UNIVERSIDADE BEIRA INTERIOR

Safety Assessment of Medications in Elderly: Contribution of the Pharmacovigilance System

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Tese para obtenção do Grau de Doutor em
Ciências Farmacêuticas
(3º ciclo de estudos)

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20 de dezembro de 2022

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Eu, Cristina Sofia de Jesus Monteiro, que abaixo assino, estudante com número de inscrição D1642 do 3º Ciclo em Ciências Farmacêuticas da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o **Código de Integridade da Universidade da Beira Interior**.

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Ao José e ao Joaquim

Ao Samuel

Agradecimentos

Esta tese é o culminar de um projeto ao qual me propus, que só foi possível graças ao contributo de muitas pessoas. Por este motivo, gostaria de expressar os meus sinceros agradecimentos:

Ao professor Doutor Gilberto Alves, meu orientador, por ter aceitado este desafio. O seu espírito crítico e o contributo científico que demonstrou foram determinantes para o desenvolvimento deste trabalho. Obrigado pelas críticas, sugestões e pela revisão cuidada dos documentos.

À professora Doutora Ana Paula Duarte, minha coorientadora, por toda a disponibilidade, dedicação, confiança e compreensão ao longo deste trabalho. Um duplo agradecimento, enquanto Coordenadora da Unidade de Farmacovigilância da Beira Interior, por ter proporcionado e agilizado todas as condições que permitiram a realização deste trabalho. Obrigado pelos ensinamentos transmitidos, pela confiança e apoio. Obrigada por tudo o que fez por mim.

A todos os membros da equipa da Unidade de Farmacovigilância da Beira Interior que, de diferentes formas, me ajudaram ao longo deste trabalho. Obrigada pelos conhecimentos, e pelas oportunidades científicas e académicas que me foram proporcionando ao longo desta caminhada.

Ao Presidente do INFARMED - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P., à Direção de Gestão do Risco de Medicamentos do INFARMED e a todos os colegas que lá trabalham, pela partilha de conhecimento na área da Farmacovigilância e por proporcionarem a utilização dos dados do Sistema Nacional de Farmacovigilância. Espero que este trabalho venha reforçar a importância da Farmacovigilância na segurança do medicamento.

A todos os colegas das diversas Unidades Regionais de Farmacovigilância, pelo trabalho que têm desempenhado ao longo destes anos, um especial agradecimento. Sem o vosso trabalho diário, esta tese não seria possível. Muito obrigada!

A todos os idosos que participaram no estudo da avaliação da medicação, que se encontra no apêndice 2 desta tese, aos médicos e enfermeiros da Associação de Socorros Mútuos Mutualista Covilhanense, à Dra. Catarina Canário e ao Dr. Manuel

Ângelo Ribeiro, que tiveram uma contribuição fundamental para a obtenção das informações necessárias para esse estudo. Muito obrigada!

A todos os Amigos que, mesmo sem serem aqui especificamente referidos, me apoiaram e incentivaram ao longo desta caminhada. Muito obrigada!

À minha família, que também viveu as alegrias e desilusões ao longo deste trabalho, e que procuraram sempre apoiar e incentivar, mesmo sem muitas vezes compreender o que estas páginas envolveram.

Ao Samuel, pelas revisões, pelas contribuições científicas e, principalmente, pelo apoio incondicional ao longo destes anos. Obrigada por seres meu companheiro e não me teres deixado desistir. Esta tese também é tua!

Por fim, agradeço ao José Miguel e ao Joaquim, que ainda não têm noção de como são importantes para mim e, mesmo sem saberem, me dão força para continuar e ir sempre mais além.

Muito obrigado a todos!

List of Publications

Papers related to this thesis

I - Monteiro C, Duarte AP, Alves G. Adverse drug reactions in elderly: a five-year review of spontaneous reports to the Portuguese pharmacovigilance system. Expert Opin Drug Saf. 2021;20(1):109-118. doi: 10.1080/14740338.2020.1849137

II - Monteiro C, Silvestre S, Duarte AP, Alves G. Assessment of suspected adverse drug reactions in elderly patients with diabetes mellitus based on a Portuguese spontaneous reporting database: analysis of reporting from 2008 to 2018. Expert Opin Drug Saf. 2021;20(7):845-853. doi: 10.1080/14740338.2021.1928072

III - Monteiro C, Silvestre S, Duarte A.P, Alves G. Safety of Non-Steroidal Anti-Inflammatory Drugs in the Elderly: An Analysis of Published Literature and Reports Sent to the Portuguese Pharmacovigilance System. Int J Environ Res Public Health. 2022;19(6):3541. doi: 10.3390/ijerph19063541

Supplementary work in appendix 2

I - Monteiro C, Canário C, Ribeiro MÂ, Duarte AP, Alves G. Medication Evaluation in Portuguese Elderly Patients According to Beers, STOPP/START Criteria and EU(7)-PIM List – An Exploratory Study. Patient Prefer Adherence. 2020;14:795-802. doi: 10.2147/PPA.S247013

Resumo Alargado

Com a industrialização e os avanços tecnológicos e científicos na área da saúde, tem-se assistido a um aumento substancial do envelhecimento da população a nível mundial, e Portugal não é exceção. De facto, em Portugal, a esperança média de vida está a aumentar e, consequentemente, o número de idosos. Além disso, a proporção de doentes idosos com múltiplas comorbilidades está a aumentar, o que, por sua vez, leva a um aumento no uso de medicamentos e a um acréscimo do risco de reações adversas a medicamentos (RAMs). Na verdade, as RAMs em idosos podem ser consideradas um problema de saúde pública, com custos elevados, pois são uma causa relevante de hospitalização e mortalidade.

A farmacovigilância é a ciência que se centra na deteção, análise, avaliação, compreensão e prevenção de RAMs. É uma área fundamental para a monitorização contínua da segurança dos medicamentos, especialmente relevante nos períodos iniciais da comercialização alargada de novos fármacos, devido à escassez relativa de informação de segurança disponível no momento da autorização de introdução no mercado, a qual advém, nesta fase, essencialmente dos ensaios clínicos conduzidos durante a fase de pré-comercialização. A farmacovigilância permite a identificação de problemas relacionados com o uso de medicamentos, frequentemente detetados apenas na fase de pós-comercialização. Isso é essencial para prevenir e minimizar os riscos iatrogénicos potenciais para a saúde dos doentes. Portanto, monitorizar a iatrogenicidade dos medicamentos, a qual afeta de uma forma mais marcada os doentes idosos, é fundamental para maximizar a informação de segurança dos mesmos nesta população especial. Além disso, há uma prevalência crescente de doentes idosos com quadros clínicos de multipatologia, incluindo a presença de diabetes *mellitus* e doenças músculo-esqueléticas, sendo importante o conhecimento gerado a partir dos dados de farmacovigilância obtidos em contexto de vida real para minimizar os riscos decorrentes do uso de medicamentos nestas condições.

O objetivo central deste trabalho consistiu na caraterização do perfil de RAMs em doentes idosos, em Portugal, notificadas espontaneamente ao Sistema Nacional de Farmacovigilância (SNF). Adicionalmente, esta tese contemplou também a caracterização das RAMs em doentes idosos diabéticos e a avaliação da segurança dos fármacos anti-inflamatórios não esteroides (AINEs) nesta faixa etária. Para tal, em primeiro lugar, foram avaliadas todas as RAMs comunicadas ao SNF de 2013 a 2017. No entanto, considerando o objetivo deste estudo, as RAMs referentes a doentes com 65 ou mais anos foram analisadas detalhadamente e comparadas com as que foram

notificadas em adultos não idosos. Em segundo lugar, foi realizada uma análise retrospetiva das notificações de suspeitas de RAMs submetidas ao SNF entre 2008 e 2018, envolvendo doentes com idade ≥65 anos com diabetes *mellitus*. Por fim, foi realizada uma revisão compreensiva da literatura sobre a segurança dos AINEs em doentes idosos e, em paralelo, considerando o mesmo período de tempo (i.e., 2008-2018) foram analisadas as suspeitas de RAMs relacionadas com este tipo de medicamentos, manifestadas em indivíduos com 65 ou mais anos e notificadas para o SNF.

As notificações foram analisadas relativamente ao género dos doentes envolvidos, gravidade e tipo de RAMs, de acordo com a terminologia "Classe de Sistemas e Órgãos" do dicionário médico para a atividade regulamentar. Nos casos com desfecho fatal, foi realizada uma análise mais aprofundada em termos do "Termo Preferencial" para cada caso. Na análise geral das notificações espontâneas em idosos, as RAMs mais frequentes enquadraram-se nas categorias de distúrbios gerais e perturbações no local de administração e afeções da pele e do tecido subcutâneo. Em relação aos grupos terapêuticos envolvidos, os medicamentos antineoplásicos foram os mais comumente implicados. Além disso, os medicamentos antineoplásicos e antitrombóticos foram os grupos farmacoterapêuticos mais representados entre os medicamentos suspeitos envolvidos na morte de doentes.

Mediante análise das RAMs em doentes idosos diabéticos, as mais frequentes foram a hipoglicémia e a acidose láctica, sendo os medicamentos especificamente indicados para o controlo glicémia os mais frequentemente envolvidos.

Finalmente, tendo em conta a revisão da literatura realizada referente à segurança de AINEs em doentes idosos, a maioria dos estudos concluiu que o risco de um evento adverso gastrointestinal é inferior com o uso de AINEs seletivos para a isoenzima cicloxigenase-2 (COX-2) do que com o uso de AINEs convencionais. Mais especificamente, entre os AINEs, o celecoxib foi considerado o fármaco mais seguro. No entanto, o risco de eventos gastrointestinais em doentes com idade ≥75 anos a tomar AINEs seletivos para COX-2 foi maior que o observado em doentes mais jovens. Além disso, o diclofenac foi associado a eventos adversos renais relevantes em doentes com 75 ou mais anos, bem como naqueles com algum grau de insuficiência renal. Em relação aos eventos adversos cardiovasculares, a sua incidência foi menor com os coxibes do que com os AINEs convencionais, e o celecoxib levou a uma incidência menor desses eventos quando comparado ao etoricoxib. Em resultado da análise realizada aos dados do SNF, foi possível constatar que a maioria das suspeitas de RAMs envolveu o diclofenac. As suspeitas de RAMs mais frequentemente relatadas enquadraram-se nas categorias de afeções da pele e do tecido subcutâneo. As RAMs

gastrointestinais graves ocorreram principalmente em doentes a tomar mais que um AINE e/ou outro medicamento concomitante, o que aumenta a incidência desses eventos, na ausência de gastroproteção. A maioria das RAMs graves relacionadas com distúrbios renais ou distúrbios cardíacos ocorreram em doentes com história clínica de distúrbios renais ou diabetes *mellitus* e de hipertensão arterial, respetivamente.
Todos os estudos realizados com os dados do SNF que suportam esta tese concluíram que a maioria das RAMs eram graves, ocorreram predominantemente em mulheres e eram expetáveis. A identificação exata de RAMs, especialmente a deteção de RAMs evitáveis, é um ponto de partida importante para melhorar a segurança dos medicamentos em idosos. Portanto, estudos direcionados para a população geriátrica são necessários para melhorar a informação de segurança desses medicamentos nesta população especial, considerando as suas múltiplas condições médicas, destacando-se assim a importância da farmacovigilância ativa. Nesse contexto, é importante enfatizar que as bases de dados de farmacovigilância são ferramentas importantes para avaliar questões relacionadas com a segurança dos medicamentos em idosos, possibilitando aprimorar o conhecimento sobre o perfil de segurança de medicamentos nestes doentes.

Palavras-chave

Anti-inflamatórios não esteroides; Diabetes *mellitus*; Farmacovigilância; Idosos; Reações adversas a medicamentos; Segurança; Sistema Nacional de Farmacovigilância.

Abstract

As a result of the industrialisation and technological and scientific advances in healthcare, there has been a substantial increase in aging of the population worldwide, and Portugal is no exception. In fact, in Portugal, the average life expectancy is increasing and therefore the number of elderly people. Additionally, the proportion of elderly patients with multiple comorbidities is rising, which in turn leads to an increase in medication use and in the risk of adverse drug reactions (ADRs). In fact, ADRs in elderly can be considered a public health problem, having high costs and being a relevant cause of hospitalization and mortality.

Pharmacovigilance is the science concerned with the detection, analysis, evaluation, understanding, and prevention of ADRs. It is a fundamental area for the continuous monitoring of the safety of medicines, particularly relevant in the initial periods of the widespread marketing of new drugs, due to relative scarcity of drug safety information available at the time of marketing authorization, which arises, at this stage, essentially based on pre-marketing clinical trials. Pharmacovigilance allows the identification of problems related to the use of drugs, which are often detected in the post-marketing phase. This is essential to prevent and minimize potential iatrogenic risks to the health of patients. Therefore, monitoring the iatrogenicity of medication that particularly affects elderly patients is fundamental to maximize the safety information of medicines in this special population. Additionally, there is an increasing prevalence of elderly patients with diabetes *mellitus* and musculoskeletal diseases, whereby is important the knowledge generated from real-world pharmacovigilance data to minimize the risk of harm that may occur with drugs used for the treatment of these conditions.

