UNIVERSIDADE DA BEIRA INTERIOR
Ciências da Saúde

Inhaled Therapy-Associated Adverse Reactions in Obstructive Respiratory Diseases: A Review of a Decade of Reporting to the Portuguese Pharmacovigilance System

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Dissertação para a obtenção do Grau de Mestre em
Medicina
(ciclo de estudos integrado)

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Covilhã, maio de 2019

Dedicatória

À minha família, principalmente ao meu avô Faustino

Agradecimentos

Agradeço a todas as pessoas que contribuíram na realização desta dissertação:

- Ao meu orientador, Professor Doutor Luís Taborda Barata por todo o empenho, pelas recomendações, sugestões e correções que permitiram a conclusão deste trabalho

- À minha coorientadora, Dr.ª Cristina Monteiro por toda a explicação que me deu relativamente a área da Farmacovigilância, pelas recomendações e sugestões e por ter estado sempre disponível para clarificar as minhas dúvidas.

- À Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED) pela cedência dos dados e informação indispensáveis à realização deste estudo.

- À minha família, principalmente à minha mãe e ao meu pai pelo carinho e apoio incondicional.

- Aos meus amigos, em especial ao João Faia por todo o apoio e à Daniela Alves pela formatação.

- Ao "*mate*" José Luís pela interajuda e camaradagem.

- À Faculdade de Ciências da Saúde da Universidade da Beira Interior por toda formação profissional e pessoal que me facultou.

- À cidade da Covilhã por ter sido a cidade que me acolheu nesta aventura que estou a fazer num país novo.

- À Tuna Médica da Universidade da Beira Interior (Tuna-MUs) por todas a aventuras que me proporcionou e amizades que ficam para vida.

A todos, muito obrigado!

Resumo

Introdução: Na terapia das doenças respiratórias (das vias aéreas) obstrutivas crónicas , nas quais estão incluídas a asma, a doença pulmonar obstrutiva crónica (DPOC), e a sobreposição asma/DPOC (ACO), há vários medicamentos que são administrados através de dispositivos inalatórios, sendo esses medicamentos pertencentes às seguintes classes: corticosteróides, agonistas de recetores β2-adrenérgicos e antagonistas dos recetores muscarínicos. Certas reações adversas a medicamentos (RAMs) associadas a este tipo de terapia têm sido reportadas em ensaios clínicos de pré-comercialização, bem como em estudos de caso / *case reports*. No entanto, há poucos estudos de vigilância pós-comercialização focados em suspeitas de RAMs notificadas espontaneamente ao sistema de Farmacovigilância, não havendo nenhum publicado em Portugal.

Objetivos: Caraterizar as notificações espontâneas (NE) de suspeitas de RAMs associadas à terapia inalatória das doenças respiratórias obstrutivas crónicas recebidas pelo Sistema Nacional de Farmacovigilância (SNP) Português, no período de 2007 a 2017.

Materiais e métodos: Estudo observacional retrospetivo baseado na análise de suspeitas de RAMs espontaneamente notificadas ao SNP, associadas aos inaladores com medicamentos das classes: LAMA (antagonistas muscarínicos de longa ação), SAMA (antagonistas muscarínicos de curta ação), LABA (agonistas β2 adrenérgicos de longa ação), SABA (agonistas β2 adrenérgicos de curta ação), ICS (corticosteróides inalados), combinação LAMA/LABA, combinação SAMA/SABA e combinação ICS/LABA. As NE foram avaliadas de acordo com as características demográficas dos pacientes, classes farmacológicas dos medicamentos suspeitos, tipo e gravidade das suspeitas de RAMs.

Resultados: Foram analisadas 230 NEs, contabilizando um total de 599 suspeitas de RAM. Observou-se uma tendência para o aumento do número de notificações ao longo dos anos em estudo, sendo que a média foi de 2 NE por 1000 habitantes com uma doença respiratória obstrutiva crónica por ano. A combinação ICS/LABA obteve a maior frequência tanto em NE (*n*=74, 32.2%) como em RAM (*n*=196, 32.7%). Houve um predomínio ligeiro nos homens (NE *n*=118, 51.3%) e os adultos não idosos foram a faixa etária mais afetada (NE *n*=90, 39.1%). A maioria das NE foram classificadas como sendo graves (*n*=162, 70.4%). No total, as reações do tipo "doenças respiratórias, torácicas e do mediastino" foram as mais notificadas (*n*=117, 19.5%), sendo a "dispneia" a suspeita de RAM mais frequente (*n*=29; 4.8%). Houve muitos casos de erros de medicação associados a sintomas e exacerbações das doenças e casos de sobredosagem / *overdose* de SABAs.

Conclusões: A maioria das NE foram associadas a medicação de manutenção e classificadas como sendo graves. A maioria das reações foram esperadas, ficando a recomendação das

autoridades analisarem as não esperadas para a atualização do perfil de segurança dos medicamentos. Os dados presentes comprovam a existência de erros na utilização dos dispositivos inalatórios, que estão associados a níveis subótimos de efeito terapêutico e, portanto, a controlo ineficaz das doenças respiratórias. Os dados recolhidos também indicam a existência de uso excessivo da medicação de alívio.

Palavras-chave: Reações adversas a medicamentos; Farmacovigilância; Asma; DPOC; Dispositivos inalatórios; Segurança.

Resumo alargado

Introdução: A asma, a doença pulmonar obstrutiva crónica (DPOC) e sobreposição asma-DPOC (ACO) fazem parte das doenças respiratórias (das vias aéreas) obstrutivas crónicas, sendo caraterizadas por um aumento da resistência ao fluxo do ar, por obstrução parcial ou completa das vias aéreas. Para o tratamento destas doenças usam-se medicamentos que são administrados através de dispositivos inalatórios pertencentes às seguintes classes: corticosteróides, agonistas de recetores β2-adrenérgicos e antagonistas dos recetores muscarínicos. Como com qualquer medicamento, a terapêutica inalatória das doenças respiratórias obstrutivas crónicas está associada a reações adversas a medicamentos (RAMs). Uma RAM está definida como sendo uma resposta nociva e não intencional a um medicamento, quer o produto seja utilizado dentro ou fora dos termos da autorização de introdução no mercado. As RAMs associadas à medicação inalatória foram reportadas em ensaios clínicos de pré-comercialização e em estudos de caso / *case reports*. No entanto, há poucos estudos de vigilância pós-comercialização focados em suspeitas de RAMs espontaneamente notificadas ao sistema de Farmacovigilância, não havendo nenhum publicado em Portugal. Como se sabe, a vigilância pós-comercialização, principalmente através das notificações espontâneas, é uma fonte preciosa de deteção de sinais de RAMs desconhecidas e raras que não foram detetadas nos estudos controlados de pré-comercialização. Este estudo foca precisamente as suspeitas de RAMs notificadas espontaneamente, associadas à terapêutica inalatória.

Objetivos: Caraterizar as notificações espontâneas (NE) de suspeitas de RAMs associadas à terapêutica inalatória das doenças respiratórias obstrutivas crónicas, recebidas pelo Sistema Nacional de Farmacovigilância (SNP) Português, no período de 2007 a 2017.

