envelopes, thereby maintaining a minimisation randomisation process. To ensure the accuracy of the use of the envelopes, the documents inside the envelope will be signed by the Data Safety Monitoring Board and must be returned by the researchers after the allocation of the participants.

Sample size calculation

Sample size was estimated using the χ^2 *independent group proportions* approach of *STATA Statistical Package*, considering the event proportion in control group of 50% (0.5 annual rate) as reported in other previous studies[21 22 44] and estimating a reduction of event rate in the intervention group to 25% (0.25 annual rate) as reported in similar studies. A 95% CI, with value (power) of 80%, an alpha level of 5% and a ratio of cases/controls of 1:1 were established. Finally, the sample size was readjusted upward, considering an estimated proportion of full compliance of the study of 80% (20% losses). The estimated sample size was 116, readjusted to a total of 146 individuals (73 in each arm).

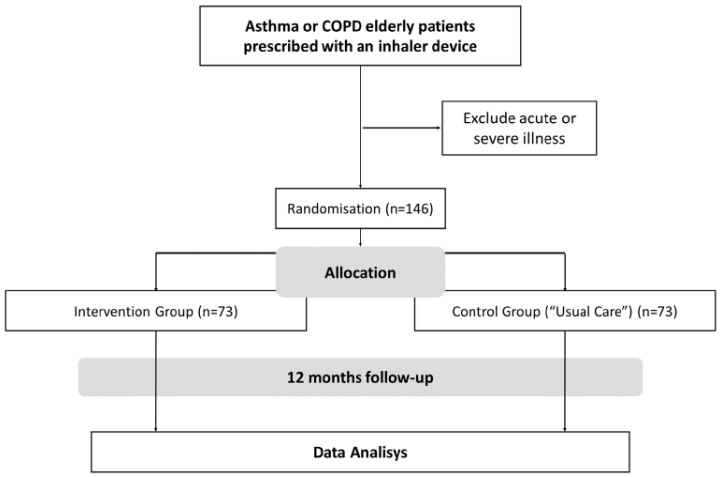

Figure 1 Study design diagram.

Inclusion criteria

Patients with a diagnosis of COPD or asthma, prescribed any kind of inhaler device (pressurised Metered Dose Inhaler (pMDI) with or without Spacer, Dry Powder Inhaler or Soft Mist), aged ≥65 years and being a regular user of primary healthcare services (defined as having had at least one appointment in the last 2 years with his/her own Family Doctor). In order to minimise diagnostic inaccuracy, asthma and COPD diagnosis will be reviewed in every participant at baseline prior to enrolment and in accordance with GINA and GOLD strategies.[45 46]

Exclusion criteria

Severe or acute illness (such as unstable cardiovascular status, unstable angina, recent myocardial infarction (within 1 month) or pulmonary embolism, haemoptysis of unknown origin, recent pneumothorax (within 1 month), recent thoracic, abdominal or eye surgery (within 1 month), acute nausea or vomiting, severe respiratory distress, dementia).

We will exclude patients who do not need inhaler medication on a daily basis, since these patients are less susceptible to the full impact of the intervention. In addition, these are mostly patients with intermittent asthma as well as patients with COPD with mild obstruction (GOLD stage I) and tend to have a low frequency of disease exacerbations, which would hamper our ability to detect a true outcome effect.

Predictors/Intervention

Intervention Group: This group will receive a structured and regular follow-up plan, with education on inhaler technique. Patients will be trained by a Family Doctor (the primary investigator) in terms of the inhaler technique using placebo devices similar to their own devices. We will start by evaluating their baseline technique, and then, a teach-to-goal approach will be used with correction of identified errors. Then, we will ask patients to demonstrate the inhaler technique, and again, committed errors will be corrected by demonstration. We will repeat all correct steps as many times as needed in order for patients to perform them correctly. This intervention will be performed at baseline, 3 and 6 months. Outcomes will be assessed at baseline and after 3, 6 and 12 months, since there is dissenting evidence about the best timeline to achieve significant exacerbation risk reductions.[21 30 32] In each visit, and prior to the main intervention with the primary investigator, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator.