The central aim of this work was to characterize the ADRs profile in elderly patients spontaneously reported to the Portuguese Pharmacovigilance System (PPS). Additionally, this work also intended to characterize the ADRs in elderly diabetic patients and to evaluate the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in this age group. For this propose, firstly, all spontaneous ADRs reported to the PPS from 2013 to 2017 were examined. However, considering the aim of this study, ADRs referring to patients aged 65 and over were analysed in higher detail and compared with those reported in non-elderly adults. Secondly, a retrospective analysis of suspected ADRs reports from PPS between 2008 to 2018 was performed, involving patients aged ≥65 years with diabetes *mellitus*. Finally, it was carried out a comprehensive literature review of NSAIDs safety in elderly patients and, in parallel, considering the same period of time (i.e., 2008-2018), the suspected ADRs related to

these drugs reported to a database of pharmacovigilance, for people aged ≥65, were analysed.

Reports were analysed in terms of gender of the involved patients, seriousness and type of ADRs, according to the "System Organ Class" from the Medical Dictionary for Regulatory Activities terminology. In the reports with fatal outcome a deeper analysis in terms of "Preferred Term" for each report was performed. In the general analysis of spontaneous reports in the elderly, the most frequent suspected ADRs fall within the categories of general disorders and administration site conditions, and skin and subcutaneous tissue complaints. Regarding the therapeutic agents involved, the antineoplastic drugs were the most commonly implicated. In addition, the antineoplastic and antithrombotic drugs were the most represented pharmacotherapeutic groups of suspected drugs involved in patient's death.

In the analyses of ADRs in elderly diabetic patients, the most frequent were hypoglycaemia and lactic acidosis, and the drugs specifically indicated for glycaemic control were the most frequently involved.

Finally, in the literature review performed on NSAIDs safety in elderly patients, most studies concluded that the risk of a gastrointestinal adverse event with the use of cyclooxygenase-2 (COX-2)-selective NSAIDs seems to be lower when compared with conventional NSAIDs. In addition, celecoxib was considered the safest of all other NSAIDs. However, the risk of gastrointestinal events in patients aged ≥75 years taking selective COX-2 inhibitors was higher when compared with younger patients. Additionally, diclofenac was associated with relevant renal adverse events in patients aged 75 years or older as well as in those with some renal impairment. Regarding cardiovascular events the incidence was lower with coxibs than with conventional NSAIDs and celecoxib led to a lower incidence of these events when compared with etoricoxib. In the analysis performed in PPS data most of suspected ADRs had diclofenac as suspected drug. The suspected ADRs most frequently reported fall within the categories of skin and subcutaneous tissue disorders. Serious gastrointestinal ADRs occurred mostly in patients taking more than one NSAID and/or another concomitant drug that increases the incidence of these events, in the absence of gastroprotection. The majority of serious ADRs related to renal and cardiac disorders occurred in patients with history of renal disorders or diabetes *mellitus* and hypertension, respectively.

All the studies performed with the data belonging to PPS concluded that the majority of ADRs were serious, occurred predominantly in female and were expected. Hence, an accurate identification of ADRs, especially the detection of preventable ADRs, is an important starting point to improve drug safety in elderly. Therefore, studies targeting

elderly patients are needed to improve the safety information of these drugs in this special population, considering their multiple medical conditions, thus highlighting the importance of active pharmacovigilance. In this context, it is important to emphasize that pharmacovigilance databases are important tools to evaluate issues related to the safety of drugs in older people, enabling to improve the knowledge on the safety profile of medicines in these patients.

Keywords

Adverse Drug Reactions; Diabetes *mellitus*; Elderly; Non-steroidal anti-inflammatory drugs; Pharmacovigilance; Portuguese Pharmacovigilance System; Safety.

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List of Abbreviations

ADRs	Adverse drug reactions
ASA	Acetylsalicylic acid
ATC	Anatomical therapeutic chemical
CNS	Central nervous system
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DPP-4	Dipeptidyl peptidase-4
EMA	European Medicines Agency
EU	European Union
GLP-1	Glucagon-like peptide-1
GVP	Good pharmacovigilance practices
IME	Important medical event
INFARMED	National Authority of Medicines and Health Products, I.P.
IV	Intravenous
MAHs	Marketing authorisation holders
MedDRA®	Medical dictionary for regulatory activities
NSAIDs	Non-steroidal anti-inflammatory drugs
PIMs	Potentially inappropriate medications
PPI	Proton pump inhibitor
PPOs	Potentially prescribing omissions
PPS	Portuguese pharmacovigilance system
PRAC	Pharmacovigilance risk assessment committee
PT	Preferred term
SGLT2	Sodium-glucose cotransporter 2
SmPC	Summary of product characteristics
SOC	Systems organ classes
START	Screening tool to alert doctors to right treatment
STOPP	Screening tool of older person's prescriptions
T1DM	Type 1 diabetes *mellitus*
T2DM	Type 2 diabetes *mellitus*
UMC	Uppsala Monitoring Center
WHO	World Health Organization
WHO-UMC	World Health Organization-Uppsala Monitoring Center

Chapter I - General Introduction

The elderly population is increasing over the years [1,2]. In fact, there has been a significant increase in average life expectancy and, consequently, in several health-related problems affecting the quality of life of older people, such as cataracts and refractive errors, chronic obstructive pulmonary disease, depression, dementia, cardiovascular diseases, diabetes *mellitus* and musculoskeletal conditions [3]. Accordingly, the number of drugs prescribed to this special population is also increasing. As a result, there are often concerns regarding the potential negative outcomes associated with medication, which can not only aggravate some of the already existing pathological conditions, but also lead to an increased expenditure of health resources, thus having a high economic impact at individual and societal levels.

I.1 Aging of the Population

The changes that constitute and influence aging are complex. Biologically, aging involves a variety of molecular and cellular changes. Over the time, these changes lead to a gradual loss of physiological reserves, an increased risk of developing various diseases, and a general decline in the intrinsic capacity of the individual. By the age of 60, disabilities are mainly due to hearing loss, age-related eye disorders, as well as heart disease, stroke, chronic respiratory disease, cancer, and dementia [1].

Population aging is a global phenomenon. Globally, the proportion of the population aged 65 and over has increased in the last years [4]. Older people represent a growing demographic group in society and account for more than one-fifth of the population in 17 countries. United Nations projections for the end of the century show that by 2100 this will be the case in 155 countries, representing the majority (61%) of the world's population [5]. In addition, women tend to live longer than men [5]. Nevertheless, nowadays, there is no globally accepted definition of the age at which a certain individual is considered elderly. The phenomenon of demographic aging itself shows high heterogeneity in different regions of the world, which has consequences in administrative differences such as a different retirement age, demographic differences and different life expectancy at birth [1,4]. Therefore, the definition of elderly has been considered dynamic and has varied between countries over the time, reflecting in many

instances the current political and economic situation of each country [4,6]. In general, it is associated with the age at which one can begin to receive pension benefits [7].
The United Nations define older persons as those who are 60 or 65 years of age or older [5]. In developing countries, an older person is considered to be someone who is 60 years or older. In developed countries, the age ranges up to 65 years. Conventionally, "elderly" has been defined as a chronological age of 65 years or older, while those from 65 through 74 years old are referred to as "early elderly" and those over 75 years old as "late elderly" [8]. Although there are different ways to classify this population, some studies have classified elderly adults between the ages of 65 and 74 years as youngest-old, those between ages 75 and 84 years as middle-old, and those aged ≥85 years as oldest-old [9].

I.1.1 Aging in the World and in Europe

Demographic aging reflects changes in age distribution of a population, expressed as a higher proportion of older people, a trend that can be observed in Europe and around the world. In this context, it is relevant to define Aging Index, which is the ratio between the elderly population and the young population, usually defined as the quotient between the number of people aged 65 and over and the number of people aged between 0 and 14 years [10]. Among the countries of the European Union (EU), Italy was the country that showed the highest Aging Index in 2019, followed by Portugal and Germany (figure I.1).

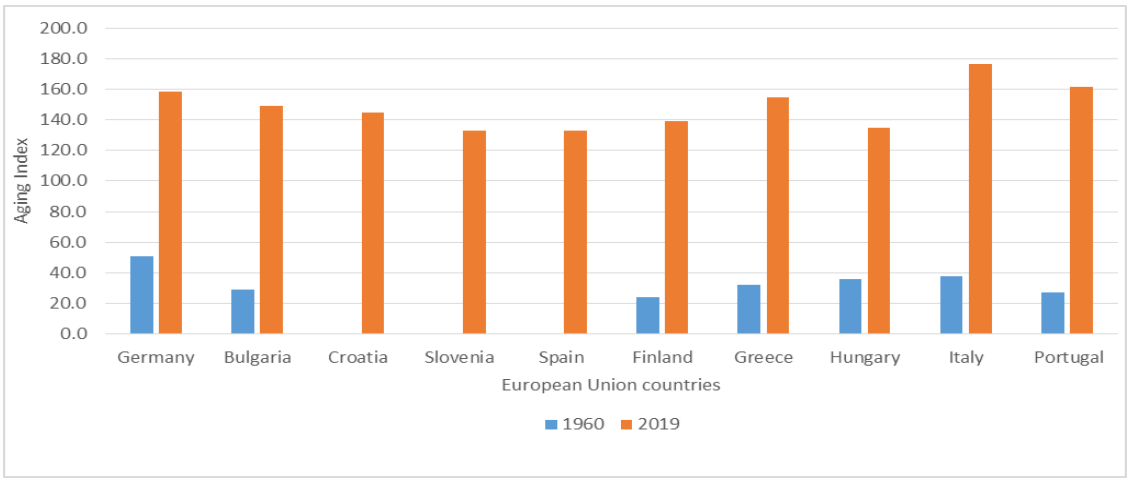

Figure I.1: European Union countries with the highest Aging Indices in 2019: top ten (Source: Pordata [10]**)**

In 2019, there were 703 million people worldwide who were 65 years and older. The number of older people is expected to double to 1.5 billion by 2050. Overall, the proportion of the population aged 65 and over has increased from 6% in 1990 to 9% in 2019. This proportion is expected to rise further to 16% by 2050, by which time one in six people in the world will be aged 65 or over. Between 2019 and 2050, the proportion of older people is expected to at least double in four regions: North Africa and West Asia, Central and South Asia, Latin America and Caribbean, and Eastern and Southeast Asia [5], (table I.1).

Table I.1: Population aged 65 years or over in the World, in 2019 and 2050 (Source: United Nations, Department of Economic and Social Affairs, Population Division, 2019 [5]**).**

Region	Number of persons aged 65 or over in 2019 (millions)	Number of persons aged 65 or over in 2050 (millions)
World	702.9	1548.9
Sub-Saharan Africa	31.9	101.4
Northern Africa and Western Asia	29.4	95.8
Central and Southern Asia	119.0	328.1
Eastern and South-Eastern Asia	260.6	572.5
Latin America and the Caribbean	56.4	144.6
Australia and New Zealand	4.8	8.8
Oceania, excluding Australia and New Zealand	0.5	1.5
Europe and Northern America	200.4	296.2

Analysing life expectancy by sex, women tend to live longer than men. At the global level, in the period 2015-2020, women's life expectancy at birth exceeds that of men by 4.8 years. Projections indicate that in 2050 women will comprise 54% of the global population aged 65 or over [5].

Overall, populations are living longer, which is also leading to a higher prevalence of chronic diseases in older people, with associated individual, social, and economic costs. This will lead to challenges for health and social support structures of older population, with significant implications for government policy and attitudes. In this context, World Health Organization (WHO) considers spending on the aging population as an investment rather than a cost; not only because it is an investment that promotes people's well-being, but also because in the long term it will help people with a significant loss of capacity to live a decent life [1].

I.1.2 Aging in Portugal

Portugal, such as other countries in the EU, has shown a significant increase in the number of elderly people [11], as it can be observed in figure I.2.

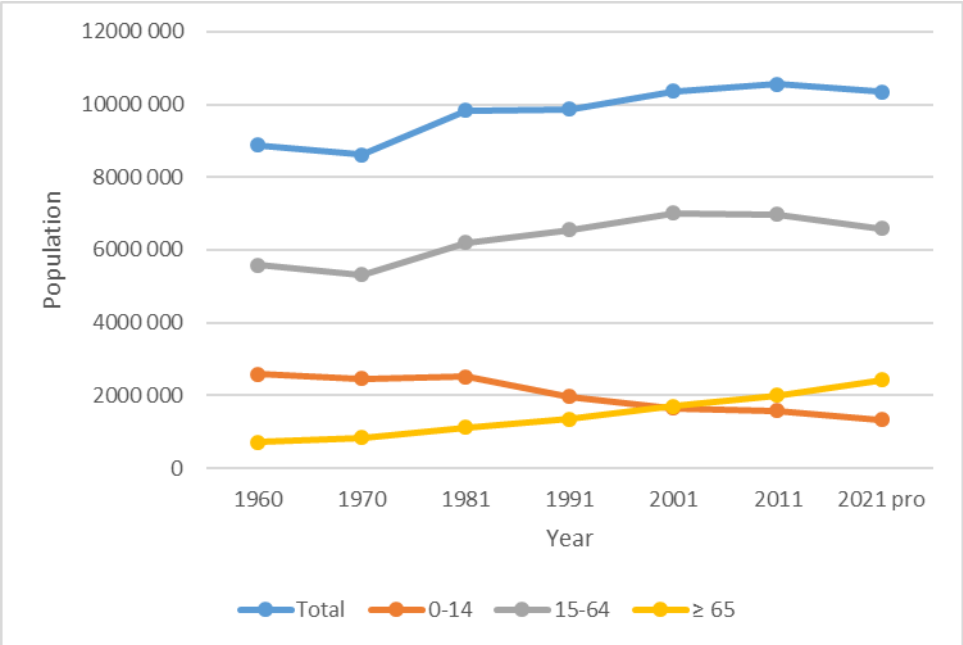

Figure I.2: Portuguese resident population according to the 2021 Census (Note: 2021 pro means that the date is still provisional; Source: Pordata [11]**)**

According to the United Nations, in 2019 the older people in Portugal represented 22.4% of the entire population and it is expected that in 2030 it will increase to 27.1% [5]. In 1961 Portugal had an aging index of 27.5%, but in 2019 it was 161.3% [10]. The projections of the National Institute of Statistics in Portugal estimate that the aging index can almost double between 2018 and 2080, i.e. from 159 to 300 elderly people for every 100 young people [12]. Population aging is seen as a challenge in various policy, social and health action areas. The changes observed in the population living in Portugal show that an accelerated demographic aging has occurred in recent years, as has happened in most developed countries. As result of the decline in birth rate and the increase in life expectancy, there has been a decline in the young population and in the working age population in Portugal. The proportion of older people in the population has increased and this trend is expected to continue. The number of older people has long exceeded the number of young people in Portugal, with the aging rate reaching 140 older people for every 100 young people in 2015 [12], (table I.2).