Materiais e métodos: Estudo observacional retrospetivo baseado na análise de suspeitas de RAMs espontaneamente notificadas ao SNP, associadas a 20 inaladores das classes: LAMA (antagonistas muscarínicos de longa ação), SAMA (antagonistas muscarínicos de curta ação), LABA (agonistas β2 adrenérgicos de longa ação), SABA (agonistas β2 adrenérgicos de curta ação), ICS (corticosteróides inalados), combinação LAMA/LABA, combinação SAMA/SABA e combinação ICS/LABA. Os dados presentes neste trabalho são totalmente anónimos, não sendo, assim, necessário obter aprovação de Comissões de Ética. Os dados foram recolhidos da base de dados do SNP, que contém todas as notificações submetidas por profissionais de saúde, consumidores e titulares da autorização de introdução no mercado dos medicamentos. As suspeitas de RAMs são submetidas ao SNP sob a forma ICSRs (*Individual Case Safety Reports*), sendo que, para ser válida uma notificação deve ter quatro informações mínimas: um paciente identificável, um notificador identificável, pelo menos uma suspeita de RAM e pelo menos um medicamento suspeito. As NE foram avaliadas de acordo com as características demográficas (sexo e grupo etário) dos pacientes, classes farmacológicas dos medicamentos suspeitos, tipo e gravidade das suspeitas de RAMs. Foi analisada a evolução temporal do número de NE e fez-

se uma estimativa da incidência de NE de cada ano, tendo em conta a prevalência descrita de asma e DPOC e a população geral Portuguesa. A gravidade das NE baseia-se na Convenção de Consenso Autoridade/Unidades para Atribuição de Grau de Gravidade a Reações Adversas Medicamentosas (ConGGrav),ou na lista de *Important Medical Event Terms* (IME) da Agência Europeia do Medicamento. Fez-se um Teste de Qui-quadrado (χ^2) para ver a relação entre a gravidade e o sexo e entre a gravidade e o grupo etário. As suspeitas de RAMs foram analisadas de acordo com o *Preferred Term* (PT) e *System Organ Class* (SOC) do *Medical Dictionary for Regulatory Activities* (MedDRA).

Resultados: Depois de excluídas as NE repetidas e aquelas cujos medicamentos tinham vias de administração diferentes, foram encontradas 230 NEs, contabilizando um total de 599 suspeitas de RAM. A tendência foi a de aumento do número de notificações ao longo dos anos em estudo, sendo que a média foi de 2 NE por 1000 habitantes com uma doença respiratória obstrutiva crónica por ano. A combinação ICS/LABA obteve a maior frequência tanto em NE (*n*=74, 32.2%) como em RAM (*n*=196, 32.7%). Houve um predomínio ligeiro nos homens (NE *n*=118, 51.3%) e os adultos não idosos foram a faixa etária mais afetada (NE *n*=90, 39.1%). A maioria das NE foram classificadas como sendo graves (*n*=162, 70.4%), sendo que NE sérias foram as mais frequentes em todas as classes com exceção da combinação SAMA/SABA. Houve três casos fatais, sendo 2 associados a um LAMA e 1 a um ICS. Em termos de frequência absoluta, as NE classificadas como graves foram mais frequentes nos homens e na faixa etária dos adultos não idosos. No teste do χ^2 foi encontrada uma associação entre gravidade e grupo etário, mas a mesma não se observou entre gravidade e sexo. No total, as reações do tipo "doenças respiratórias, torácicas e do mediastino" foram as mais notificadas (*n*=117, 19.5%), sendo a "dispneia" a suspeita de RAM mais frequente (*n*=29; 4.8%). Houve muitos casos de erros de medicação associados a sintomas e exacerbações das doenças. Por classes, as suspeitas de RAMs graves mais frequentemente notificadas foram: "dor no peito" e "cefaleias" nos LAMA, "overdose" nos SABA, "síndrome de Cushing" nos ICS e "dispneia" nos outros todos. "Dispneia" foi a suspeita de RAM grave mais frequentemente notificada em ambos os sexos e em todos os grupos etários, exceto nas crianças, onde foi "edema periféricos".

Conclusões: Este foi o primeiro estudo focado no padrão de suspeitas de RAMs notificadas espontaneamente, associadas à terapêutica inalatória das doenças respiratórias obstrutivas crónicas. Houve uma tendência no aumento do número de notificações ao longo do período em estudo. A maioria das NE foram associadas a medicação de manutenção e classificadas como sendo graves. A maioria das reações foram esperadas, ficando a recomendação das autoridades analisarem as não esperadas para a atualização do perfil de segurança dos medicamentos. Os dados presentes comprovam a existência de erros na utilização dos dispositivos inalatórios, que estão associados a níveis subótimos de efeito terapêutico e, portanto, controlo ineficaz das doenças. Os dados também sugerem a existência de uso excessivo da medicação de alívio. O estudo teve algumas limitações, sendo as principais o viés da baixa taxa de notificações

espontâneas de RAMs, a variabilidade na qualidade das notificações e a existência de fatores que dificultam o estabelecimento de causalidade das suspeitas de RAMs com os medicamentos suspeitos. Recomenda-se desenvolver mais estudos de pós-comercialização, para uma melhor caraterização da RAMs associadas à terapêutica inalatória, bem como estudos para entender melhor os fatores associados a erros na medicação e estudos para melhor analisar o uso excessivo dos SABA. Recomenda-se também maior consciencialização da importância de notificar reações adversas a medicamentos, independentemente da gravidade.

Abstract

Introduction: Obstructive lung diseases (OLDs) include asthma, chronic obstructive pulmonary disease (COPD), and asthma/COPD overlap (ACO). OLDs therapy includes medications that are administered through inhalation devices belonging to the following classes: corticosteroids, β2-adrenergic receptor agonists and muscarinic receptor antagonists. Certain adverse drug reactions (ADRs) associated with this therapy have been reported in pre-marketing clinical trials and case reports. However, there are few post-marketing surveillance studies focused on suspected ADRs spontaneously reported to the Pharmacovigilance system, and none has been published in Portugal.

Objectives: To characterise spontaneous reports (SRs) of suspected ADRs associated with OLDs inhaled therapy received by the Portuguese Pharmacovigilance System (PPS), from 2007 to 2017.

Materials and methods: Retrospective observational study based on the analysis of suspected ADRs spontaneously reported to the PPS, associated with 20 inhalers of the following classes: LAMA (long-acting muscarinic antagonists), SAMA (short acting muscarinic antagonists), SABA (short-acting β2 agonists) and LABA (long-acting β2 agonists), ICS (inhaled corticosteroids), LAMA / LABA combination, SAMA / SABA combination and ICS / LABA combination. SRs were evaluated according to the demographic characteristics of the patients, pharmacological classes of suspected drugs, type and seriousness of suspected ADRs.

Results: 230 SRs were analysed, accounting for a total of 599 suspected ADRs. There was a trend towards an increase in the number of notifications over the years under study, with the average being 2 SRs per 1000 inhabitants with one OLD per year. The ICS/LABA combination obtained the highest frequency in both SRs (*n* = 74, 32.2%) and in ADRs (*n* = 196, 32.7%). There was a slight predominance in men (SR *n* = 118, 51.3%) and non-elderly adults were the most affected age group (SR *n* = 90, 39.1%). The majority of SRs were classified as being serious (*n* = 162, 70.4%). In total, "respiratory, thoracic and mediastinal diseases" ADRs were the most reported ones (*n* = 117, 19.5%), with "dyspnoea" being the most frequent one (*n* = 29; 4.8%). There were many cases of medication errors associated with symptoms and exacerbations, and also cases of SABAs overdose.

Conclusions: Most of the SRs were associated with controller medications and classified as being serious. Most of the reactions were expected, with the authorities' recommendation being to review those not expected to update the drug safety profile. The present data confirm the existence of errors in the use of inhalation devices, which are associated with suboptimal levels of therapeutic effect and, therefore, ineffective control of the diseases. The data also indicate the existence of overuse of relieving medication.