Control Group: This group will receive usual care from their own Family doctors, with no specific intervention. Each doctor will perform the necessary clinical appointments according to his/her real life judgement. Besides this, this group will have visits at baseline and after 3, 6 and 12 months to assess secondary outcomes. At each visit, assessment of the inhaler technique and application of all questionnaires (clinical control, treatment adherence and quality of life) will be performed by a secondary blinded investigator. At any appointment, if the patient asks for or if the clinician decides to teach inhaler technique, that will be recorded, since it will be important to analyse and control for the true effect size of intervention.

If any adjustments are made in drug classes or device types in any participant, this information will be recorded.

Outcomes of interest

Primary outcome

Adverse events (continuous, time to event).

For asthma, an event will be defined as increased respiratory clinical symptoms leading the patient to search for medical care and resulting in any of the following:

- Need for increased inhaled corticosteroid dose of at least 4× the regular dose.
- Need for increase of short-acting $_2$ agonists on a daily basis.
- Need for oral corticosteroids.
- Need for oral antibiotics.
- Hospitalisation or emergency room (ER) visit with increased respiratory clinical symptoms.

For COPD, an event will be defined as increased respiratory clinical symptoms prompting the patient to search for medical care, and resulting in any of the following:

- Need for increase of long-acting $_2$ agonists on a daily basis.
- Need for oral corticosteroids.
- Need for oral antibiotics.
- Hospitalisation or ER visit with increased respiratory clinical symptoms.

Respiratory-related mortality and all-cause mortality will also be considered an adverse event.

All adverse events and mortality causes will be carefully analysed in order to assess their eligibility by two independent and external investigators, who will constitute a Data Safety Monitoring Board. This will be performed using different platforms of clinical records, from the ER of the regional reference hospital, from the Primary Healthcare facilities (such as PEM for prescribed drugs, SCLINICO for clinical records and PDS for ER records) and even by asking the participant for additional information. After any event, and if necessary for ethical reasons, inhaler technique and adherence improvement will be addressed by the primary investigator regardless of the participant allocation, and in accordance with the recommendation of the Data Safety Monitoring Board.

Secondary outcomes

- Clinical assessment using COPD Assessment Tools and modified Medical Research Council for COPD; Control of Allergic Rhinitis and Asthma Test[47] and Asthma Control Test for asthma.[48]
- Quality of Life using St. George's Respiratory Questionnaire[49] and Clinical COPD Questionnaire[50] for COPD and Asthma Quality of Life Questionnaire.[51]
- Functional control using Forced Expiratory Volume in 1 s (FEV1), forced vital capacity (FVC), peak expiratory flow and maximum expiratory flows of 25%–75% of FVC (MEF25-75) as a % of predicted value; and FEV1/FVC ratio.
- Adherence rate using the Brief Medication Questionnaire (this will also evaluate the frequency of using the devices).[52]
- Number of errors in inhaler technique (that will be standardised to a score up to 100% scale).
  (To evaluate inhaler technique performance with each device, the Aerosol Drug Management Improvement Team (ADMIT) protocols and guidelines will be used,[53] evaluating all the recommended steps for inhaler use in each one of them (pMDI with or without chamber, Qvar Autohaler, Turbohaler, Diskus, Aerolizer, Handihaler, Breezhaler, Novolizer, Genuair, Twisthaler and Easyhaler). For those devices that do not have any protocol from the ADMIT group we will use the recommendations from the manufacture`s Summary of Product Characteristics (Soft Mist Inhaler, Budesonide from *Farmoz*, Ellipta, Spiromax and Forspiro)).

All questionnaires will be used in validated Portuguese versions.[47–52 54 55] All participants will perform spirometry with bronchodilation test at baseline visit for diagnostic confirmation, as well as a baseline spirometry without bronchodilation for functional control at subsequent visits. A certified provider will perform spirometry.