Table I.2: Demographic projections for the Portuguese population (adapted from Relatório de Portugal - Terceiro Ciclo de Revisão e Avaliação da Estratégia de Implementação Regional do Plano Internacional de Ação de Madrid sobre o Envelhecimento [12]**)**

	2010	**2015**	**2030**	**2060**
Resident population (in millions)	10.6	10.3	9.9	8.6
0-14	1.6	1.5	1.1	1.0
15-64	7.0	6.7	6.0	4.5
≥65	2.0	2.1	2.7	3.0
Longevity index (80+/65+)	25.9	29.3	30.5	46.7
Aging Index (65+/0-14)	125.0	140.0	242.6	306.5
Life expectancy at age 65	18.84	19.19		
Man	16.94	17.32		
Woman	20.27	20.67		

The demographic projections are that the longevity index [ratio of the number of oldest old persons (aged 75 and over) to the number of elderly persons of an age when they are generally economically inactive (aged 65 and over [13])], should also raise over the years [12].

In Portugal, as in other EU countries, life expectancy for women is increasing. The gender gap in life expectancy is significant: women lived 6.2 years longer than men in 2017, which is over the EU average (5.2 years) [12].

Since 2000, the increase in life expectancy in Portugal is mainly due to a decrease in mortality rate from cardiovascular diseases, with particular relevance to stroke and ischaemic heart disease [14]. However, these conditions still remain the main causes of death in Portugal. Diabetes *mellitus* mortality rate also remains very high in Portugal, with a mortality rate of 38.7 per 100,000 population compared to an EU average of 22.2 in 2016 [14]. In addition, about half of people aged 65 and over in Portugal (53%) report having at least one chronic illness, with many of them reporting two or more chronic conditions - a situation similar to the EU average [15]. Moreover, there is an increasing prevalence of elderly patients with musculoskeletal conditions [6]. These are non-fatal diseases but lead to an increase in non-steroidal anti-inflammatory drugs (NSAIDs) use. Similarly to EU, Portugal has also about 17% of the population over 65 years with some limitations in basic activities of daily living, such as dressing and bathing [15]. These limitations have been related to the clinical conditions commonly associated to age.

I.2 Physiological Changes Associated with Aging and its Impact on Drugs

Aging is associated with multiple morbidities that frequently require drug therapy to control symptoms, prolong life, and maintain functional independence. With advancing age, changes in body composition occur, namely manifested by a decrease in the proportion of lean mass (i.e., water, muscle, bone and viscera) and an increase in the proportion of fat mass, particularly in the abdomen region [6] (table I.3). The physiological and functional capacity of the body is also gradually reduced, affecting the processes of absorption, distribution, metabolism, and excretion of drugs, as well as their pharmacodynamics, which may affect the drug efficacy and safety [16]. These physiological alterations can compromise treatments and makes older people more vulnerable to adverse drug reactions (ADRs), drug interactions, and other medication-related problems [16].

Table I.3: Physiological changes associated with aging with potential impact on drug therapy (Adapted from Veríssimo 2014 [6]**, Coleman 2014** [17]**, Kane et al 2004** [18] **and Masoro 2003**[19]**)**

Organ System	Alteration
Body composition	Decreased in total body water Decreased serum albumin Increased body fat Increased α1-acid glycoprotein
Cardiovascular	Decreased myocardial sensitivity to β-adrenergic stimulation Decreased baroreceptor activity Decreased cardiac output Increased total peripheral resistance
Gastrointestinal	Decreased gastrointestinal blood flow Increased gastric pH Delayed gastric emptying Slowed intestinal transit
Liver	Decreased hepatic size Decreased hepatic blood flow
Renal	Decreased glomerular filtration rate Decreased renal blood flow Decreased tubular secretory function Decreased renal mass Increased filtration fraction

I.2.1 Pharmacokinetics

Pharmacokinetics is the pharmacology branch involved in the study of drugs fate in the body, focusing particularly on the processes of absorption, distribution, metabolism and excretion of drugs and their metabolites. Nowadays, it is well-known that ageing is characterized by a progressive decline in the functional reserve of multiple organs and systems (table I.3), which can influence the pharmacokinetic processes and drug disposition.

Absorption

Older people have a delayed gastric emptying, a decreased intestinal motility and a decreased splanchnic blood flow, which can slow drug absorption for orally administered medicines [16]. With aging, gastric pH may increase due to an increase in achlorhydria, which may lead to changes in the bioavailability of drugs with pH-dependent solubility and ionization [6,16,20]. However, in practice, few drugs have significantly delayed rates of absorption. This is probably due to the fact that rate-limiting factors in the small intestine (such as surface area and luminal pH) are not critically changed with aging [20]; additionally, most drugs are absorbed via passive diffusion and age-related physiologic changes appear to have little influence on the bioavailability of drugs transported by passive mechanisms [21].

It is widely recognized that liver plays a central role in the systemic bioavailability of drugs. Indeed, after drugs absorption from the gut, a fraction of the dose may be eliminated by the liver before reaching the systemic circulation. This pre-systemic or first pass hepatic elimination can be reduced by aging, which can affect the plasma concentration of some drugs. More specifically, regarding this issue, the bioavailability of most polar or water-soluble drugs is not usually affected because they are not highly extracted by the liver; however, for lipophilic drugs, the first pass effect through the liver is frequently accompanied by marked drug extraction (sometimes over 90%), so that only 5% to 10% of the dose enters the systemic circulation, which can significantly reduce the plasma concentration of drugs such as propranolol [20].

Although oral route is the most frequently used for drug administration, as well as the most convenient and economic, there are age-dependent changes that can influence the rate and/or extent of drug absorption. For instance, aging-related changes may impair the absorption of drugs administered by intramuscular route, particularly due to the reduced peripheral blood flow and increased connective tissue [22].

Distribution

In the elderly, the relative percentage of adipose tissue increases from about 18% to 36% in men and from 33% to 45% in women, and total body water is reduced by about 10% [16]. Besides, the blood flow and plasma protein binding are often altered with aging, which may also have implications in drug distribution in elderly, with potential clinical consequences. Thereby, the volume of distribution of water-soluble drugs decreases, increasing the risk of toxicity associated with these drugs [23]; hence, some hydrophilic drugs may require a dose adjustment [16]. On the contrary, fat-soluble drugs, such as benzodiazepines, have a higher volume of distribution, resulting in a slower excretion and prolonged drug action, which may require an extension of the dosing interval [16,17,20]. In this context, serum albumin levels decrease with age, which may have clinical implications for drugs with a small volume of distribution and narrow therapeutic index. Therefore, it is necessary to adjust the dosage of these drugs, because with the decrease in serum albumin levels there will be a greater free fraction of a drug, increasing its pharmacological activity (including adverse effects). In contrast, α1-acid glycoprotein levels increase with age, leading to a decreased free fraction of basic drugs, as lidocaine, such that a higher dose is required to obtain the desired therapeutic effect [20].

Metabolism

Aging is associated with a 40% reduction in hepatic blood flow and 30% reduction in liver mass [24]. Although some drugs are eliminated directly by the kidneys in unchanged form, many drugs undergo metabolism in the body, mainly in the liver. The drug metabolism by the liver depends on the activity of hepatic enzymes and blood flow, which determines the rate of drug delivery to the liver. A decrease in liver metabolism has been associated with a decrease in liver volume and hepatic blood flow. Apparently, the decline in phase I metabolism observed in elderly is more likely the result of the reduced hepatic volume than the reduced enzymatic activity [21]. With advancing age, phase I reactions, mediated primarily by cytochrome P450 isoenzymes, tend to be reduced, decreasing hepatic drug metabolism, contributing subsequently to reduce the total body clearance of drugs, prolonging their half-lives [19]. This may increase the plasma concentrations and effects of drugs that are extensively cleared by the liver [16]. Phase II reactions remain relatively unchanged in the elderly. However, in frail elderly, after injury or surgery, all enzyme activity may be significantly decreased, leading to higher drug concentrations in the blood and an increased risk of ADRs [16,17,19,25]. An example of a class of drugs affected by aging are the benzodiazepines because their metabolism may involve phase I followed by phase II

reactions. Diazepam, for example, despite suffering phase I and II metabolic reactions, is highly metabolised oxidatively (phase I) and is partially converted to an active metabolite, desmethyldiazepam, which has a half-life of up to 220 h in the elderly [19]. However, other benzodiazepines, such as lorazepam, are conjugated in the liver, and their metabolism is not significantly changed by age [17].

Excretion

In elderly, both renal function and renal reserve decline. Structural changes include decreased renal weight, thickening of the intrarenal vascular intima, decreased number of glomeruli with increasing sclerosis in the remaining glomeruli, and infiltration by chronic inflammatory cells and fibrosis in the stroma [18,19]. Altered renal tubule function may also lead to impaired water, sodium, and glucose handling in the elderly. The glomerular adaptation rate steadily decreases. Drug clearance may be decreased even in patients with normal serum creatinine concentrations because the production of creatinine (i.e., a biomarker of kidney function) decreases with age [16,26]. The loss of renal parenchyma in conjunction with a decrease in renal plasma flow determines a progressive decline in glomerular filtration rate [26,27]. At least 0.4 ml/min of glomerular filtration rate is lost per year in Caucasian persons and this decline is also associated with an age-related prolongation in the half-life of different drugs eliminated with a first-order kinetics [26,27]. Therefore, many drugs that depend on the kidney function for excretion can reach toxic concentrations when given to the elderly at the usual dose. Moreover, the reduction in excretion of active metabolites of certain drugs may increase the risk of toxicity, especially in very elderly patients [17]. In addition to physiological changes, some diseases such as hypertension or diabetes, and the use of nephrotoxic drugs, e.g. NSAIDs, may cause a decline in renal function, affecting the excretion of drugs [16].

I.2.2 Pharmacodynamics

The pharmacological actions of drugs can also be affected with aging, leading to variations in therapeutic response, particularly due to changes in receptor sensitivity and drug tolerance [16]. Table I.4 summarizes pharmacodynamics changes in some drugs associated with aging.

Table I.4: Examples of pharmacodynamic changes with aging (adapted from Massoud et al 2017 [28]**, Ryan et al 2016** [29] **and Mangoni et al 2003** [27]**)**

Drug	Pharmacodynamic effect	Age-related change
Adenosine	Heart rate response	No significant change
Diazepam	Sedation, postural sway	Increase
Diltiazem	Acute and chronic antihypertensive effect Acute PR interval prolongation	Increase Decrease
Verapamil	Acute and chronic antihypertensive effect Acute PR interval prolongation	Increase Decrease
Isoprenaline	Chronotropic effect	Decrease
Furosemide	Peak diuretic response	Decrease
Heparin	Anticoagulant effect	No significant change
Warfarin	Anticoagulant effect	Increase
Morphine	Analgesic effect Respiratory depression	Increase No significant change
Propranolol	Antagonism of chronotropic effects	Decrease
Temazepam	Postural sway	Increase

In fact, changes in drug-receptor interaction (e.g., affinity and/or number of receptors) and changes in post-receptor signalling may occur in elderly. Altered homeostatic protective mechanisms may increase the risk of ADRs. Brain mass and the number of neurons and synapses decrease with age, and the blood-brain barrier becomes more permeable to xenobiotics, including drugs. Therefore, the adverse effects of central nervous system (CNS)-active drugs (e.g., confusion, sedation, and extrapyramidal effects) increase with age. Drug classes with a higher risk of adverse CNS effects are opioids, benzodiazepines, anaesthetics, antimuscarinics, and antipsychotics [17]. Additionally, the number of neurons and cholinergic receptors involved in cognitive functions can also be reduced. A decrease in the cell proliferation with aging can be attributed to defects in receptors of growth factors and signal transduction mechanisms

[30]. The mechanisms that contribute to functional changes in the brain associated with aging include: altered concentration of neurotransmitters and/or receptors; hormonal changes, particularly in sex and growth hormones; and the impaired glucose metabolism or decreased availability of glucose and oxygen with decline in cerebrovascular function [31].