Keywords

Adverse drug reactions; Pharmacovigilance; Asthma; COPD; Inhalation devices; Safety.

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List of acronyms

ACO	Asthma-COPD overlap
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical
ConGGrav	*Convenção de Consenso Autoridade/Unidades para Atribuição de Grau de Gravidade a Reações Adversas Medicamentosas*
COPD	Chronic obstructive pulmonary disease
ICS	Inhaled corticosteroids
ICSR	Individual Case Safety Report
IME	Important Medical Event
INE	National Institute of Statistics
INFARMED	National Authority of Medicines and Health Products I.P
INN	International Nonproprietary Name
LABA	Long-acting b2 agonists
LAMA	Long-acting muscarinic antagonist
LLT	Low Level Term
MedDRA	Medical Dictionary for Regulatory Activities
OLD	Obstructive lung disease
P	p-value
PT	Preferred Term
SABA	Short-acting b2 agonists
SAMA	Short-acting muscarinic antagonist
SmPC	Summary of product characteristics
SOC	System Organ Class
SR	Spontaneous report
χ^2	Chi-Square Test

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) belong to the group of obstructive lung diseases (OLDs). These are characterised by an increase in resistance to airflow due to partial or complete obstruction in the airways.[1,2,3] More recently, the asthma-COPD overlap (ACO) entity has been described, although it does not yet have a universally accepted definition. ACO more commonly involves patients who are usually older than 40 years, and who have a persistent airflow obstruction with both asthma and COPD features.[2, 4] ACO is, thus, also part of OLDs.

The main treatments for OLDs involve medication delivered via inhaler devices. Inhaled medications used belong to the following classes: inhaled corticosteroids (ICS), β2-adrenergic receptor agonists (with short-acting β2 agonists [SABA] and long-acting β2 agonists [LABA] subclasses) and muscarinic receptor antagonists (with short-acting muscarinic antagonist [SAMA] and long-acting muscarinic antagonist [LAMA] subclasses). ICS and long-acting bronchodilators (LABA and LAMA) are used as controllers while short-acting bronchodilators (SABA and SAMA) are used as relievers.[2,3,4]

As with any drug, inhaled therapy for OLDs is associated with adverse drug reactions (ADRs), especially at high doses. ADR is defined as a noxious and unintended response to a medicine, whether the product is being used within or outside the terms of the marketing authorisation.[5] Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.[5] There must be a suspected causality between the reaction and the drug.[5]

The known reactions associated with inhalers have been reported in pre-marketing clinical trials and case reports.[6-8] ADRs associated with ICS may be local, by deposition in the oropharynx, or systemic when absorbed into the systemic circulation through the lungs or gastrointestinal tract, when swallowed.[6] The most frequently reported local ADRs are oropharyngeal candidiasis, dysphonia and cough during inhalation.[6] Systemic ADRs occur primarily with high doses of ICS, and include easy bruising, adrenal suppression, thinning of the skin, increased risk of cataracts and glaucoma, decreased bone density, psychiatric effects and, in COPD, increased risk of pneumonia and tuberculosis.[6] β2-agonists also have systemic absorption through the lungs or gastrointestinal tract if they are swallowed. Most of the ADRs described are sympathomimetic. The most common ones are increased heart rate, palpitations, transient decrease in oxygen partial pressure in arterial blood, hyperglycaemia, hypokalemia, cardiac arrhythmias and tremors.[7] Muscarinic antagonists are poorly absorbed, and therefore associated with few systemic effects. The most common ADRs are dry mouth, constipation, blurring of vision, urinary difficulty/retention and cardiac effects (increased heart rate, arrhythmias, angina).[8]

To the best of our knowledge, there are few studies focused on spontaneous ADR reports to Pharmacovigilance Systems, and there is no study published in Portugal. Pharmacovigilance is responsible for detection, assessment, and prevention of ADR, in post-marketing authorisation

phase.[9] Spontaneous reporting is a source of information on previously unknown, rare occurring and serious reactions that are not detected in controlled studies.[10]

Taking into account that the use of inhaled therapy for OLDs is widespread, the importance of spontaneous ADRs reports in Pharmacovigilance and the absence of studies in Portugal, it was decided to carry out a study leading to this dissertation.

2. Objective

To analyse and characterise the spontaneous adverse drug reaction reports associated with inhaled therapy used in obstructive lung diseases, received by the Portuguese Pharmacovigilance System from 2007 to 2017.

3. Materials and methods

3.1 Type and object of study

This was a retrospective and observational research study based on the collection and analysis of spontaneous reports (SRs) of suspected ADRs associated with inhaled medications used in obstructive lung diseases (COPD, Asthma and ACO), received by the PPS from 2007 to 2017. As data are anonymous, Ethics Committee approval was not needed.

3.2. Included medications

Based on WHO Anatomical Therapeutic Chemical (ATC) Classification System[11], the drugs belonging to the following subgroups were selected: R03AC (Selective beta-2-adrenoreceptor agonists), R03AK (Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics), R03AL (Adrenergics in combinations with anticholinergics incl. triple combinations with corticosteroids), R03BA (Glucocorticoids) and R03BB (Anticholinergics). In this work the substances are identified by the International Nonproprietary Name (INN).

We analysed the suspected ADR associated with 20 inhalers of three pharmacological classes: muscarinic antagonists (MA) [with the long-acting muscarinic antagonists (LAMA) and short-acting muscarinic antagonists (SAMA) subclasses], β2 adrenergic receptor agonists / β2-agonists (β2A) [with the short-acting β2 agonists (SABA) and long-acting β2 agonists (LABA) subclasses] and inhaled corticosteroids (ICS). Both single-substance inhalers (inhalers with only one active substance) and combination inhalers (inhalers with more than one active substance) are present. Table 1 shows how the inhalers were grouped. The term "multiple inhalers" refers to cases where there was more than one suspected inhaler.

Table 1: Single-substance and combination inhalers.

Single-substance Inhalers				
Muscarinic Antagonists (MA)		**β2-agonists (β2A)**		**ICS**
LAMA	**SAMA**	**LABA**	**SABA**	
Aclidinium Br.	Ipratropium Br.	Formoterol	Salbutamol	Beclometasone
Glycopyrronium Br.	-	Indacaterol	Terbutaline	Budesonide
Tiotropium Br.	-	Salmeterol	-	Fluticasone

Combination Inhalers		
LAMA/LABA	**SAMA/SABA**	**ICS/LABA**
Aclidinium Br./Formoterol	Ipratropium Br./Salbutamol	Budesonide/Formoterol
Glycopyrronium Br./Indacaterol	-	Fluticasone/Salmeterol
Tiotropium Br./Olodaterol	-	Fluticasone/Vilanterol
Umeclidinium Br./Vilanterol	-	-

(Br: Bromide)

3.3. Procedures

3.3.1. Data collection

The data presented in this work were obtained from the PPS database, which was created in 1992 and is coordinated by the National Authority of Medicines and Health Products I.P. (INFARMED). We collected the reports submitted by healthcare professionals, marketing authorisation holders and consumers.

Individual Case Safety Report (ICSR) is the document used for submission of individual report of suspected ADR(s) that occur in a single patient at a specific timepoint, to a regulatory authority. Four minimum criteria are required for an ICSR to be considered valid for submission: 1) one single identifiable patient (with at least one of the following pieces of information: age, sex, initials or medical record number), 2) one or more identifiable reporter (with at least one of the following pieces of information: qualification, initials or contacts), 3) one or more suspected product, 4) one or more suspected ADR.[5] Reporters are encouraged to provide as much information as possible.