Other variables collected at baseline

- Demographics (body mass index, age, sex).
- Classification of clinical status, according to:
  - Exacerbation history.
  - Years of diagnosis.
  - Asthma classification/stage according to GINA guidelines (clinically as well controlled, partially controlled or uncontrolled; and therapeutically as in STEP 1, 2, 3, 4 or 5).[45]
  - COPD stage according to 2017 GOLD guidelines (combined assessment stages A, B, C and D; and severity of airflow limitation GOLD 1, 2, 3 and 4).[46]
- Social class according to Graffar classification (Portuguese version).[56]
- Comorbidities (such as concomitant allergic rhinitis, cancer, cardiac heart failure, alcohol or drug abuse, current smoking and smoking pack years, diabetes mellitus, previous stroke or acute myocardial infarction, thoracic, abdominal or cerebral aneurysms, severe osteoarthrosis in hands and upper limbs).
- Depression using Geriatric Depression Scale in Portuguese.[57]
- Frailty state in elderly, using a self-reported instrument in Portuguese.[58]
- Cognitive function using Montreal Cognitive Assessment (MOCA) in Portuguese.[59]
- Influenza and pneumococcal vaccination status.
- Previous teaching of inhaler technique, specifying the education type (placebo device, video, leaflet, multimedia and so on).
- Years of use with current device.

The principal investigator will collect all baseline data prior to allocation and randomisation, and this will be recorded in a proper form.

Statistical analysis

The hypothesis testing approach will be the following:

Null hypothesis

Teaching inhalation technique performance with a placebo device approach does not reduce the exacerbation

risk in elderly patients with asthma or COPD after a 1-year follow-up.

Alternative hypothesis

Teaching inhaler technique performance with a placebo device approach reduces the exacerbation risk in elderly patients with asthma or COPD after a 1-year follow-up.

Dichotomous predictor

Usual Care VS Regular teach-to-goal education with placebo device.

Dichotomous outcome

Exacerbation: Yes/No.

Data will be analysed using the *STATA Statistical Package*© software.

Test statistic for primary outcome

Dichotomous data will be analysed with a two-sample proportions χ^2 test and a COX proportional hazard time-to-event analysis, and both arms will be compared using the measures of association: risk ratio; risk difference; HR and number needed to treat analyses.

Test statistic for secondary outcomes

Continuous data will be analysed using parametric tests, such as T test for comparison of mean values and dichotomous data will be analysed using χ^2 test. In order to test differences between groups in the mean values of continuous analysis, mixed effects models for repeated measures will be used. For binary outcomes, linear regression models with group-time interactions will also be adapted, and generalised linear models (such as Poisson regression) will be applied for exacerbations, as recommended in the literature.[60] As an alternative approach, generalised estimating equation models will be used to handle unmeasured dependence between outcomes.

In case of cohort losses above 20%, comparative analysis for intention to treat, per-protocol and a multidata imputation will be carried out. Missing data will be treated as missing completely at random. Subgroup analysis will be performed according to secondary variables, such as diagnosis, age (including stratification into the following categories: 65–75, 75–85 and >85 years), sex, years of diagnosis, disease classification/stage, comorbidities, educational level, previous teaching of inhaler technique, device type as well as the specific types of detected errors (in order to identify the most critical ones). This will be performed using regression models to multivariate analyses.

An interim analysis will be performed midway through the follow-up, namely at 6 months, defining a significance level adjusted by the Bonferroni technique of 0.025.[61]

Study setting

The study will be conducted in a multicentre network that will include two or three primary care centres, which will be coordinated by a team of experts in the field. All of them will be in urban or suburban areas. A Portuguese primary care centre usually accounts approximately for more than 10 000 patients, and about 30% of them are aged above 65 years. Considering an approximate prevalence of asthma and COPD of 8% in this population, there is a potential target population of almost 250 patients in each healthcare facility. Recruiting patients at more than one site will improve the feasibility, reproducibility and credibility of the study, but will increase all the logistic issues.