As aforementioned, with aging occurs a decrease of function baroreceptors and in the peripheral venous tone [32], resulting in postural hypotension episodes. Additionally, with advancing age, adrenergic receptors become less sensitive to agonists and antagonists. Thus, older people experience a lesser bronchodilator response to β2-adrenergic receptor agonists and a lower reduction in blood pressure to β-adrenergic receptor blockers than younger people [16,17,27,29]. Relatively to α-receptors, there is no relevant decrease in its sensitivity with aging. In this context, angiotensin-converting enzyme inhibitors do not show age-related differences in elderly patients [31].

I.3 Main Medical Conditions Affecting Older People

The International Conference on Harmonization considers older people a 'special population' as they differ from younger adults in terms of comorbidity, polypharmacy, pharmacokinetics, pharmacodynamics and vulnerability to ADRs [33]. In general, elderly patients have multiples comorbidities. According to the definition, multimorbidity refers to the co-occurrence of two or more medical or psychiatric conditions, which may or may not directly interact with each other within the same individual [34].

The prevalence of multimorbidity according to a systematic review that attempted to measure it in a primary care setting in people aged 65 years and older was 95.1% [34]. The most frequent patterns of multimorbidity included osteoarthritis together with cardiovascular and/or metabolic conditions [3,5,34,35]. In a Scottish study of primary care patients aged over 75 years the most prevalent conditions were hypertension (61.9%), ischaemic heart disease (31.2%), pain (23.6%) and chronic kidney disease (18.5%) [36]. Depression, diabetes *mellitus*, constipation, stroke, thyroid disease and hearing loss made up the top 10 of the most prevalent conditions, according the WHO [35].

Considering the degree of disability, the most common and important causes are sensory impairment (particularly in low- and lower-middle-income countries), back and neck pain, chronic obstructive pulmonary disease (particularly in low- and lower-

middle-income countries), depressive disorders, falls, diabetes *mellitus*, dementia and osteoarthritis [35]. A study analysed the disability adjusted life years for people aged 60 years and older and concluded that 23% of the total global burden of disease is attributable to disorders in persons aged 60 years and over [2], (table I.5 and table I.6). In this study the data of global burden of disease were estimated by the Institute of Health Metrics and Evaluation, and by WHO (2004 update with projections to 2030) [2].

Table I.5: Numbers and proportion (%) of Disability Adjusted Life Years (DALYs) attributable to particular causes, for people aged 60 years and older in 1990, 2010, and 2004 with projections to 2030, by the Institute of Health Metrics and Evaluation (IHME) and World Health Organization (WHO) (adapted from Prince et al [2])

	1990 IHME GBD	**2010 IHME GBD**	**Change 1990–2010 (%)**	**2004 WHO GBD**	**Change 2004-2030 (%)**
General					
Population aged ≥60 years (millions)	487·5	754·9	..	658·7	..
DALYs per 1000 population	891·9	760·9	..	684·5	..
Chronic disease categories					
Cardiovascular diseases	137·3(31·6%)	173·9 (30·3%)	+26·7%	157·4(34·9%)	+40·6%
Cancer	64·4 (14·8%)	87·0 (15·1%)	+35·1%	65·3 (14·5%)	+69·2%
Chronic respiratory diseases	54·9 (12·6%)	54·3 (9·5%)	−1·1%	41·0 (9·1%)	+84·3%
Digestive diseases	15·8 (3·6%)	19·4 (3·4%)	+22·8%	15·2 (3·4%)	+15·8%
Mental, behavioural, and neurological disorders	22·2 (5·1%)	38·0 (6·6%)	+71·2%	31·0 (6·9%)	+79·5%
Sensory impairment	12·3 (2·8%)	18·0 (3·1%)	+46·3%	43·9 (9·7%)	+82·0%
Musculoskeletal	27·9 (6·4%)	43·3 (7·5%)	+55·2%	12·1 (2·7%)	+70·3%

GBD: global burden of disease. Disability Adjusted Life Years (DALYs) - One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population [37].

Table I.6: Numbers and proportion (%) of Disability Adjusted Life Years (DALYs) attributable to particular chronic diseases for people aged 60 years and older in 1990, 2010, and 2004 with projections to 2030, by the Institute of Health Metrics and Evaluation (IHME) and World Health Organization (WHO) (adapted from Prince et al [2])

	1990 IHME GBD	**2010 IHME GBD**	**Change 1990–2010 (%)**	**2004 WHO GBD**	**Change 2004 to 2030 (%)**
Chronic diseases					
Ischaemic heart disease	60·7 (14·0%)	77·7 (13·5%)	+28·0%	67·6 (15·0%)	+34·7%
Cerebrovascular disease	54·5 (12·5%)	66·4 (11·6%)	+21·8%	55·4 (12·3%)	+44·4%
Diabetes *mellitus*	12·6 (2·9%)	22·6 (3·9%)	+79·4%	13·9 (3·1%)	+95·7%
Chronic obstructive pulmonary disease	44·7 (10·3%)	43·3 (7·5%)	−3·1%	33·1 (7·3%)	+88·7%
Dementia	4·7 (1·1%)	10·0 (1·7%)	+112·8%	18·8 (4·2%)	+82·6%
Vision impairment	7·0 (1·6%)	10·4 (1·8%)	+48·6%	30·9 (6·8%)	+86·3%
Hearing impairment	5·3 (1·2%)	7·5 (1·3%)	+41·5%	13·0 (2·9%)	+70·6%

GBD: global burden of disease. Disability Adjusted Life Years (DALYs) - One DALY represents the loss of the equivalent of one year of full health. DALYs for a disease or health condition are the sum of the years of life lost to due to premature mortality and the years lived with a disability due to prevalent cases of the disease or health condition in a population [37].

In addition to comorbidities, elderly is predisposed to the occurrence of several specific conditions with potential impact on their well-being and quality of life due to all the physiological changes associated with aging. These conditions are known as geriatric syndromes and include gait instability with the occurrence of falls, immobility, urinary and faecal incontinence, cognitive latency and iatrogenic drug-induced diseases [6].

Frequently associated to the elderly also appears the term frailty. Frailty is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality [38]. Frailty syndrome requires at least 3 of the following 5 characteristics: unintentional weight loss, muscle weakness, physical slowness, weak endurance, and low physical activity [38,39]. Frailty seems to be secondary to several conditions. Biological (e.g., inflammation, hormone loss), clinical (e.g., osteoporosis), as well as social (e.g.,

isolation, financial situation) factors are involved in the process of vulnerability [40]. However, frailty status seems to be more strongly associated with altered pharmacokinetic responses than chronological age [41]. In frail elderly the benefit–risk balance of a drug can be different when compared with the general population and therefore the risk of ADRs increase in these patients [41,42]. Additionally, it is necessary to consider that practice guidelines are often based on the results of clinical trials, in which frail, elderly and comorbid people have been mostly excluded, making it difficult to reliably predict from the 'real world' the prevalence and types of ADRs that might be expected in this population [43].

In addition to the disabilities caused by the diseases themselves, elderly patients are usually taking medications that must be used with caution as they are more prone to develop ADRs. In this context, mental, behavioural, and neurological diseases characterized by mild short-term memory loss, word-finding difficulty, and slower processing speed are normal parts of aging that are often noticeable by age 85. The rates of dementia also increase with age [44]. In addition to the decline in ability to perform daily activities associated with the disease itself, some medications can exacerbate this decline. An example of these medications that are commonly prescribed are benzodiazepines. In a study, 14% of adverse drug events were found to be related to the use of benzodiazepines [45]. These events are related to changes in pharmacokinetics and pharmacodynamics that increase the risk for falls and memory loss in the elderly associated to short- and long-acting benzodiazepines [46,47]. Antidepressants, especially tricyclics, and antipsychotics are also related to falls in this special population [48]. Drugs with anticholinergic properties are common contributors to confusion, urinary retention, constipation, among others; these include tricyclic antidepressants, certain serotonin reuptake inhibitors, some antihistaminic, and anti-spasmodic agents [17,49].

Regarding cancer, one of the main causes of death in older adults, the treatments are highly variable and depend on the type of cancer. These patients suffer, in general, more frequent and serious ADRs due to the intrinsic biologic toxicity of antineoplastic agents, their narrow therapeutic ranges, and the high doses and rigid timing of therapeutic regimens. The most prevalent types of cancers in the elderly are lung, colorectal, prostate, stomach and breast cancer [50]. The treatment for cancer includes surgery, radiotherapy, and/or systemic medications (chemotherapy, endocrine therapy, and/or biologic therapy with targeted agents). Several classes of drugs are used in cancer treatment, for example, alkylating agents, antimetabolites, platinum-containing compounds, hormonal agents, and monoclonal antibodies [51,52]. Moreover, cancer treatment can be more challenging and complicated for older adults due to

comorbidities, polypharmacy and variability in pharmacokinetics and pharmacodynamics comparatively to young adults, making them more susceptible to suffer drug-related problems [44,51–54]. Therefore, for each elderly patient, a special attention should be given to the benefit-risk relationship of cancer treatments.

In older adults, the cardiovascular diseases continue to be one of the leading causes of death. This category of diseases includes chronic ischemic heart disease, congestive heart failure, hypertension and cardiac arrhythmias [55]. Ischemic heart disease may be underdiagnosed in the elderly [44,55]. Hypertension, a major contributor to atherosclerosis, is the most common chronic disease in older adults [56]. Commonly prescribed antihypertensive medications, particularly angiotensin-converting enzyme inhibitors and α-blockers, have been associated with syncope and orthostatic hypotension in the elderly [57]. Diuretics have also been associated with falls and are more likely to cause hyponatremia in elderly than in younger patients because of impaired renal function. Altered pharmacokinetics in the elderly, combined with altered physiology of the cardiovascular and renal systems, make this population more susceptible to the effects of common antihypertensive agents, including calcium channel blockers, especially in patients with comorbidities such as heart failure or previous syncope [28]. Statins are used to reduce cardiovascular risk in the elderly, who often have comorbidities such as diabetes *mellitus* and hypertension [58]. Although cardiovascular risk reduction is important, the use of statins also increases the risk of myopathy with loss of muscle mass, especially in the elderly, and decline in liver function [59].

Additionally, other highly prevalent diseases in the elderly are type 2 diabetes *mellitus* (T2DM) and musculoskeletal disorders. T2DM has increased with age, constituting a major risk factor for cardiovascular diseases, especially in the elderly. Diabetes mellitus is also associated with peripheral arterial disease and peripheral neuropathy, contributing to diabetic foot ulcers and amputations [44]. Management approaches in diabetes *mellitus* should be individualized considering the risk of hypo-glycaemia associated with the medication and the characteristics of this vulnerable population [60,61].

Regarding musculoskeletal disorders, they are debilitating conditions that significantly impair the state of health and patients' quality of life. Approximately 1.71 billion people suffer from some type of musculoskeletal disorder worldwide [62]. Musculoskeletal conditions are typically characterized by pain (often persistent) and limitations in mobility, dexterity and overall level of functioning, reducing people's ability to work. It increases the risk of falls and fractures, resulting from loss of mobility and physical independence, which can be particularly devastating in the elderly [63]. Additionally, to

manage the associated chronic pain, NSAIDs are commonly prescribed for long periods of time, often leading to gastric and duodenal ulcers, as well as other common and characteristic ADRs [49].

According to the WHO, the main causes of mortality in older people are heart disease, stroke, and chronic lung disease [35]. In 2004, the leading causes of death among Americans aged 65 and older were: heart disease (1,418 deaths per 100,000 people), cancer (1,052 per 100,000), stroke (346 per 100,000), chronic lower respiratory diseases (284 per 100,000), Alzheimer's disease (171 per 100,000), diabetes *mellitus* (146 per 100,000) and influenza infection and pneumonia (139 per 100,000) [64]. In 2019, according to the Institute of Health Metrics and Evaluation, the leading causes of death for people with 70 years or older continues to be cardiovascular diseases (12.17 million) followed by cancer (4.91 million), respiratory diseases (2.87 million), such as chronic obstructive pulmonary disease and asthma (excluding infectious respiratory diseases), Alzheimer's disease and other dementias (1.51 million), lower respiratory infections (1.23 million), digestive diseases (1.06 million) and diabetes *mellitus* (843,598) [65].

Concerning the Portuguese reality, a cross-sectional study concluded that the most pathologies diagnosed were osteoarthritis, arterial hypertension and dementia, being that this last disease also considered a frequent factor for disability, along the stroke and the fracture of the femur [66]. In Portugal, arterial hypertension is one of the cardiovascular risk factors affecting 36% of people aged 25-74 years, with a higher prevalence in men than in women, and increasing with age, affecting more than 71% of Portuguese people aged 65-74 years. T2DM affects 10% of the Portuguese population between 25 and 74 years, especially men and older age groups (23.8% of people between 65 and 74 years) [67]. In this context, it is important to mention that the number of diabetic patients in Portugal is increasing. Diabetes *mellitus*, isolated, is the tenth leading cause of death, but it is the second leading cause of disability [68]. Regarding musculoskeletal disorders, although they are not usually fatal, they are one of the groups of medical conditions that most contribute to the disease burden in the world population, with Portugal being no exception. For instance, due to the suffering they cause, musculoskeletal disorders are responsible for many absences from work [67,68].