The data provided by the PPS contain information that identifies: 1) the year of the SR reception; 2) the active substance(s) of the suspected drug(s); 3) seriousness; 4) criteria of seriousness; 5) the age of the patient 6) the age group of the patient; 7) the sex of the patient; 8) suspected ADR(s) according to the Low Level Term (LLT) of the Medical Dictionary for Regulatory Activities (MedDRA); 9) suspected ADR(s) according to MedDRA Preferred Term (PT); 10) suspected ADR(s) according to MedDRA System Organ Class (SOC); 11) reporter qualification; 12) the therapeutic indication of the suspected medicinal product(s); 13) the therapeutic form of the suspected medicinal product(s); 14) dose of the suspected medicinal product(s); (15) causal relationship with reactions; (16) evolution of the patient. In all reports there is a narrative that summarises all relevant clinical information. We did not have access to information that concerned confidentiality of patients and reporters.

Duplicate SRs and those whose routes of administration of the drug are different from those intended in this study were excluded.

3.3.2. Characterisation of spontaneous reports

Based on the information found in the SRs, an analysis focused on the following parameters was performed: patient's sex and age group, pharmacological classes of suspected medicines, type and seriousness of suspected ADRs.

The frequency distribution of SRs over the involved time period is also represented, adjusted to the estimated population with asthma and COPD. It was calculated by summing up the estimated population with asthma, considering the estimated prevalence of 6.8%[12], with the estimated population with COPD, considering the estimated prevalence of 5.34%[13]. The general data for the Portuguese population for each year were obtained from the National Institute of Statistics (INE) website[14].

3.3.2.1. Demographic characterisation

Each SR corresponds to a patient. They were classified according to sex and divided into three age groups: children (0-17 years), adults (18-64 years) and the elderly (65 years and older).

3.3.2.2. Characterisation of the suspected drug reactions

As mentioned above, each SR corresponds to one patient. However, there may be more than one ADR in each SR. Each suspected ADR was analysed in accordance with the PT and SOC of the MedDRA terminology from which it was coded.

3.3.2.3 Seriousness

The seriousness of SRs was previously attributed by the PPS, based on *Convenção de Consenso Autoridade/Unidades para Atribuição de Grau de Gravidade a Reações Adversas Medicamentosas* (ConGGrav) or on Important Medical Event Terms (IME) List (MedDRA version). SRs with the following criteria were classified as serious: fatal, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, resulting in a congenital anomaly/birth defect, or considered clinically important.[15] All other SRs were classified as non-serious.

3.4. Statistical analysis

Data analysis was performed using a descriptive statistic. Variables under study are qualitative and are described in absolute (n) and relative (%) frequencies. Chi-Square Test (χ^2) was performed to examine the relation between seriousness and sex, and between seriousness and age group of the patients. P-value (p) equal or less than 0.05 was regarded statistically significant.

Data were processed and analysed using the Microsoft® Office® Excel® 365 and IBM® SPSS® (Statistical Package for the Social Sciences) version 22.0 software programmes.

4. Results

4.1. Spontaneous reports received

We started with a total of 271 SR. After all duplicate reports were eliminated, we obtained 254 SR. Finally, after excluding SRs of suspected drugs with a different administration route from that intended in this study, we were left with 230 SR (see the flowchart in figure 1).

We considered SRs that had no information on the therapeutic indication and also those with different therapeutic indications (*e.g.* wheezing). A total of 599 suspected ADRs were identified in the 230 SR.

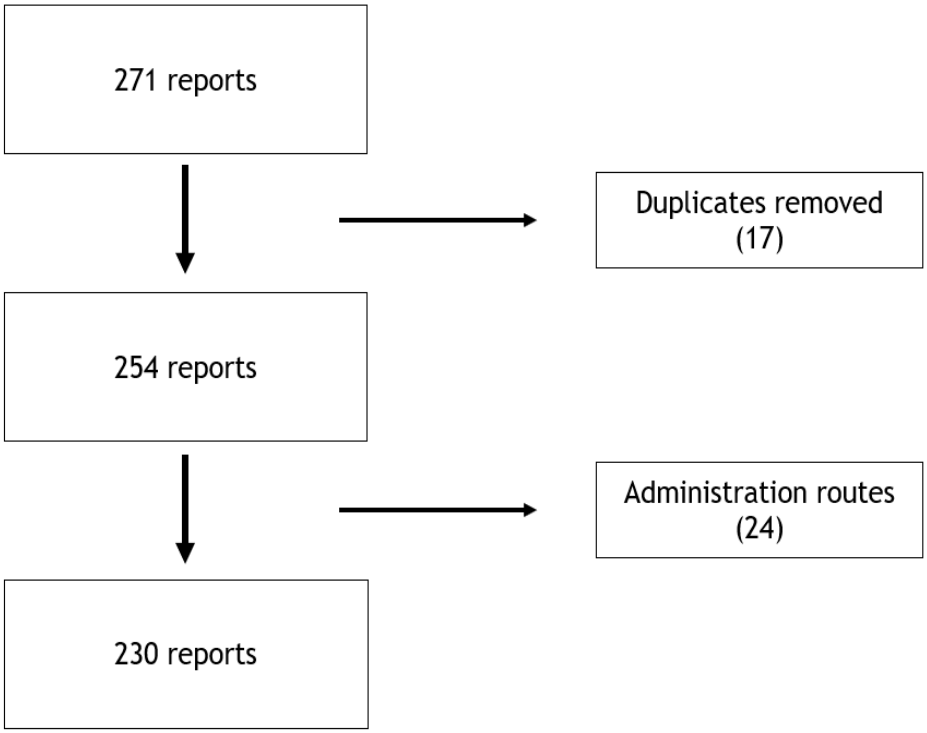

Fig. 1: Flowchart of spontaneous reports selection

Table 2 shows the frequency distribution of SRs over the years, adjusted to the estimated Portuguese population with asthma and COPD.

Table 2: Annual distribution of SR frequency

Year	SRs, *n* (%)	SRs/1000 inhabitants with an OLD
2007	9 (3.9)	0.9
2008	7 (3)	0.7
2009	7 (3)	0.7
2010	15 (6.5)	1.4
2011	19 (8.3)	1.8
2012	24 (10.4)	2.3
2013	14 (6.1)	1.3
2014	28 (12.2)	2.7
2015	45 (19.6)	4.3
2016	25 (10.9)	2.4
2017	37 (16.1)	3.6
Total	230	2/Year

In general, there was an increase in reporting over the years, with more than half (58.7%) occurring in the last 4 years (2014-2017). The mean was 2 SRs per 1000 inhabitants with an OLD per year.

4.2. Involved drugs

Table 3 shows the frequency distribution of SR and ADR by pharmacological class.

Table 3: Frequency of SR and suspected ADR by pharmacological class.

Pharmacological Class	SRs, *n* (%)	ADRs, *n* (%)
LAMA	32 (13.9)	76 (12.7)
SAMA	14 (6.1)	44 (7.3)
LABA	33 (14.3)	78 (13)
SABA	15 (6.5)	32 (5.3)
ICS	28 (12.2)	84 (14)
LAMA/LABA	21 (9.1)	62 (10.4)
SAMA/SABA	1 (0.4)	3 (0.5)
ICS/LABA	74 (32.2)	196 (32.7)
Multiple inhalers	12 (5.2)	24 (4)
Total	230 (100)	599 (100)

In terms of pharmacological classes, the ICS/LABA combination showed the highest frequency in both SR (*n*=74, 32.17%) and in suspected ADRs (*n*=196, 32.72%). The budesonide/formoterol combination obtained the highest frequency of SRs (*n*=34; 14.78%) while the fluticasone/salmeterol combination had the highest record in terms of suspected ADRs (*n*=91, 15.19%), both belonging to the ICS/LABA class.