All invited participants will have a first contact will the primary investigator to confirm the diagnosis and all the eligibility criteria, and to carefully explain all the study procedures before their inclusion and subsequent randomisation. Diagnosis will be confirmed according to state of the art and the previously mentioned updated guidelines and with spirometry. The number of patients screened and deemed ineligible as well as the number of patients who are considered eligible but decline participation will be also recorded.

Timeline

- Study protocol final version: August 2017.
- Ethics consent and scientific academic authorisation: December 2017.
- Clinical administrative authorisations: first semester of 2018.
- Multicentre team gathering: first semester of 2018.
- Beginning of recruitment: second semester of 2018.
- End of recruitment: second semester of 2019.
- Data analysis and dissemination: during 2020.

Patient and public involvement

No patient or public were involved in the design of this protocol, or in the establishment of the intervention and the outcome measures. Results from all participants will be given to their own family doctors in order to be used if deemed necessary to clinical practice.

DISCUSSION

This study is innovative because it includes exclusively elderly patients with asthma or COPD, addressing a specific placebo device education programme, alone, without any other aspects, and it was designed to detect a significant reduction on disease exacerbation rate. It is expected to detect approximately 55 adverse events, 18 in the intervention group and 37 in the control group. In addition, it is expected to find a more significant improvement in the intervention group, in all clinical and functional parameters during the follow-up.

This study has some limitations, mainly in selection bias due to the risk of missing data and follow-up losses. To overcome this problem, different strategies will be applied, such as an increase in estimated sample size, readjusted for an estimation of 20% losses and sending a reminder prior to each visit using SMS/Email/Call to contact the participant.

Another aspect that could bias our study is the Hawthorne effect throughout the study (ie, behaviour change in participants due to their involvement in the study). However, we believe that by establishing a cohort time of 1 year, this effect will not be sustained. On the other hand, the control group ('usual care') will maintain their usual care at their own family doctors, who are completely free from any influence of the study design. For this reason, the control group ('usual care') participants will not receive any intervention from the primary investigator. They will only contact with the secondary investigator in order to collect endpoints and outcome data, and the latter is completely blinded to randomisation. With this approach, the Hawthorne effect will not contaminate the control group and will represent a real life usual care. On the other hand, the Data Safety Monitoring Board will be composed of two external investigators, who will, together with the statistician, be blinded to the endpoints and outcomes (PROBE setting). Using usual care as the comparator arm also brings some limitations to consider, because it is not a perfect comparator due to its nature. It is not sufficient for good patient outcomes and it is not standardised. This aspect is due, for instance, to the fact that patients on usual care can receive interventions on inhaler education and self-management tools from other uncontrolled sources. To overcome that we will retrospectively query patients in this arm and their own family doctor for any type of interventions that may have been delivered during the study period.

Another possible limitation of our study is that we will not use electronic measures of adherence and inhalation techniques. These are a very useful approach to monitoring real world adherence to inhaler therapy. In fact, these electronic measures overcome the bias seen with self-report and other problems observed with objective medication checks such as prescription refill rates. However, most electronic measures of adherence do not measure timing of device activation but rather the overall number of activations performed, and, in addition, this measure does not mean that medication was taken on a regular basis (patients may just activate the inhaler several times, prior to handing over the device). It is not until recently that a new device has been studied, which seems to overcome this problem, and which also analyses inhaler technique, but it is not widely available—INCA device.[62] Nevertheless, these devices are expensive and their use could not be implemented in our study. We therefore decided to use the adherence questionnaire (BMQ), which is a well-validated tool in several languages worldwide and also in Portuguese.[52] Furthermore, it is a very simple and easy method to detect non-adherence, which also allows separating subdomains of adherence. Thus, it is a good tool for assessing adherence in our study involving the general population of patients with asthma and COPD. Regarding inhalation technique, we decided to use regular checklists, since they are the most widely method used in other studies, thereby allowing further comparisons. They are also easy to use and allow detection of critical errors in each device.