Hence, bearing in mind the high prevalence of diabetes *mellitus* and musculoskeletal disorders in Portugal [68], safety data of drugs used in the management of these conditions were studied in more detail in this thesis. Therefore, a more detailed description of diabetes *mellitus* and musculoskeletal diseases, as well as the drugs usually used for their treatment is provided below.

I.3.1 Diabetes *Mellitus*

The global diabetes prevalence in 2021 was 10.5% (figure I.3), being expected to rise to 12.2% by 2045 [69]. Among adults aged 75–79 years, diabetes prevalence was estimated to be 24.0% in 2021 and is expected to rise to 24.7% in 2045 [69].
The total number is predicted to rise to 643 million (11.3%) by 2030 and to 783 million (12.2%) by 2045.

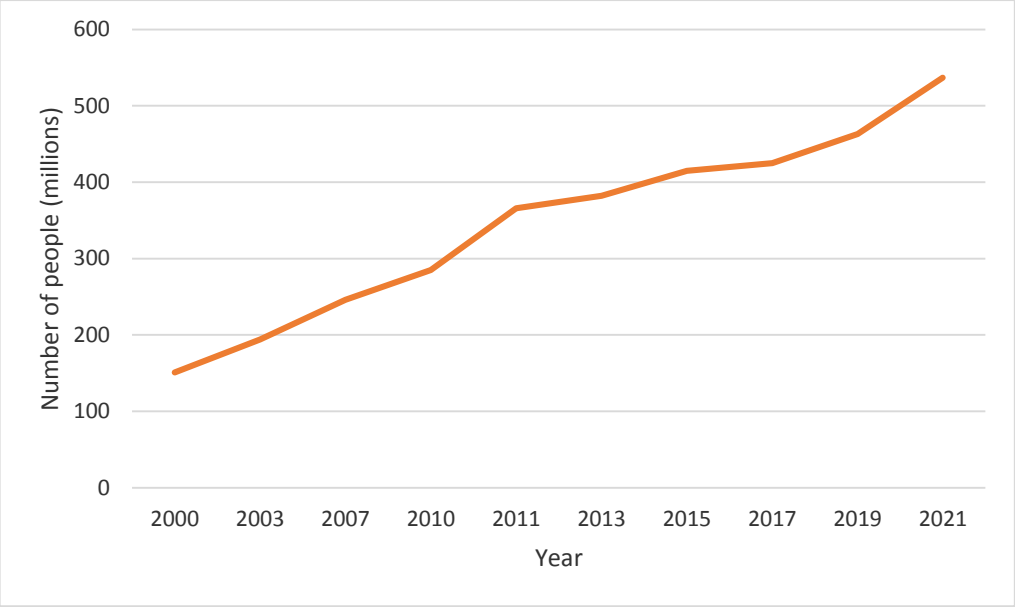

Figure I.3: Number of people with diabetes in World (Source IDF DIABETES ATLAS 10th edition 2021 [69]**)**

The three main types of diabetes are type 1 diabetes *mellitus* (T1DM), T2DM, and gestational diabetes *mellitus*. For T2DM, which accounts for approximately 90% of the total cases, its rising trend can be attributed to aging and increasingly sedentary lifestyle in younger adults [69–71].
In Portugal, the prevalence of diabetes has increased. In addition, Portugal is one of the European countries with the highest prevalence, corresponding to 13.6% of the Portuguese population in 2018 [72].
T2DM is a metabolic disease with high prevalence in elderly population [73]. It is associated with high levels of mortality and morbidity, polypharmacy, and cognitive and functional decline in this population [74]. In general, T2DM is a metabolic regulatory disorder characterized by chronic hyperglycaemia. The underlying causes include impaired insulin production, resistance to its action, and/or often a

combination of both [6]. In the elderly, the main factors leading to hyperglycaemia are decreased insulin secretion with age and increased insulin resistance caused by changes in body composition (there is an increase in visceral adipose tissue) and sarcopenia (with age, muscles lose strength and mass, and this phenomenon is called sarcopenia) [75]. The sensitivity of pancreatic β-cells to incretins (group of metabolic hormones that stimulate a decrease in blood glucose levels) decreases, leading to lower postprandial insulin levels and to a weaker suppression of glucagon secretion [74]. There is also dysregulation of the hypothalamic-pituitary-adrenal axis, leading to an increase in cortisol levels. Cortisol, as a catabolic hormone, is responsible for proteolysis, and its higher levels lead to a decrease in muscle mass. In addition, cortisol conduces to insulin resistance [76]. Moreover, obesity, decreased adrenergic activity, a decline in renal function and the use of potentially diabetogenic medications (e.g. some diuretics, β-adrenolytics, corticosteroids, psychotropic drugs, amiodarone) often further promote impaired glucose metabolism and diabetes in the elderly [75].

Chronic hyperglycaemia leads to microvascular complications, causing sequelae mainly in the eyes, kidneys, and nervous system, and also leads to macrovascular complications mainly in the heart, brain, and peripheral arteries [77]. In this context, elderly diabetics have a higher risk of suffering microvascular and macrovascular complications [6]. Consequently, diabetes is associated with higher rates of amputation, myocardial infarction, vision loss, kidney disease, and death from hypo- or hyperglycaemia in this age group [78]. Additionally, this condition is associated with increased mortality and risk of institutionalization [79]. Considering all these reasons, it is important to improve diabetes control in this growing subpopulation, either for health or economic reasons.

The goal of diabetes treatment is to maintain adequate glucose levels. In this context, it is important to mention that the risk of hypoglycaemia increases with age as does the risk of associated complications, including worsening of cognitive impairment, falls, and decreased quality of life in general [6]. Any occurrence of hypoglycaemia increases the risk of cardiac death and may worsen cognitive function or exacerbate dementia [75]. It is also necessary to take into account that the clinical manifestation of hypoglycaemia in elderly patients may occur at lower blood glucose levels when compared to younger people [60,80]. Probably due to the atypical symptoms, patients are often unaware of hypoglycaemia. Warning signs caused by stimulation of the adrenergic system, such as sweating, tremor, or hunger, may not occur. Moreover, the counter-regulatory response of glucagon secretion is often limited and insufficient in elderly patients [75]. In addition, impaired renal and hepatic function, which is common in this population, may impair drug metabolism and excretion, contributing

to an increased risk of hypoglycaemia [74,78]. Impaired renal function can also lead to hyperglycaemia due to dehydration, which also increases the risk of delirium [6,75,78]. In fact, the control of blood glucose levels is critical in the management of diabetes. However, to achieve the recommended goals, the risk of hypoglycaemia is also increased.

Therefore, in these patients, it is important to consider an individualised approach of treatment that takes into account life expectancy, patient involvement in the treatment process, ability to use injections and self-monitoring of blood glucose levels, and the presence of frailty and other coexisting conditions. Pharmacological treatment must also consider a high frequency of ADRs and drug interactions due to polypharmacy.

Metformin has been considered the first-line therapy for T2DM, which may be beneficial for elderly due to its low risk of causing hypoglycaemia in monotherapy, although gastrointestinal intolerance and weight loss may be detrimental [60,75]. This biguanide mainly acts by increasing the liver sensitivity to insulin, suppressing gluconeogenesis, and also stimulating glucose uptake and its use by muscle and adipose tissue [61]. Nevertheless, this drug has some limitations when used in seniors. In fact, it is not recommended for individuals suffering from renal failure (glomerular filtration rate of 30 ml/min/1.73 m^2), heart failure (New York Heart Association class III and IV) and chronic respiratory failure [60,61].

Sulfonylureas constitute another group of oral antidiabetic drugs used to treat T2DM. These drugs are effective in lowering blood glucose levels, have a relatively good tolerability, and are often added to metformin or used as monotherapy. The main concern associated with the use of these drugs is the increased risk of hypoglycaemia when compared with other blood glucose-lowering agents [80–82]. This risk is increased in the presence of renal or hepatic impairment, as well as with concomitant use of drugs that potentiate the effects of sulfonylureas, such as salicylates, acenocoumarol or fibrates [83]. Among sulfonylureas, gliclazide is safer than glimepiride because it is metabolised to inactive metabolites, resulting in a lower risk of hypoglycaemia in the event of declined renal function [75,83]. Due to the risk of hypoglycaemia, the use of short-term sulfonylureas is more beneficial and safer than long-term sulfonylureas in the elderly [78].

α-Glucosidase inhibitors (e.g., acarbose) delay intestinal monosaccharide absorption and prevent complex carbohydrate breakdown, lowering postprandial hyperglycaemia. These drugs present a low risk to induce hypoglycaemia, which would be expected considering their mechanism of action. However, the gastrointestinal intolerance that they can cause may be a limiting factor in the elderly [78].

Meglitinides, which also stimulate insulin secretion, are administered before meals. Their short half-life is useful for controlling postprandial hyperglycaemia and are associated to a lower risk of hypoglycaemia compared with sulfonylureas [61].

Gliptins - dipeptidyl peptidase-4 (DPP-4) inhibitors - are a relatively new group of drugs that have been successfully used in the elderly. DPP-4 increases the levels of endogenous incretin inhibitors, mainly glucagon-like peptide-1 (GLP-1), which increases insulin secretion and inhibits glucagon release. These drugs have a safer profile and good efficacy and tolerability [75].

GLP-1 analogues are another group of drugs that effectively reduce blood glucose while reducing the risk of hypoglycaemia. They have been associated to a beneficial effect on the cardiovascular system [84].

Thiazolidinediones, due to their action on peroxisome proliferator activated receptors, affect the transcription of numerous genes, leading to an improvement in insulin sensitivity in peripheral tissues, especially in adipose tissue. They also have a beneficial effect on lipid profile. However, they can cause fluid retention (being contraindicated in patients with heart failure), decrease bone mineral density and increase the risk of bone fractures [85].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, the newest class of oral pharmacological agents used to treat diabetes *mellitus*, inhibit glucose reuptake in the proximal renal tubule, resulting in an increased urinary glucose excretion. This mechanism of action results in decreased blood glucose levels and caloric loss. Therefore, there is a low risk of hypoglycaemia. However, these drugs can induce glycosuria and increase the risk of genitourinary system infections [75,86,87].

It is also important to mention that, due to progressive loss of β-cell function and insulin sensitivity, most patients with T2DM eventually require human insulin or insulin analogues to control hyperglycaemia [88]. In fact, some insulin analogues (e.g., glargine or detemir) are usually added to oral therapy when it becomes inadequate, and rapid-acting insulin analogues (lispro, aspart, glulisine) can also be used to control postprandial glycaemic peaks in the elderly [88]. Insulin analogues offer a better pharmacokinetic profile, are more convenient, and lead to a lower variation in glycaemic control than human insulin. Long-acting basal insulin therapy is usually the first choice for insulin therapy in older adults because of their efficacy, simplicity, and once-daily administration [89]. They provide a prolonged, nearly 24-hour duration action similarity to physiological basal insulin secretion [89,90]. Insulin analogues tend to have less intraindividual variability in their time-action profiles and may be associated with a lower risk of hypoglycaemia than human insulin [91]. However, in older adults with dementia or others comorbidities, who have unpredictable eating

habits, rapid-acting analogues are a more favourable therapeutic option because they can be administered immediately after a meal reducing the risk of hypoglycaemia [92,93].

I.3.2 Musculoskeletal Diseases

With aging, a gradual decline in the function, strength, and regenerative capacity of several tissues and organs occurs. Thus, a decrease in muscle strength, motor coordination, and cognitive function are characteristics of advancing age, also increasing the risk of falls. Additionally, there is also a progressive loss of bone mass promoting the occurrence of fractures and fragility [6]. Due to changes in the immune system, the prevalence of rheumatic diseases is also higher in the elderly. In summary, musculoskeletal diseases are widespread and have a critical impact on the quality of life of older people. They are usually chronic and non-fatal diseases [4].

The most common osteoarticular diseases in the elderly are osteoarthritis, rheumatoid arthritis and osteoporosis. They have been considered a reason for the high prevalence of chronic pain and impairment of functionality, muscle strength, balance, motor coordination, and daily living activities, causing pain and stiffness and affecting patients' quality of life [94–96].

Osteoarthritis is a painful complex disease that affects millions of people worldwide, being common in older people [97,98]. Osteoarthritis is a disease of the whole joint, which involves many pathophysiological processes that result in dysregulation of the function of cytokines and growth factors, prostaglandins, cartilage matrix fragments, neuropeptides, reactive oxygen intermediates, proteolytic enzymes and protease inhibitors. Dysregulation of these factors triggers a cycle of degeneration of cartilage, bone, ligaments and synovium that coincides with an inflammatory response and peripheral and CNS sensitization [97]. The osteoarthritis clinical symptoms are pain and functional impairment that includes joint stiffness and dysfunction [99]. Current treatments for osteoarthritis include acetaminophen, opioids, NSAIDs and intra-articular hyaluronic acid or steroid injections [97–99].

Rheumatoid arthritis is a chronic, inflammatory autoimmune disease characterized by joint inflammation that can lead to destruction of articular and periarticular tissues [100]. It causes pain, deformity, and bone and cartilage destruction [101]. Treatment includes disease-modifying antirheumatic drugs, as well as analgesics and anti-inflammatory drugs for pain and inflammation relief [100]. Commonly used conventional disease-modifying antirheumatic drugs include methotrexate,

leflunomide, hydroxychloroquine, and sulfasalazine [102]. Biologic disease-modifying antirheumatic drugs are also usually prescribed after the failure of conventional disease-modifying antirheumatic drug therapy. Some biological agents include infliximab, adalimumab, etanercept, rituximab, abatacept, rituximab, tocilizumab, among others [102].