4.3 Demographic characterisation

Demographic aspects of the patients referred to in the SRs are shown in Table 4.

Table 4: Demographic aspects of SRs, by pharmacological classes.

Class	Sex			Age group			
	Male *n* (%)	Female *n* (%)	NI *n* (%)	0-17 Y *n* (%)	18-64 Y *n* (%)	≥ 65 Y *n* (%)	NI *n* (%)
LAMA	21 (65.6)	11 (34.4)	0 (0)	0 (0)	6 (18.8)	23 (71.9)	3 (9.4)
SAMA	11 (78.6)	3 (21.4)	0 (0)	1 (7.1)	4 (28.6)	7 (50)	2 (14.3)
LABA	17 (51.5)	14 (42.4)	2 (6.1)	2 (6.1)	12 (36.4)	11 (33.3)	8 (24.2)
SABA	5 (33.3)	10 (66.7)	0 (0)	8 (53.3)	5 (33.3)	0 (0)	2 (13.3)
ICS	17 (60.7)	11 (39.3)	0 (0)	11 (39.3)	13 (46.4)	4 (14.3)	0 (0)
LAMA/LABA	14 (66.7)	7 (33.3)	0 (0)	0 (0)	3 (14.3)	9 (42.9)	9 (42.9)
SAMA/SABA	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
ICS/LABA	29 (39.2)	42 (56.8)	3 (4.1)	4 (5.4)	40 (54.1)	19 (25.7)	11 (14.9)
Multi Inhal	4 (33.3)	8 (66.7)	0 (0)	0 (0)	6 (50)	4 (33.3)	2 (16.7)
Total	118 (51.3)	107 (46.5)	5 (2.2)	26 (11.3)	90 (39.1)	77 (33.5)	37 (16.1)

(Multi inhal: multiple inhalers; NI: not identified; Y: years-old)

Overall, non-elderly adults were the most affected ones (SRs *n*=90, 39.1%). Reports on LAMA, SAMA, and LAMA/LABA were more frequent in elderly adults. In contrast, reports on LABA, ICS, SAMA/SABA and ICS/LABA were more frequent in non-elderly adults. Finally, reports on SABA were more frequent in children. Information on the patient's age group was unknown in 37 SRs (16.1%).

There was a slight male predominance (reports *n*=118, 51.3%). Reports related to males were more frequent in all classes, except SABA, SAMA/SABA and ICS/SABA. Information on the gender of patients was unknown in five cases (2.2%).

4.4 Seriousness

Table 5 shows the distribution of SR in terms of seriousness by pharmacological class.

Table 5: SR seriousness by pharmacological classes.

Pharmacological Class	Serious *n* (%)	Non-serious *n* (%)
LAMA	22 (68.8)	10 (31.3)
SAMA	14 (100)	0 (0)
LABA	30 (90.9)	3 (9.1)
SABA	10 (66.7)	5 (33.3)
ICS	22 (78.6)	6 (21.4)
LAMA/LABA	13 (61.9)	8 (38.1)
SAMA/SABA	0 (0)	1 (100)
ICS/LABA	42 (56.8)	32 (43.2)
Multiple inhalers	9 (75)	3 (25)
Total	162 (70.4)	68 (29.6)

Most SRs were labelled as serious (*n*=162, 70.4%). SRs labelled as serious were more frequent in all classes, except for the SAMA/SABA combination.

Of the 162 serious SRs, 117 had the criteria of clinically important, 19 hospitalisation, 9 disability, 5 clinically important and hospitalisation, 3 life-threatening, 2 clinically important and life-threatening, 2 death, 1 life-threatening and disability, 1 hospitalisation and life-threatening, 1 clinically important and disability, 1 hospitalisation and death, 1 congenital anomaly.

SR with the hospitalisation and the disability criteria were both more frequent in LABAs. There were three fatal cases, one being initially related to an ICS (budesonide), presumably being due to acute kidney injury and overdose, and the other two to a LAMA (glycopyrronium bromide), presumably being due to lung cancer and bronchopulmonary aspergillosis, respectively. However, experts concluded afterwards that none had causality with these drugs.

Table 6 shows the demographic aspects of the distribution of seriousness of SRs.

Table 6: Demographic aspects of SRs seriousness distribution

	Male *n* (%)	Female *n* (%)	NI *n* (%)	0-17 Y *n* (%)	18-64 Y *n* (%)	≥ 65 Y *n* (%)	NI *n* (%)
Serious (*n*=162)	87 (53.7)	72 (44.4)	3 (1.9)	24 (14.8)	57 (35.2)	54 (33.3)	27 (16.7)
Non-serious (*n*=68)	31 (45.6)	35 (51.5)	2 (2.9)	2 (2.9)	33 (48.5)	23 (33.8)	10 (14.7)

(NI: not identified; Y: years-old)

SRs labelled as serious were the most frequent ones in both sexes and in all age groups. Males and non-elderly adults had the highest absolute frequency. The relation between seriousness and age group was significant, $\chi^2(2)=8.06$, $p=0.018$, which means that SRs labelled as serious were more likely to be associated with non-elderly adults. The relation between seriousness and sex group was not significant, $\chi^2(1)=1.12$, $p=0.289$.

4.5 Suspected adverse drug reactions

Table 7 shows the five SOCs where the suspected ADRs were more frequently included.

Table 7: The five more frequently reported suspected ADRs, according to the SOC, with all inhalers.

System Organ Class (SOC)	*n*	%
Respiratory, thoracic and mediastinal disorders	117	19.5
General disorders and administration site conditions	100	16.7
Skin and subcutaneous tissue disorders	60	10
Gastrointestinal disorders	51	8.5
Cardiac disorders	41	6.8
Others	230	38.4
Total	599	100

Suspected ADRs included in the "Respiratory, thoracic and mediastinal disorders" SOC were the most frequently reported ones (*n*=117, 19.5%).

Table 8 shows the eleven more frequently reported suspected ADRs, according to the PT where they were included.

Table 8: The eleven suspected ADRs more frequently reported, according to the PT, from all the inhalers.

Preferred Terms (PT)	*n*	%
Dyspnoea	29	4.8
Tachycardia	19	3.2
Cough	17	2.8
Drug ineffective	16	2.7
Pruritus	16	2.7
Asthmatic crisis	14	2.3
Palpitations	13	2.2
Product quality issue	13	2.2
Chest pain	10	1.7
Rash	9	1.5
Throat irritation	9	1.5
Others	434	72.5
Total	599	100

"Dyspnoea" was the most frequent suspected ADR reported (*n*=29; 4.8%) in the total of the SRs analysed.

4.5.1. Suspected ADRs (SOC) by pharmacological classes

Table 9 shows the most frequently reported ADRs associated with each pharmacological class, by SOC classification.