The standardisation of the protocol intervention is another issue to be considered. In order to overcome different approaches among different investigators from different multicentre sites, a protocol with detailed instructions will be created to guide them during the intervention (investigators) and assessment visits (secondary investigators). This protocol will explain all the steps and procedures for training inhaler technique as well as for assessing it, and all the procedures to follow in each visit for assessing the outcomes.

Primary investigators will be trained in communication techniques related to inhaler education of different devices and all of them will have a kit of placebo devices for use with participants. Such training will allow the standardisation of all procedures of intervention and it will be provided ahead by the coordination team of the study.

Ethics and dissemination

The study protocol has already been analysed by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017–025 and was approved on 22 November 2017.

Every participant will sign a written consent form (online supplementary appendix I). We decided to use 'usual care' as the main comparator instead of another intervention method, since all interventional methods have shown some degree of efficacy in clinically relevant outcomes, as previously mentioned. We thus believe that comparing with other education methods would minimise the effect detection of our teach-to-goal placebo-device intervention. Moreover, all of the randomised studies that included mostly elderly patients also used 'usual care' as a comparator, which will be important when comparing them with our results. However, we highlight the fact that those studies did not use the same age criteria as we are using, since they also included non-elderly adult patients in their samples. In addition, they did not just focus on inhaler teaching, since they provided additional sessions with other programme elements, such as self-management care. There is, thus, insufficient evidence about the efficacy of inhaler education as an isolated intervention, and for that reason, our approach will be novel and will significantly contribute towards clarifying those issues.

A Data Safety Monitoring Board will be set up, composed of two external investigators with a board expertise in this clinical field and in academic and scientific activities, to evaluate data obtained throughout the study. Evaluations will occur every 6 months, whatever the number of participants enrolled or the follow-up time reached at that point. The stop earlier criteria will be defined as any moment on follow-up in which the collected data show statistically significant differences in the primary outcomes. The study may be suspended earlier if sufficient data are obtained for at least 6 months of follow-up or if significant evidence of intervention effectiveness is

obtained, providing that statistical significance values are met by the Bonferroni adaptation.

Invited participants who refuse to participate will be evaluated at baseline, according to previously mentioned characteristics, in order to compare them with the included cohort. They will also be invited to sign a written informed consent form that will allow investigators to collect such data. The documents used to collect the data of the participants will contain only an identification code of each participant, in order to protect their identity. The code of each participant must be composed of the initials of the first two names, followed by the last two digits of the National Healthcare Service Number (eg, *Name FirstSurname SecondSurname*, 123456789 ——>code 'NF89').

The number of participants considered ineligible will be recorded, as well as the number of eligible participants who refuse to participate in the study.

The results obtained from this study will be published in peer-reviewed journals and presented at scientific meetings of primary healthcare and respiratory fields. All data recorded during the study will be stored for a period of 5 years, in accordance with the Portuguese Clinical Research Law, in a safe and proper place in the primary investigator`s health centre. After this period, all data that contain participants' codes will be destroyed.

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Patient consent Not required.

Ethics approval Ethics Committee of University of Beira Interior, Covilhã, Portugal.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data from the trial will be kept in a safe place of the principal investigator's institutional facilities and by the Data Safety Monitoring Board, in accordance with the national and international clinical research policies.

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Sub-appendix I - Informed consent form:

APPENDIX I - Informed consent form, according to Portuguese Directorate-General of Health.

Consentimento Informado nos termos da Norma nº 015/2013 da DGS

Estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações"

A sua unidade de saúde convida-o a participar no estudo "Ensino da técnica inalatória em idosos com Asma e DPOC: impacto nas exacerbações". Foi convidado para participar neste estudo porque se trata de um doente com uma doença respiratória crónica (como Asma ou DPOC) e está a ser medicado com um dispositivo inalatório diariamente.
Os objetivos deste estudo são:

- Verificar se utiliza corretamente o seu dispositivo inalatório
- Testar se o ensino regular do uso do inalador melhora o controlo da sua doença.
- Testar se o mesmo ensino regular diminui a probabilidade de ter alguma crise de agudização/exacerbação pela sua doença, e que pode ser potencialmente fatal.