Osteoporosis is characterized by reduced bone mass and deterioration of bone tissue, which affects its quality and strength and increases the risk of fractures [103]. As the population ages, the osteoporosis incidence and resulting osteoporotic fractures is increasing. Although osteoporosis is more common in women than in men, the incidence in men is increasing [104]. Reduction of potentially modifiable risk factors, along with exercise, calcium and vitamin D supplementation constitutes an important adjunct to pharmacological treatment. Drugs such as alendronate and risedronate (or other bisphosphonates) and raloxifene are available to prevent the risk of bone fracture [105,106]. The chronic pain associated to these musculoskeletal diseases is one of the most frequent complaints in older adults and is related with significant disability [107]. Chronic pain in older adults limits mobility, is associated with depression and anxiety, and can disrupt family and social relationships [108]. NSAIDs are widely used for symptomatic control of pain and inflammation, but other drug classes, such as antidepressants, anticonvulsants, muscle relaxants and opioids can also be used to treat these painful conditions [109]. Pharmacological agents should be selected based on pharmacokinetic and pharmacodynamic considerations in elderly, including the risk of ADRs and potential drug interactions due to polypharmacy.

Pain is frequently associated with inflammatory events and processes in various organs, but it can also occur without apparent inflammatory signs. Pain and hyperalgesia are common features of the inflammatory process. Part of the pain arises as an immediate sensation after tissue injury due to direct stimulation of sensory nerve endings. The pain results from a combination of chemical stimulation due to vascular changes inherent to the inflammatory process and direct chemical stimulation by pain-producing substances [108,110].

It is not the purpose to address here the central components or psychological aspects of pain or to analyse in detail the physiopathological aspects of pain transmission. It will only be addressed the involvement of chemical mediators in the initiation of inflammatory pain to explain the analgesia caused by anti-inflammatory agents.

Conventionally, the inflammatory process is characterized as the passive result of tissue injury and the production of mediators that cause biochemical, cellular, and vascular changes to restore homeostasis [111]. This process is initiated by an acute phase in which there is an increase in blood flow and vascular permeability, stimulating

leukocyte migration and activation, and the production of pre- and post-injury mediators. If the aggressive stimulus persists, the process becomes chronic, being associated to other characteristics controlled by humoral and cellular responses with high specificity and immunologic memory [112].

Acute inflammation is primarily driven by mediators released by resident cells, including preformed mediators (as histamine, serotonin, and heparin) and postformed mediators (as lipid mediators, cytokines, and reactive oxygen species). These mediators increase vascular permeability and blood flow to facilitate leukocyte migration and plasma protein extravasation. Cytokines such as interleukin-1, interleukin-6 and tumor necrosis factor α play a fundamental role in this phase [112]. Upon return to homeostasis, multiple mediators act in an organized and sequential manner to promote the resolution of the inflammatory response. Firstly, mast cells release preformed mediators such as histamine and serotonin [113]. As a result, vasodilation and increased endothelial permeability occur, allowing leakage of a protein-rich fluid through changes in hydrostatic pressure. This results in a high concentration of red blood cells and allows leukocytes to migrate to the peripheral layer of the circulation, initiating the process of leukocyte marginalization, followed by diapedesis and migration. In this phase, adhesion molecules and chemokines play a crucial role [114]. Leukocytes are the first cells to be targeted at the site of tissue injury, followed by monocytes. During this process, activation of platelets, interleukin-8, complement factor 5a and integrins also occurs [115]. Still associated with preformed mediators, activated leukocytes release bioactive amines as well as lysosomal enzymes that cause additional tissue damage. In addition, activation of these leukocytes stimulates biochemical pathways involved in the production of postformed mediators such as reactive oxygen species, lipid mediators, and protein mediators such as cytokines, chemokines, and adhesion molecules [116].

Eicosanoids (e.g., prostaglandins and leukotrienes) are among the most important mediators of inflammatory hyperalgesia and are mainly formed from arachidonic acid by the activity of cyclooxygenases and lipoxygenases enzymes. Prostaglandins act through a series of second messenger-coupled receptors [110,117]. Although prostaglandins are normally produced by the cyclooxygenase constitutive form, cyclooxygenase-1 (COX-1), and mediate a number of physiological functions [117,118], prostaglandin formation during inflammation is enhanced by induction of another isoform of the enzyme, cyclooxygenase-2 (COX-2) [110].

Although it can be considered a physiological process, increased inflammation can cause additional tissue damage and produce adverse effects such as pain. In this sense, NSAIDs are among the most used drugs for the treatment of algesic and/or

inflammatory diseases [108]. NSAIDs have anti-inflammatory, analgesic and antipyretic properties and their action results from the inhibition of the prostaglandins synthesis by inhibition of the enzymes COX-1 and COX-2 [119].

Most NSAIDs reversibly inhibit cyclooxygenases, with the exception of acetylsalicylic acid, which is a non-selective and irreversible inhibitor [119]. Therefore, the duration of acetylsalicylic acid action depends on the *novo* synthesis of cyclooxygenases [109,119]. Overall, NSAIDs are well absorbed in the stomach and intestine, are extensively bound to plasma proteins, and are excreted by renal filtration and tubular secretion. NSAIDs can be classified based on their chemical and pharmacological properties, and cyclooxygenase selectivity [119].

On the basis of their chemical structure, they can be classified as presented below [120,121]:

- Salicylic acid derivatives: acetylsalicylic acid (aspirin), diflunisal
- Indole and indene acetic acids: indomethacin, etodolac, acemetacin, proglumetacin
- Aryl- and heteroaryl acetic acids: diclofenac, ketorolac, aceclofenac, bendazac
- Aryl- and heteroarylpropionic acids: ibuprofen, ketoprofen, flurbiprofen, naproxen, dexketoprofen, dexibuprofen
- Anthranilic acids: etofenamate
- Enolic acids (oxicams): piroxicam, tenoxicam, meloxicam
- Alkanones: nabumetone
- Sulfanylamides: nimesulide
- Diarylheterocycles (selective COX-2 inhibitors): celecoxib, parecoxib, etoricoxib.

The COX-1 isoform, present in most tissues, is a constitutive enzyme that promotes homeostasis and produces prostaglandins responsible for multiple physiological actions (e.g., gastrointestinal cytoprotection). The COX-2 is an enzyme that produces prostaglandins, which are responsible for the perception of pain and inflammation and is essentially present in the CNS, kidneys, and endothelium. Both are directly involved in prostaglandins production, which play a notorious role in the maintenance of homeostasis. Thus, inhibition of these enzymes impairs the regulation of these organs, leading to functional alterations [107,119].

In this context, despite their therapeutic efficacy, the main side effects induced by NSAIDs include gastrointestinal complications, cardiovascular events and renal toxicity [122]. In table I.7 are presented the most common adverse effects associated to NSAIDs.

Table I.7: Adverse effects profile associated to non-steroidal anti-inflammatory drugs (adapted from Wongrakpanich et al 2018 [122], **Pilotto et al 2010** [123] **and Harirforoosh et al 2009** [124]**)**

Organ toxicity	**Adverse effects**
Gastrointestinal toxicity	Dyspepsia Gastroduodenal ulcers Gastrointestinal bleeding and perforation
Cardiovascular adverse effects	Edema Hypertension Congestive heart failure Myocardial infarction Stroke and other thrombotic events
Nephrotoxicity	Electrolyte imbalance Sodium retention Edema Reduce glomerular filtration rate Nephrotic syndrome Acute interstitial nephritis Renal papillary necrosis Chronic kidney disease

Non-selective NSAIDs increase the risk of side effects because they inhibit both COX-1 and COX-2 isoforms. Their inhibition is the main cause of the higher incidence of gastrointestinal ulceration and gastrointestinal tract perforation and bleeding associated with their use [107]. Therefore, selective COX-2 inhibitors can improve the gastrointestinal safety profile, but there is an increased cardiovascular risk [107,119,125]. Other side effects unrelated to the therapeutic target may occur, namely hepatic, immunological and CNS effects [107]. The renal toxicity occurs in 5% of patients taking these agents [126]. Older adults may be at higher risk for renal toxicity

than younger patients. Non-selective and selective COX-2 inhibitors have been shown to cause renal dysfunction and it is recommended that NSAIDs should be avoided in patients with a creatinine clearance lower than 30 ml/minute [109]. Concerning cardiovascular risks, studies have shown that selective and non-selective NSAIDs increase the risk of heart failure and worsen the symptoms of this condition [127].
NSAIDs are a major cause of drug-associated morbidity in elderly [107]. Their use, especially the chronic use, increases with age and it is estimated that a large proportion of people over 65 years take NSAIDs daily [119]. Thus, elderly is a population especially vulnerable to ADRs induced by these drugs, highlighting the gastrointestinal, cardiovascular, renal, hepatic and cerebrovascular events [128].

I.4 Polypharmacy in Elderly and Clinical Consequences

In the elderly population, as mentioned above, multiple clinical conditions and chronic diseases that may require a high number of medications are prevalent. Therefore, the existence of polypharmacy, that is often defined as the concurrent use of five or more different drugs, is common in the elderly [17].
There are several reasons for polypharmacy in the elderly. Firstly, as mentioned earlier, the prevalence of many diseases is age-dependent, and several may coexist in the same patient. Secondly, it may not be possible to achieve an adequate therapeutic response with a single drug. Thirdly, there is a need to neutralize or minimize the risk of occurrence of an adverse drug event. The difficulty in distinguishing drug-induced symptoms from a definitive medical diagnosis often results in the addition of another drug to treat the symptoms, which increases the risk of drug-drug interactions and ADRs – a phenomenon known as the "prescribing cascade" [17,129].
Patients aged ≥65 years use an average of four prescribed medications [16,130]. This is relevant because patients taking more than five medications are approximately three times more likely to be using an inappropriate medication, with higher risk of ADRs and drug-drug and drug-disease interactions [16,20,124,131,132]. In table I.8 and table I.9 some examples of drug-disease interactions and drug-drug interactions, respectively, are presented.

Table I.8: Some prescribed drugs and potential drug–disease interactions (adapted from Burrage et al 2014 [16], **Vandraas et al 2010** [131], **Lavan et al 2016** [132] **and Harirforoosh et al 2009** [124]**)**

Class of drugs	Effect on comorbid disease
Angiotensin-converting enzyme inhibitors	May exacerbate hyperkalaemia and acute kidney injury
Non-steroidal anti-inflammatory drugs	May exacerbate asthma, cardiac failure and chronic kidney disease
Opioid analgesia (including weak opioids like codeine)	May exacerbate constipation, cognitive impairment or dementia and falls
Antimuscarinics	May exacerbate arrhythmias or tachycardia, confusion or dementia, heart failure, hypertension, hyperthyroidism and glaucoma
Benzodiazepines	May exacerbate cognitive impairment or dementia, falls and respiratory failure
Bisphosphonates	May exacerbate dysphagia and gastro-oesophageal reflux disease
Diuretics	May worsen hyponatraemia and dehydration

As a result of these interactions, some drugs may aggravate a disease already present in the patient or increase or decrease the effect of a drug used to treat a disease.
Thus, when evaluating the balance of benefits of medications taken by the elderly, the number and drug classes of medications should be considered [16,17,20].

Table I.9: Some drug-drug interactions with potential clinical significance (adapted from Mann 2002 [20]**, Tesfaye et al 2017** [133]**, and Snowden 2016** [134]**)**

First drug	Second drug	Effect of Interaction
ACE inhibitors	NSAIDs	Hyperkalaemia, reduced renal function
Antidepressants (tricyclic)	Cytochrome P450 enzyme inhibitors (e.g., cimetidine)	Increased effect of antidepressants (tricyclic)
Antihypertensive agents	Vasodilators (e.g., nitrates for angina), antipsychotics and some antidepressants	Postural hypotension
Acetylsalicylic acid (low dose)	NSAIDs	Peptic ulceration
Carbamazepine	Cytochrome P450 enzyme inhibitors (e.g., verapamil)	Increased effect of carbamazepine
Corticosteroids (oral)	NSAIDs (including ASA)	Peptic ulceration
Digoxin	Amiodarone, diltiazem, verapamil, diuretics (loop and thiazides)	Increased effect of digoxin
Diuretics (potassium sparing)	ACE inhibitors, potassium supplements	Hyperkalaemia, impaired renal function
Quinolones	NSAIDs	Seizures
Antihypertensives (e.g., ACE inhibitors, thiazides and β-adrenoceptor antagonists (β-blockers))	NSAIDs	Reduced effect of antihypertensives
Calcium antagonists	Cytochrome P450 enzyme inducers	Reduced effect of calcium antagonists
Thyroxine	Cytochrome P450 enzyme inducers	Reduced effect of thyroxine

ACE inhibitors: angiotensin-converting enzyme inhibitors; ASA: Acetylsalicylic acid; NSAIDs: non-steroidal anti-inflammatory drugs

I.4.1 Potentially Inappropriate Medication in Older People Population

Considering the increase of number of drugs used by this special population, inevitably rises the risk of use of potentially inappropriate medications (PIMs) [135]. PIMs are considered a global health problem that leads to an increase in associated ADRs, which enhancers the rate of hospitalization and consequently healthcare costs [136,137]. According to the literature, adverse events associated to PIMs occur in >15% of the elderly population and are considered preventable [138].