Table 9: Most frequently reported ADR according to the SOC, by pharmacological class

SOCs where the suspected ADR were included	*n*
LAMA	
Nervous system disorders	12
General disorders and administration site conditions	11
SAMA	
Respiratory, thoracic and mediastinal disorders	11
Cardiac disorders	7
LABA	
Respiratory, thoracic and mediastinal disorders	25
Cardiac disorders	10
SABA	
Injury, poisoning and procedural complications	7
General disorders and administration site conditions	6
ICS	
General disorders and administration site conditions	16
Skin and subcutaneous tissue disorders	15
LAMA/LABA	
General disorders and administration site conditions	12
Respiratory, thoracic and mediastinal disorders	7
SAMA/SABA	
Cardiac disorders	1
Nervous system disorders	1
Respiratory, thoracic and mediastinal disorders	1
ICS/LABA	
Respiratory, thoracic and mediastinal disorders	48
General disorders and administration site conditions	38

"Respiratory, thoracic and mediastinal disorders" were the most frequently reported ADR with SAMA, LABA and ICS/LABA inhalers, whereas "General disorders and administration site conditions" were most commonly reported ADR with ICS and LAMA/LABA inhalers.

4.5.2. Serious suspected ADRs (PT) by pharmacological classes

Table 10 shows the most frequently reported serious suspected ADRs ($n \geq 2$) associated with each pharmacological class, according to the PT classification.

Table 10: Serious suspected ADRs ($n \geq 2$) by pharmacological classes

Preferred Term **(PT)**	***n***
LAMA	
Chest pain	4
Headache	4
Tachycardia	3
Cough	2
Death	2
Drug level increased	2
Palpitations	2
SAMA	
Dyspnoea	4
Bronchospasm	3
Delirium	3
Tachycardia	3
Hyperhidrosis	2
Nausea	2
Oedema peripheral	2
Pruritus	2
Stress cardiomyopathy	2
LABA	
Dyspnoea	7
Cough	4
Palpitations	3
Tachycardia	3
Wheezing	3
Abdominal pain	2
Atrial fibrillation	2
Bronchospasm	2
Chest pain	2
Constipation	2
Face oedema	2
Syncope	2
Urinary incontinence	2
SABA	
Overdose	3
ICS	
Cushing's syndrome	4
Drug ineffective	3
Erythema	3
Pruritus	3

Drug interaction	2
Face oedema	2
Lip oedema	2
Osteoporosis	2
Rash	2
LAMA/LABA	
Dyspnoea	2
Product quality issue	2
Urticaria	2
ICS/LABA	
Asthmatic crisis	9
Dyspnoea	9
Drug ineffective	7
Product quality issue	5
Cough	4
Tachycardia	4
Fatigue	3
Off label use	3
Palpitations	3
Rash	3
Adrenal insufficiency	2
Angioedema	2
Chest pain	2
Device malfunction	2
Hypertensive crisis	2
Swelling face	2

In terms of suspected serious ADRs, “chest pain” and “headache” were the most frequently reported ones with LAMA, “dyspnoea” was the most frequently reported serious ADR with SAMA, LABA, LAMA/LABA and ICS/LABA. It should be noted that “overdose” was the most frequent suspected serious ADRs with SABA, whereas with ICS, it was “Cushing’s syndrome”.

4.5.3. Demographic characterization of suspected serious ADRs (PT)

Tables 11 and 12 show the suspected serious ADRs (according to the PT) most frequently reported in each sex and age group, respectively.

Table 11: Most frequent serious suspected ADRs in each sex group

Preferred Term **(PT)**	***n***
Female	
Dyspnoea	14
Cough	9
Drug ineffective	7
Pruritus	7
Asthmatic crisis	6
Erythema	6
Palpitations	6
Male	
Dyspnoea	13
Tachycardia	9
Chest pain	7
Asthmatic crisis	6
Drug ineffective	6
Product quality issue	6

Table 12: Most frequent serious suspected ADRs in each age group

Preferred Term **(PT)**	***n***
≥ 65 Y	
Dyspnoea	8
Tachycardia	8
Chest pain	7
Palpitations	6
Product quality issue	5
Cough	4
18-64 Y	
Dyspnoea	14
Drug ineffective	8
Bronchospasm	6
Cough	6
Asthmatic crisis	5
0-17 Y	
Oedema peripheral	4
Asthmatic crisis	3
Drug ineffective	3
Pruritus	3

(Y: years-old)

In terms of serious suspected ADRs, “dyspnoea” was the most frequently reported one in both sexes and in all age groups, except in children where “oedema peripheral” was the most frequent one.

5. Discussion

In this first Portuguese study of reporting of ADRs to the Portuguese Pharmacovigilance System over a 10 year-long period, regarding inhaler-delivered medication for obstructive lung diseases, we were able to determine the overall reporting frequency, the demographic features of reported cases and the most frequently reported ADRs in terms of severity, clinical features and specific frequency, associated with each inhaler medication type. This is one of few international pharmacovigilance reports of this nature.

ADRs are a major public health problem worldwide, being a considerable cause of mortality, morbidity and financial cost.[16] They may occur associated with any medicinal product, and, therefore, inhaled therapy used in OLDs is no exception. Spontaneous ADRs reporting is the cornerstone of post-marketing drug safety surveillance which is an important part of Pharmacovigilance. Due to the fact that this monitoring occurs in real world conditions, it becomes one of the best methods to generate signals on rare and new ADRs, which were not detected in pre-marketing controlled clinical trials.[10]

In our study, 230 spontaneous reports referring to 599 suspected adverse drug reactions were analysed. This constitutes about 0.6% of the total SRs received by the PPS from 2007 to 2017.[17] The inclusion of SRs in which the therapeutic indication was not identified or had a different indication contributed to the identification of rare reactions.
In the analysed period of time, there was an overall trend towards increasing reporting. This may be related to the overall increase in the total of spontaneous ADRs reports received by PPS in recent years.[17] The true incidence rate of ADRs cannot be correctly determined because of the lack of information on the actual number of patients exposed to the drugs being studied. In this study, a speculation of this rate was made by adjusting the number of annual SRs to an estimate of the Portuguese population with an OLD based on the prevalence values of asthma and COPD, obtaining a mean of about 2 SRs per 1000 per year.

In general, controllers (ICS, LABA, LAMA, ICS/LABA combination and LABA/LAMA combination) had a higher frequency of SRs compared to relievers (SABA, SAMA and SABA/SAMA combination) (81.7% vs 13%). According to guideline recommendations[2,3], controllers are used daily as maintenance therapy while relievers must be used only as needed for quick symptom relief. Because they are more regularly used, one may expect to have a higher frequency of ADRs with the controllers.

Although, in general, women and older patients are regarded as the most susceptible groups to ADRs[18], in our study the suspected ADRs were more frequently reported for males and non-elderly adults. However, it should be noted that in some reports there was a lack of information about the patient's sex (2.2%) and age group (16.1%). Although both are obstructive lung

diseases, asthma and COPD have differences in prevalence in terms of sex. In asthma, there is a male predominance up to 18 years and female predominance in adulthood [19], whereas COPD has a male prevalence in all age groups [20]. Since most patients were 18 years-old or older, it is tempting to assume that ADRs in people with asthma were more frequent in women and in COPD were more frequent in men, and an attempt to explain the greater overall prevalence of ADRs in men could be tried by analysing the therapeutic indications of the drugs to see if there was a greater proportion of COPD. However, because we included SRs in which the therapeutic indication was not identified or was different from those intended in this study, it is difficult to make this assumption. The authors are, therefore, left without an explanation regarding the higher frequency of ADRs in men. Although asthma is more prevalent in children [21] and COPD is more prevalent in older patients [13], in this study ADRs were more common in non-elderly adults, and this can be partly explained by the fact that this is the age group that makes up the majority of the Portuguese population [14].