Para verificar estes objetivos iremos dividir, de forma aleatória, os utentes convidados a participar em dois grupos diferentes. Ambos os grupos irão ser avaliados regularmente sobre o controlo da sua doença, quer quando aos sintomas, qualidade de vida e quanto à sua capacidade pulmonar/respiratória. Isto será feito através da aplicação de questionários bem como da realização de um exame complementar simples e não invasivo, a espirometria.
A principal diferença entre os dois grupos, é que, um deles irá receber adicionalmente de um investigador, um ensino e treino regular sobre o uso correto dos dispositivos inalatórios, enquanto o outro grupo irá apenas receber os cuidados médicos regulares que necessitar pelo seu próprio Medico de Família.
A sua participação no estudo irá durar 12 meses. Ao aceitar participar neste estudo, será sorteado para um dos dois grupos, e após isso irá ser avaliado nesta Unidade de Saúde passados 3, 6 e 12 meses pelos investigadores. Não irá saber em nenhum momento (nem o seu Medico de Família) a qual dos grupos pertence, pois, o objetivo do estudo é não influenciar a forma como os dois grupos se comportam. Todas as consultas realizadas no âmbito deste estudo serão gratuitas para si, bem como a realização das avaliações pelos investigadores.
O estudo será coordenado pelo Dr. Tiago Maricoto, da USF Aveiro-Aradas, que é o investigador principal. A sua participação no estudo é voluntária. Poderá decidir não participar no estudo a qualquer momento sem prejuízo dos seus cuidados médicos. Todos os dados recolhidos neste estudo permanecerão confidenciais. O seu Medico de Família terá acesso no final do estudo aos resultados dos seus exames e avaliações.
O potencial benefício para a sua Saúde ao participar neste estudo é melhorar o controlo clínico da sua doença respiratória, melhorar a capacidade respiratória dos seus pulmões e diminuir o risco de crises de agudização graves e potencialmente fatais. Não existem riscos significativos para a sua saúde. Ao não participar neste estudo perde ainda a oportunidade de poder melhorar a forma como usa os seus dispositivos inalatórios, o que pode comprometer o bom controlo da sua doença a longo prazo.

[Parte declarativa do profissional]
Confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os procedimentos necessários ao ato referido neste documento. Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão. Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome legível do profissional de saúde: |_____|
Assinatura, nº de cédula profissional/mecanográfico: ……....
Unidade de Saúde: _____
Contato institucional do profissional de saúde: _____

À Pessoa/representante
Por favor, leia com atenção todo o conteúdo deste documento. Não hesite em solicitar mais informações se não estiver completamente esclarecido/a. Verifique se todas as informações estão corretas. Se tudo estiver conforme, então assine este documento.

[Parte declarativa da pessoa que consente]
Declaro ter compreendido os objetivos de quanto me foi proposto e explicado pelo profissional de saúde que assina este documento, ter-me sido dada oportunidade de fazer todas as perguntas sobre o assunto e para todas elas ter obtido resposta esclarecedora, ter-me sido garantido que não haverá prejuízo para os meus direitos assistenciais se eu recusar esta solicitação, e ter-me sido dado tempo suficiente para refletir sobre esta proposta. Autorizo/Não autorizo ***(riscar o que não interessa)*** *o ato indicado, bem como os procedimentos diretamente relacionados que sejam necessários no meu próprio interesse e justificados por razões clínicas fundamentadas.*

NOME: |_____|

Assinatura ……..... ……/……/…… (data)

SE NÃO FOR O PRÓPRIO A ASSINAR POR IDADE OU INCAPACIDADE
(se o menor tiver discernimento deve também assinar em cima)
NOME: .....
DOC. IDENTIFICAÇÃO N.º ..... DATA OU VALIDADE ….. /...… /….....
GRAU DE PARENTESCO OU TIPO DE REPRESENTAÇÃO: .....
ASSINATURA……

O presente documento é emitido em duplicado, ficando um na posse do participante, e outro arquivado pelos investigadores em local próprio