The drugs most frequently associated with PIMs are antiplatelet agents and benzodiazepines in long term use [139]. In Portugal, a study carried out in institutionalized people found an average of 15 drug-related problems per patient [140]. PIM-related ADRs were observed in some studies, with digoxin, benzodiazepines, and imipramine being the most common drugs involved. In hospitalized elderly patients, NSAIDs inducing upper gastrointestinal bleeding were the most common PIMs. Benzodiazepines inducing falls with fractures and depressed mental status and digoxin 0.125 mg/day inducing cardiac arrhythmias and visual disturbances due to digoxin intoxication are also common in the hospital setting [141–143].

Given the pharmacoeconomic impact that polypharmacy can have, the British Geriatrics Society recommends a medication review based on the principles of geriatric assessment for all older people identified with indicators of higher frailty (falls, delusions, immobility) using an evidence-based checklist, such as the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria [144]. The STOPP/START criteria were originally developed in Ireland using the Delphi method and based on physiological systems [145]. They were published in 2008 and were revised in 2014 [146]. The STOPP criteria intended to identify PIMs and the START criteria intended to identify potentially prescribing omissions (PPOs) [146]. The use of this tool has shown to reduce PIMs, associated adverse events and healthcare costs, as well as the rate of iatrogenic hospitalizations [147].

There are other criteria for medication review, such as the American Geriatric Society Beers criteria, which were originally published in 1991 and have received several updates using the Delphi method, being the latest version of 2019 [57]. These criteria were created to support clinical prescribing in older people over the age of 65. In addition to allow detecting PIMs, this criteria also present information on drugs to be used with caution in elderly, as well as a summary of potentially clinically important drug-drug interactions to be avoided in older adults and a list of medications that should be avoided or their dosage reduced based on kidney function [57,148]. In the

same scope, in 2015, 27 experts from 7 European countries came together to develop a European list of potentially inappropriate drugs. This resulted in the EU[7]-PIM list with 6282 drugs from 34 pharmacological classes, including for each drug the rationale for its inadequacy, as well as dose adjustments/special use considerations [when applicable] and possible alternatives to that drug [149]. In this context, a study performed in Portugal with these tools, detected a high prevalence of PIMs, and showed that the prevalence was different depending on the tool selected; therefore, it is necessary to have care in the choose of the tool to be used for medication review (appendix 2) [150].

In addition to these tools, there are many others with similar objectives: to reduce the number of medications and to increase the appropriateness of the medication regimen. Although all these screening tools can be helpful, they will never replace clinical assessment and evaluation. However, they can be used as a systematic approach to improve prescribing practices in older populations and, consequently, reducing the negative impact of PIMs.

I.4.2 Adverse Drug Reactions in Elderly and their Impact

According to European Medicines Agency (EMA) guideline on good pharmacovigilance practices (GVP) VI, an ADR is a response to a harmful and unintended drug and may result from use of the product within or outside the terms of the marketing authorization (including off-label use, overdose, misuse, abuse and medication errors) or from occupational exposure [151]. An adverse reaction, in contrast to an adverse event, is characterized by a presumed causal relationship between a drug and an event [151].

Age-related changes in pharmacokinetics and pharmacodynamics, along with a higher burden of disease and specific problems in older adults (e.g., instability, prostatism, cognitive impairment) put older patients at higher risk for ADRs such as falls, confusion, and urinary retention, with a subsequent worsening of morbidity when such events occur. In addition, elderly often experience non-specific ADRs that may mimic underlying disease processes, such as generalized functional deterioration similar to dementia [129].

ADRs can be classified into six types

1-Type A reactions (dose-related)

They result from the exaggerated pharmacological action of the drug administered at the indicated dose. Pharmacokinetic or pharmacodynamic factors have been shown to be responsible for these ADRs. They are predictable, common, dose-dependent, cause significant morbidity but low mortality and can be minimized by reducing the dose or drug withdrawal. Some examples are nephrotoxicity caused by aminoglycosides and anticholinergic effects of tricyclic antidepressants [152,153].

2-Type B reactions (non-dose related)

These adverse reactions are bizarre and unpredictable, unrelated to the dose or pharmacological action of the drug and are frequently allergic in nature. The effects have been noted in a marginal number of patients and are often sensitive or idiosyncratic adverse reactions. In addition, type B ADRs can be classified as non-immunological ADR's and immunological ADRs. The non-immunological ADR's, normally, are idiosyncratic reactions resulting from mechanisms that are not fully understood and affect patients that may have particular genetic differences in the way their body responds to specific drugs. The immunological ADRs occur due to immunoglobulin E-dependent drug reactions, immune complex-dependent drug reactions, cytotoxic drug-induced reactions, and cell-mediated reactions. They are rare but often severe and cause high mortality. Examples of type B reactions include penicillin-induced urticaria and anticonvulsant hypersensitivity syndrome reaction [152,153].

3-Type C reactions (dose-related and time-related)

These adverse reactions are chronic (long term) and are related to the cumulative dose. Particularly, type C reactions were considered to have chronic effects related to long-term drug use, such as analgesic nephropathy or extrapyramidal effects. These reactions were found to be related to the cumulative toxic effects of a drug taken over a long period of time, in which the adverse effects gradually increase. In addition, the adjustment on discontinuation of the drug can be associated to abstinence syndrome. As an example, it can be referred the suppression of the hypothalamic-pituitary-adrenal axis by corticosteroids [152–154].

4-Type D reactions (time-related)

These adverse reactions are delayed (i.e., have a lag time) after the use of a drug. The development of secondary cancers in patients treated with alkylating agents such as cyclophosphamide is probably the best example of type D adverse reactions [152–154].

5-Type E reactions (withdrawal)

These adverse reactions occur soon after the end of use (i.e., withdrawal) and are uncommon. The examples of these reactions include withdrawal seizures on terminating anticonvulsant therapy and adrenocortical insufficiency subsequent to glucocorticoids termination [152–154].

6-Type F reactions (unexpected failure of efficacy)

These adverse reactions occur when there is a failure of efficacy [152–154].

The type A - Augmented reactions, represent almost 80% of all ADRs in older patients and type B - Bizarre, represent approximately 20% of all ADRs in older patients. Drugs associated with type A reactions usually have a low therapeutic index and are often used in elderly patients. Therefore, most ADRs in this age group are type A reactions, with a predictable pharmacologic effect [143,152,154].

However, ADRs can be difficult to diagnose in older patients as they often originate nonspecific symptoms, namely falls, fatigue, cognitive decline, or constipation, all of which can have different aetiologies [132].

Considering the factors that determine the risk of ADRs, in general, in elderly, it is important to consider both metabolic and non-metabolic effects. Age-related changes in pharmacokinetics, pharmacodynamics, chronic inflammation (to which has recently been attributed an important role in pharmacokinetics and pharmacodynamics changes related with age) and interindividual variability in drug response should be considered [22,143,155,156]. Additionally, geriatric conditions (i.e., a set of clinical and functional problems, partly constitutive and partly related to frailty), a history of falls, and loss of independence in daily living activities seem to define a condition of particular susceptibility of elderly patients to ADRs [20,22,157]. The sex of the patient can also be considered. In fact, female patients have a 1.5- to 1.7-fold higher risk of developing an ADR, including adverse skin reactions, compared with male patients. The reasons for this increased risk are not entirely clear, but include gender differences in pharmacokinetics, immunological and hormonal factors, and differences in drug use by females compared to males [158,159].

It is important to mention that ADRs in older population constitute an important healthcare problem, resulting in significant morbidity, healthcare consumption, and high costs. The nursing home residents and frail elderly patients in general are at higher risk of ADRs [29,41,42,160,161]. One in 30 urgent hospital admissions of patient's ≥65 years is due to ADRs. These ADRs can be as serious and potentially fatal as any other acute illness that warrants urgent hospitalization. Most cases involve patients exposed to polypharmacy and result from known reactions to some commonly used drugs [162]. The reports of ADRs received in Portugal, between 2018-2020, by age group, are presented in figure I.4, and it is possible to observe the high number of ADRs reports occurring in the elderly [163], as had already been observed in a study carried out by us, between 2013-2017, which is presented later in of this thesis [164]. In 2020, there was a reversal of the increasing trend in the number of reports, probably as a result of the COVID-19 pandemic, but the number of reports of suspected ADRs continued to be high in the elderly [165].

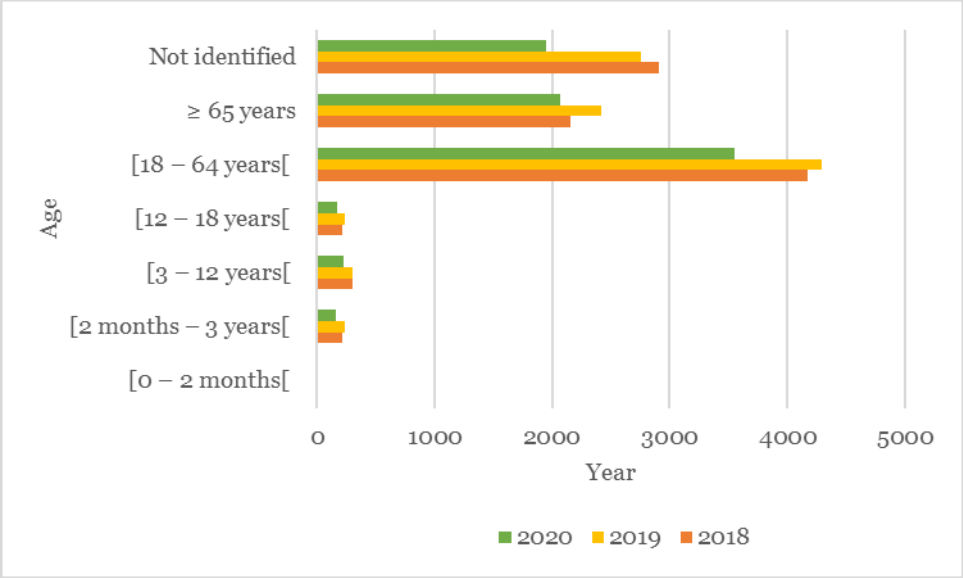

Figure I.4: Reports of adverse drug reactions received in Portugal, between 2018-2020, by age group (Source: INFARMED [163]**)**

The mostly involved drugs are antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, anticancer drugs, and NSAIDs. Most of these ADRs are predictable and dose-dependent [166–168]. A smaller number of more serious ADRs are idiosyncratic hypersensitivity reactions (e.g., hepatotoxicity with flucloxacillin or amoxicillin and clavulanic acid, anaphylactic shock with penicillins). Anticholinergic effects (namely caused by tricyclic antidepressants, antiparkinsonian agents and

smooth muscle relaxants) may cause delirium or worsen cognitive function, especially in older patients with pre-existing cognitive impairment [29,162].

The most common ADRs leading to hospitalization in this age group are related to gastrointestinal complications (gastrointestinal bleeding, peptic ulcer, erosive gastritis, nausea, vomiting), cardiovascular disease (hypotension, bradycardia, falls, arrhythmias), metabolic/endocrine complications (hypoglycaemia), renal and urinary disorders (renal failure), electrolyte disorders (hypokalaemia, hyperkalaemia, hyponatremia) and central nervous system disorders (impaired consciousness, mental status changes) [143,169].

The ADRs are responsible for 6.5% of hospital admissions in the United Kingdom, 0.15% of deaths and 72% of them were considered preventable. Patients admitted with ADRs were significantly older (median 76 years, interquartile range 65-83) than patients without ADRs (66 years, 46-79) [170].

A prospective study was conducted over a 6-month period in the medical department of a hospital in Greece, comparing ADR- and non-ADR-related admissions [120]. In this study, authors concluded that the mean number of medications and age were significantly higher in patients admitted for an ADR [120]. Another study concluded that most patients with ADRs leading to urgent hospitalization (86%) were exposed to polypharmacy, and drug-drug interactions were suspected in 49% of ADRs [162]. In addition, a study concluded that at least one drug interaction explain nearly 40% of the ADRs classified as "serious requiring hospitalization" [171].

Many of the ADRs are generally considered preventable due to inadequate prescribing and/or due to an inappropriate use of the drugs [17,167,172]. On the other hand, an important risk factor for the development of ADRs is their earlier occurrence. Re-exposure to the offending drug due to poor documentation may result in the patient experiencing the same ADR again. Therefore, it is important to emphasize the need for accurate documentation of an ADR at the time of the event and to provide the patient with relevant information about the ADR to prevent recurrence or ensure appropriate monitoring [17] .

In addition to the morbidity and mortality caused by ADRs in the elderly, it is necessary to highlight the economic impact that they cause, not only through health care visits but also through hospitalizations. In fact, ADRs cause a significant burden on the health care system. They account for 6.5% of hospital admissions and are responsible for the death of 0.15% of hospitalized patients [143]. A study about the direct costs of ADRs in Germany concluded that the incidence of hospital admissions due to at least "possible" serious ADRs was 3.25% and the average treatment cost of a single ADR was €2250, translating a total cost of €434 million per year in Germany [168]. The same

study concluded that 20.1% of the cases were preventable with a potential saving of €87 million per year [168].