Suspected serious ADRs were the most reported ones (70.4%). This may in part be related to the fact that serious reactions are more likely to be reported, as was shown in a previous pharmacovigilance study involving general reporting of ADRs with any medication, in Portugal.[22] Furthermore, this observation can be found in other studies on spontaneous reports of ADR associated with other pharmacological classes [23-25]. With the data of this work, we can verify that the probability of a reaction being serious is not influenced by the sex group, being, however, influenced by the age group. In a Bulgarian study of suspected ADRs associated with COPD therapy reported to the Bulgarian Drug Agency (BDA) [26] and in a Danish study of suspected reported ADRs associated with asthma medication licensed for paediatric use located in the European ADR database (EudraVigilance) [27], the majority of ADRs analysed were serious.

Across medications, the majority of the ADRs reported were of the “respiratory, thoracic and mediastinal disorders” type, followed by “general disorders and administration site conditions”, and “skin and subcutaneous tissue disorders”. In the Bulgarian study [26], the most reported suspected ADRs types were "nervous system" followed by "respiratory system" and "cardiovascular system". However, this study included drugs from other classes, such as roflumilast (a long-acting inhibitor of the enzyme phosphodiesterase-4), aminophylline and theophylline (xanthine derivatives). In the Danish study [27], the majority of reported ADRs were of the "psychiatric disorders" type, followed by ‘‘respiratory, thoracic and mediastinal disorders’’ and ‘‘skin and subcutaneous disorders". Montelukast (a leukotriene receptor antagonist) was also included in this study.

As previously mentioned, the majority of the reported ADRs were of the “respiratory, thoracic and mediastinal disorders” type SOC. Although there may be adverse respiratory effects with any of the inhaled medication types, respiratory SOC, particularly in terms of “dyspnoea” ADR may be due to drug ineffectiveness. In fact, in our report, there were many cases of drug

ineffectiveness and product quality issues leading to symptoms such as dyspnoea and cough, and even exacerbations. At least in part, such ineffectiveness may be due to errors in inhaler device handling which are associated with reduced drug delivery to the lungs and ineffectiveness of treatment, thereby resulting in both asthma and COPD suboptimal control.[28-32] Actually, the overall error rate appears to be high across all inhaler devices, approximately 50-100%. [28] In a study conducted in 4 community pharmacies in Portugal central region, in which 67 adult patients with asthma or COPD were invited to demonstrate their technique, 87% of the participants had at least one error. [31] In another study, carried out in the same region, inhaler technique errors were very common in both elderly and non-elderly patients with asthma or COPD.[32] There are multiple factors involved, related to the device (manipulation, dexterity and hand strength required and hand-lung coordination), consumers (physical capabilities, health beliefs/beliefs about medications, adherence and device preference) and healthcare professionals (demonstration of correct inhaler technique and frequent reviews of the patient's technique).[30] The solution is based on individualised adaptation of the therapy to each patient taking into account these factors, with special focus on preferences, correct training and frequent re-evaluation of the technique.

In our study, most of the frequently reported serious suspected ADRs were expected (84.5%), since they are described in the summary of product characteristics (SmPC) of, at least, one drugs of the pharmacological class. Regulatory authorities should be encouraged to evaluate unexpected ADRs and to update SmPCs regularly.

There were 3 serious cases of drug overdose associated with SABAs, which may indicate that the patients did not have an optimal control of their disease, leading to an overuse of quick reliever medications. This finding is also described in the aforementioned Danish and Bulgarian studies[26,27]. As previously described, SABA overuse has been associated with worse disease control and more frequent symptoms and exacerbations in both asthma and COPD[33,34]. In an American study with a sample of 416 asthmatic patients, 27% were SABA overusers [33]. In another American study with a sample of 32 COPD patients, nearly 50% overused their SABA medications at least once during the period of observation[34]. In a Portuguese study aimed at describing SABA overuse using the Portuguese Electronic Medical Prescription (PEM) database, 1.9% of all patients for whom SABA was prescribed were overusers[35]. The causes are multifactorial and complex, and an important factor is overdependence on the quick effect of SABA to manage their COPD and persistent asthma instead of the recommended controller medications. As can be expected, overuse and overdosing are associated with an increased risk of ADRs.

To the best of our knowledge, this is the first analysis of suspected ADRs spontaneously reported to a national pharmacovigilance system, focused only on the inhaled therapy of obstructive lung diseases and including all age groups.

Nevertheless, our study has various limitations. The first one involves underreporting bias. Indeed, it is estimated that only 6% of all ADRs are reported [36], and thus it is impossible to determine the true ADR incidence rate, a value that can only be speculated. Secondly, the variability of the quality of the reported data has to be taken into consideration. In fact, since only four minimum criteria are needed to submit an ICSR, a significant proportion of the reports lack critical information. And finally, since this study is not controlled, the presence of confounding factors, such as underlying medical disorders and concomitant medications, hinders the establishment of causality between adverse reaction and suspected drug.

Nevertheless, in spite of the obvious limitations, our study is novel and yields very relevant information obtained from real-life context of inhaler drug usage in obstructive lung diseases.

6. Conclusions and future prospects

The incidence of inhaled therapy spontaneous ADR reports has increased over time. Suspected ADR were more associated with controller medication, and most of the reports and ADRs were related with the LABA/ICS combination class. There was a slight male predominance and non-elderly adults were the age group more affected. The majority of the reports were labelled as serious. Respiratory tract was the most frequently affected organ system, with dyspnoea as the most reported reaction.

In order to further analyse the context of inhaler-delivered medication-associated ADRs in obstructive lung diseases, we believe various studies may be carried out, and actions should be implemented. These may include:

1. A multinational study focusing on the spontaneous reports found in the European ADR database (EudraVigilance), to be aware of the characteristics of inhaled therapy associated ADRs in all age groups of the European zone.
2. In order to reduce the rate of underreporting and improve the effectiveness of PPS, we suggest there should be greater awareness targeting consumers and healthcare professionals. The need to report any suspected ADRs regardless of seriousness should be reinforced.
3. A multicentre national study, including a high sample of patients from multiple health institutions in Portugal with the objective of better understanding the factors associated with medication errors, and implementation measures to address these problems. It would be of value to have at institutional level a greater awareness of the need for correct training and regular assessment of patients' technique, with a special focus on the most susceptible age groups.
4. A national multicentre study, with a large sample of patients aiming to determine the rate of SABA overuse, and better understand factors associated with this problem. Reinforce with patients the need for regular use of the controller, by limiting the use of relievers only to as-needed situations.

Disclaimer: The results and conclusions obtained from analysis of this data are responsibility of the authors and do not reflect any position of INFARMED.

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Appendices

Appendix 1 – List of all suspected ADRs analysed.

Preferred Terms (PT)	***n***	**%**
Dyspnoea	29	4.8
Tachycardia	19	3.2
Cough	17	2.8
Drug ineffective	16	2.7
Pruritus	16	2.7
Asthmatic crisis	14	2.3
Palpitations	13	2.2
Product quality issue	13	2.2
Chest pain	10	1.7
Rash	9	1.5
Throat irritation	9	1.5
Tremor	8	1.3
Bronchospasm	7	1.2
Headache	7	1.2
Oedema peripheral	7	1.2
Urticaria	7	1.2
Condition aggravated	6	1.0
Dysphonia	6	1.0
Erythema	6	1.0
Face oedema	6	1.0
Off label use	6	1.0
Angioedema	5	0.8
Chest discomfort	5	0.8
Cushing's syndrome	5	0.8
Device malfunction	5	0.8
Dry mouth	5	0.8
Fatigue	5	0.8
Drug hypersensitivity	5	0.8
Lip oedema	5	0.8
Wheezing	5	0.8
Chronic obstructive pulmonary disease	4	0.7
Diarrhoea	4	0.7
Dizziness	4	0.7
Drug dose omission	4	0.7
Hyperhidrosis	4	0.7
Myalgia	4	0.7
Overdose	4	0.7
Pneumonia	4	0.7
Adrenal insufficiency	3	0.5
Agitation	3	0.5
Asthenia	3	0.5

Back pain	3	0.5
Churg Strauss syndrome	3	0.5
Constipation	3	0.5
Delirium	3	0.5
Drug interaction	3	0.5
Epistaxis	3	0.5
Eyelid oedema	3	0.5
Glaucoma	3	0.5
Hyperglycemia	3	0.5
Hypotension	3	0.5
Intentional product misuse	3	0.5
Malaise	3	0.5
Nausea	3	0.5
Osteoporosis	3	0.5
Product use issue	3	0.5
Swelling face	3	0.5
Tongue oedema	3	0.5
Wrong technique in drug usage process	3	0.5
Abdominal pain	2	0.3
Abnormal behaviour	2	0.3
Adverse Drug Reaction	2	0.3
Aggression	2	0.3
Anxiety	2	0.3
Aphtha	2	0.3
Arthralgia	2	0.3
Atrial fibrillation	2	0.3
Blindness	2	0.3
Bone pain	2	0.3
Cerebrovascular accident	2	0.3
Circumstance or information capable of leading to medication error	2	0.3
Death	2	0.3
Device failure	2	0.3
Discomfort	2	0.3
Drug administration error	2	0.3
Drug level increased	2	0.3
Dysphagia	2	0.3
Eye swelling	2	0.3
Facial pain	2	0.3
Feeling abnormal	2	0.3
Glossodynia	2	0.3
Hypertensive crisis	2	0.3
Hypothalamic pituitary adrenal axis suppression	2	0.3
Hypoxia	2	0.3
Incorrect route of drug administration	2	0.3
Insomnia	2	0.3
Localised oedema	2	0.3
Medication error	2	0.3

Muscle spasms	2	0.3
Paraesthesia	2	0.3
Pharyngitis	2	0.3
Product substitution issue	2	0.3
Psychomotor hyperactivity	2	0.3
Pyrexia	2	0.3
Rash erythematous	2	0.3
Rash generalised	2	0.3
Stress cardiomyopathy	2	0.3
Syncope	2	0.3
Throat tightness	2	0.3
Tongue discolouration	2	0.3
Urinary incontinence	2	0.3
Urinary retention	2	0.3
Weight decreased	2	0.3
Abdominal distension	1	0.2
Acholia	1	0.2
Acne	1	0.2
Acute coronary syndrome	1	0.2
Acute pulmonary oedema	1	0.2
Ageusia	1	0.2
Alveolitis allergic	1	0.2
Anaphylactic reaction	1	0.2
Anaphylactic shock	1	0.2
Anti-neutrophil cytoplasmic antibody positive vasculitis	1	0.2
Aphonia	1	0.2
Aphthous stomatitis	1	0.2
Atrial septal defect	1	0.2
Aura	1	0.2
Blister	1	0.2
Blood pressure increased	1	0.2
Blood prolactin increased	1	0.2
Bradycardia foetal	1	0.2
Breast pain	1	0.2
Bronchial disorder	1	0.2
Bronchopulmonary aspergillosis	1	0.2
Bundle branch block right	1	0.2
CD4 lymphocytes decreased	1	0.2
Chills	1	0.2
Choluria	1	0.2
Concomitant disease aggravated	1	0.2
Conjunctival haemorrhage	1	0.2
Conjunctival hyperaemia	1	0.2
Crying	1	0.2
Cyanosis	1	0.2
Cystitis bacterial	1	0.2
Deafness	1	0.2

Dermatitis acneiform	1	0.2
Dermatitis allergic	1	0.2
Diabetes	1	0.2
Diastolic hypertension	1	0.2
Direct hyperbilirubinaemia	1	0.2
Drug administered to patient of inappropriate age	1	0.2
Drug dispensing error	1	0.2
Drug effect incomplete	1	0.2
Drug intolerance	1	0.2
Drug use disorder	1	0.2
Dry eye	1	0.2
Dysgeusia	1	0.2
Dysuria	1	0.2
Emphysematous bulla	1	0.2
Eosinophilic oesophagitis	1	0.2
Erythema multiforme	1	0.2
Extrasystoles	1	0.2
Eye haemorrhage	1	0.2
Facial paraesthesia	1	0.2
Fall	1	0.2
Gait disturbance	1	0.2
Gastrointestinal haemorrhage	1	0.2
General physical health deterioration	1	0.2
Gingival bleeding	1	0.2
Gingivitis	1	0.2
Gynaecomastia	1	0.2
Hallucination	1	0.2
Halo vision	1	0.2
Haematochezia	1	0.2
Haemoglobin decreased	1	0.2
Hypoglycaemia	1	0.2
Hyponatremia	1	0.2
Impaired renal function	1	0.2
Impulse-control disorder	1	0.2
Inflammation	1	0.2
Injection site erythema	1	0.2
Jaundice	1	0.2
Joint swelling	1	0.2
Lacrimation increased	1	0.2
Lactic acidosis	1	0.2
Laryngeal oedema	1	0.2
Ligament rupture	1	0.2
Lip discolouration	1	0.2
Lip disorder	1	0.2
Lip dry	1	0.2
Lip swelling	1	0.2
Lung neoplasm malignant	1	0.2

Lymphocyte count decreased	1	0.2
Melena	1	0.2
Mouth swelling	1	0.2
Mucosal inflammation	1	0.2
Muscle contracture	1	0.2
Musculoskeletal pain	1	0.2
Myocardial ischemia	1	0.2
Nasal congestion	1	0.2
Nasal dryness	1	0.2
Nasal polyps	1	0.2
Nasopharyngitis	1	0.2
Neck pain	1	0.2
Necrotising fasciitis	1	0.2
Noninfective gingivitis	1	0.2
Nuchal rigidity	1	0.2
Obstructive airways disorder	1	0.2
Ocular discomfort	1	0.2
Oedema mouth	1	0.2
Oral candidiasis	1	0.2
Oral discomfort	1	0.2
Oral pain	1	0.2
Oropharyngeal swelling	1	0.2
Oropharyngitis fungal	1	0.2
Osteonecrosis	1	0.2
Pain	1	0.2
Pain in extremity	1	0.2
Pain in jaw	1	0.2
Pallor	1	0.2
Penile erythema	1	0.2
Periorbital oedema	1	0.2
Peripheral coldness	1	0.2
Peripheral swelling	1	0.2
Photophobia	1	0.2
Pulmonary haemorrhage	1	0.2
Rales	1	0.2
Renal failure	1	0.2
Renal pain	1	0.2
Respiratory arrest	1	0.2
Respiratory disorder	1	0.2
Respiratory distress	1	0.2
Respiratory failure	1	0.2
Respiratory tract infection	1	0.2
Rhinorrhoea	1	0.2
Salivary gland pain	1	0.2
Seizure	1	0.2
Sensation of foreign body	1	0.2
Skin lesion	1	0.2

Sneezing	1	0.2
Somnolence	1	0.2
Sputum increased	1	0.2
Thrombocytopenia	1	0.2
Tongue dry	1	0.2
Tongue injury	1	0.2
Tonsillitis	1	0.2
Toxic shock syndrome streptococcal	1	0.2
Urinary tract infection	1	0.2
Ventricular extrasystoles	1	0.2
Visual acuity reduced	1	0.2
Visual impairment	1	0.2
Wells syndrome	1	0.2
Wolff-Parkinson-White syndrome congenital	1	0.2
Total	599	100