In Portugal, a retrospective observational study assessing the frequency of adverse event in inpatients in Mainland Portuguese public hospitals from 2000 to 2015 concluded that 5.8% of all Portuguese hospitalizations had at least one adverse event registered. Hospitalizations with registered adverse events had a median length of stay of 8 days, median hospitalization costs of 3060.7 euros, and an in-hospital mortality of 6.7% [173].

All these data show that adverse events are common in hospitalized patients and have an important clinical and economic impact. In this context, the knowledge of their occurrence in the real world provides additional information about their characteristics as well as the associated risks, which help to prevent them. Therefore, it is important to have studies that focus on these events.

I.5 Pharmacovigilance

During the development process of a drug, it is not possible to identify all the adverse reactions associated with it, because the number of people exposed in clinical trials is limited, as is their duration. Therefore, the rare ADRs and those that only occur after a long-term exposure are difficult to identify. In this context, it is essential to continuously monitor the effects of drugs once they are on the market. The science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions or other problems associated with medicines are called pharmacovigilance [174].

Worldwide, in the 1960s, after the tragedy caused by the administration of thalidomide to pregnant women, the need to establish Pharmacovigilance Systems was recognized. As a result of what became known as "Thalidomide Disaster", a pilot project, coordinated by WHO was launched in 1968 to create an international pharmacovigilance system. To manage and coordinate this international program, a Drug Monitoring Center was established, operating since 1978 in Uppsala, Sweden, under the name Uppsala Monitoring Center (UMC) [175,176]. Supported by a global network, member countries submit reports of suspected ADRs to the VigiBase database (the name of the WHO global database) [175]. In the EU, it is EMA that coordinates the pharmacovigilance system and operates pharmacovigilance support services and processes [174,176]. EMA is responsible for the development, maintenance and

coordination of EudraVigilance, a system for reporting suspected ADRs cases, and communication of such information to the UMC [176].

In Portugal, the National Pharmacovigilance System, called in this work as Portuguese Pharmacovigilance System (PPS), was created in 1992, according to the normative Regulation No. 107/92 of 27 June [177], and subsequently decentralized and distributed throughout the country in 2000 with the creation of Regional Pharmacovigilance Units. It is coordinated by the National Authority and Health Products (INFARMED), and becomes part of the European pharmacovigilance network [163,176]. Until the end of 2016 the PPS included four regional units (North, Midlands, Lisbon and Tagus Valley, and South). These were overseen by the Medicines Risk Management Department which was also responsible for processing reports from the archipelagos of Azores and Madeira islands. In 2017 INFARMED decided to increase the number of regional units, with the aim of developing pharmacovigilance activities closer to professionals, to widen population catchment areas and to reduce geographical dispersion and, additionally, to allow INFARMED to fulfil its commitments with the EMA [178,179]. Nowadays, there are 10 pharmacovigilance regional units, which contribute to a more dynamic PPS [163]. The PPS (as well as those of other European countries) acts mainly based on spontaneous reporting of suspected ADRs. The evolution of ADRs reports received in PPS between 1992 and 2020 is presented in figure I.5 [163], with a clear increase after the creation of more regional units in 2017. In 2020 there was a slight decrease, but that is very likely due to the COVID-19 pandemic [165].

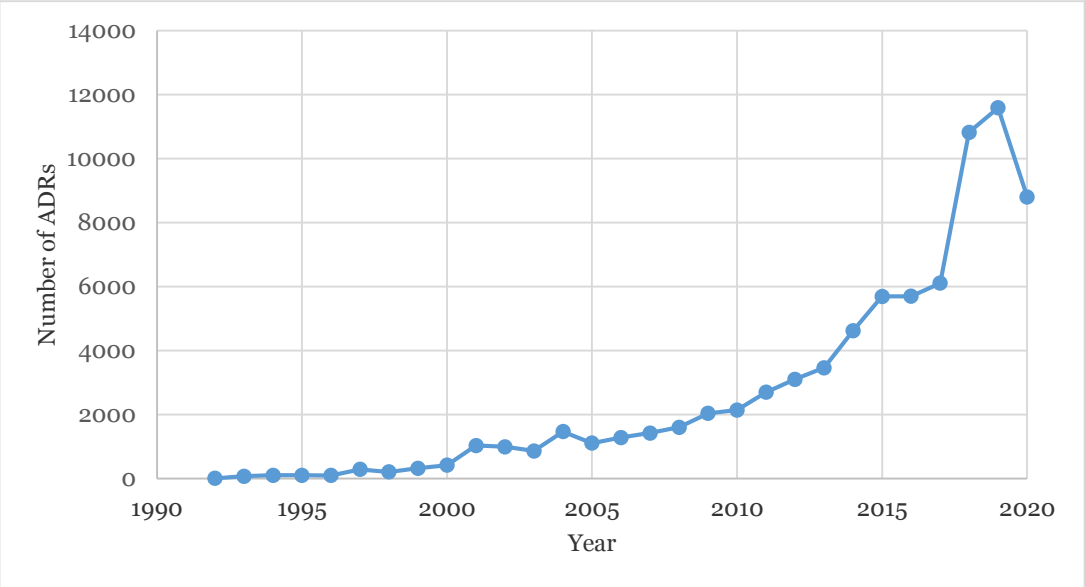

Figure I.5: Evolution of adverse drug reactions (ADRs) reports received in Portuguese Pharmacovigilance System between 1992 and 2020 (Source: INFARMED [163]**)**

As a result of the changes introduced in 2012 in the European Pharmacovigilance legislation, consumers can directly report suspected ADRs, in addition to healthcare professionals and Marketing Authorisation Holders (MAHs) [176,179]. Additionally, the Pharmacovigilance Risk Assessment Committee (PRAC) was created to play a central role in pharmacovigilance. PRAC is responsible for all aspects of risk management, including the identification, assessment, minimisation, and reporting of all aspects related to human medicines [179,180].

The objectives underlying EU pharmacovigilance legislation are essentially to prevent harm from adverse reactions resulting from the use of medicinal products authorized within or outside the terms of the marketing authorisation or occupational exposure, to promote the safe and effective use of medicinal products and to contribute to the protection of public health and patients [176,178] .

The information gathered through adverse event reporting is critical to ensure continuous and effective monitoring of the safety of marketed medicines. They allow the identification of potential unknown adverse reactions, the quantification and/or better characterization of already identified adverse reactions, and the implementation of measures to minimize the risk of their occurrence [176]. This method allows the monitoring of all drugs on the market throughout their life cycle, in all patients, does not interfere with prescribing habits, allows the identification of new ADRs and rare and unexpected ADRs in groups and scenarios not studied and also allows the identification of risk factors [143,176]. However, there are also limitations, namely the presence of underreporting and the quality of reporting, the difficulty of detecting reactions with a long latency period and reactions with clinical pictures that occur very frequently, the lack of knowledge of the number of exposed individuals and the fact that it is based on the subjective criterion of the reporter [181,182].

Concerning the underreporting, some of the known barriers to spontaneous reporting were [183]:

- Ignorance – belief that only severe ADRs need to be reported;
- Diffidence – fear of appearing ridiculous for reporting merely suspected ADRs;
- Lethargy – an amalgam of procrastination, lack of interest or time to report the ADRs, and other excuses;
- Indifference – belief that one case might not contribute to medical knowledge;
- Insecurity – belief that it is nearly impossible to determine whether or not a drug is responsible for a particular adverse reaction;
- Complacency – belief that only safe drugs are allowed on the market;
- Fear – fear of possible involvement in litigation or investigation of prescribing costs by health departments;

- Guilt – guilt at having administered treatment that may have harmed a patient;
- Ambition – ambition to compile and publish a personal case series.

Indeed, each of the notifications is an important source of information regarding the risk of marketed medicines and can per se contribute to the generation of a safety signal. According to the definition proposed by guideline on GVP XI, a signal is the information arising from one or more sources [184]. The sources include observations and experiments, that suggest a new potentially causal relationship or a new aspect of a known relationship between an intervention and an event or series of associated events, either adverse or beneficial, that are judged sufficiently likely to warrant review action [184–186]. Beyond the spontaneous reports, safety signals can be detected from clinical studies and scientific literature. The evaluation of them is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a medicine's benefits and risks [185].
Signal management involves several steps [176]:

1. Signal detection - identification process of data from any source;
2. Validation of signal analysis - preliminary analysis process to verify that the documentation contains evidence showing a potential new causal relationship or a new aspect of a known relationship;
3. Confirmation and prioritization - aims to identify signs that indicates risks with potential impact on patient health;
4. Signal evaluation - previously validated signal evaluation process that aims to determine if there are new risks or if the known risks for these drugs have changed;
5. Action - PRAC recommended action resulting from the signal evaluation. It may be directly enforceable by MAHs or by regulatory action. In the last case, they must be submitted by the Committee for Medicinal Products for Human Use or Coordinating Group for Mutual Recognition and Decentralized Human Procedures for approval.

Signal management is extremely important in pharmacovigilance, as it contributes to the identification of new risks associated with medicines or to the development of knowledge about already identified risks.
In this context, serious ADRs have a higher importance, which according to guideline on GVP VI, are ADRs that cause death, endanger life, motivate or prolong hospitalization, motivate disability, and/or cause congenital anomalies [151].

Causality of an ADR is a critical issue that requires linking of an adverse event to a drug or other cause. If a particular symptom occurs after the administration of a drug, it does not necessarily mean that the drug is responsible. Numerous other possibilities may be responsible for the adverse event. Sometimes, for example, a certain drug was not taken for a certain period of time and an adverse event occurred in the period thereafter and it is not always possible to exclude the drug as the cause of the event. Therefore, several associations are important to support the causality between a drug and an event adverse.

The following associations support the causal relationship between a drug and a suspected adverse event [187]:

- Strength of the association - if the probability of an observed event is known and high, the case for causality is strengthened;
- Consistency of the observed evidence - if a drug and an ADR have an association that has been consistently demonstrated over years of clinical practice, causality becomes more likely;
- Temporality of the relationship - the closer the association between the administration of the drug and the occurrence of the ADR, the more likely it is that the drug is the actual cause of the reaction. However, this temporality is not always a true indication, as some adverse events may occur several days or weeks after administration of the causative drug;
- Dose-response relationship - often, an adverse event occurs as a function of the dose administered. The higher the dose of the drug, the more likely an ADR is a result of the administered drug. A lower dose results in a corresponding decrease of the likelihood of a causal link with an ADR. However, this relationship cannot be true in all circumstances, as very low doses of some drugs (e.g., penicillin) can cause severe anaphylactic reactions;
- Confounding factors - minimizing confounding factors is important in determining causality. Confounding factors such as administration of other medications, foods, and beverages may be responsible for the observed events. The presence of concurrent diseases and infections may also cause certain observed effects, making it difficult to distinguish them from the suspected drug. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role.

In this context, several methods of causality assessment have been proposed, which can be divided into three groups: methods based on probability calculations; methods based on algorithms; and the method of global introspection. In terms of methods

based on probability calculations, these are complex methods that require the use of computer programmes. These methods express the probability of a drug will cause an adverse event, before and after determining factors. Methods based on algorithms consist of a sequence of questions with an associated qualification scale, and at the end it is possible to determine causality using categories. Examples include the Naranjo Algorithm, which is simple and fast, but has several parameters whose acquisition has a higher degree of difficulty; the Jones Algorithm, which consists of a decision tree evaluated by only six questions and the Karch-Lasagna Algorithm, which evaluates five items and assigns a score to each item, resulting in different degrees of probability [176,188,189]. One of the disadvantages of the algorithm method is that there is a wide variety of ADRs and it is difficult to adapt an algorithm that corresponds to all of them. Global introspection, the method used by the PPS, refers to an assessment made by a team of experts that takes into account the information related to the case and includes several factors, such as [176,189,190]:

- Temporal relationship between the intake of the drug and the occurrence of the ADR;
- Result of the suspension of the drug;
- Pharmacological plausibility;
- Alternatives that explain the occurrence of ADR;
- Prior knowledge of the existence of similar ADR.

In practice, few adverse reactions are ‘certain’ or ‘unlikely’ and the majority are somewhere between these extremes, i.e. ‘possible’ or ‘probable’. In an attempt to solve this problem, WHO developed a structured and harmonised assessment of causality. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. According to WHO recommendations, by analysing different characteristics of the reported episode, ADRs are rated as definitive, probable, possible, unlikely, conditional, or unclassifiable [176,191]. The causality categories by the WHO Uppsala Monitoring Centre, Uppsala, Sweden are presented in table I.10.

Table I.10: Causality assessment categories by the World Health Organization Uppsala Monitoring Centre, Uppsala, Sweden [191]**.**

Category of causality	**Assessment criteria**
Definitive (Certain)	A clinical event or laboratory change that occurs with a plausible temporal relationship and cannot be explained by concomitant diseases or other medications. The response to discontinuation of the drug must be clinically plausible. The event must be convincing from a pharmacologic or phenomenologic perspective, using re-exposure data as appropriate.
Probable	A clinical event or laboratory change that occurs within an acceptable temporal context, for which the causal relationship with concomitant disease or other medications is unlikely, and for which the course after discontinuation of the drug is clinically acceptable. Information on the outcome of re-exposure is not required to assign this probability level.
Possible	A clinical event or laboratory change that occurs in an acceptable temporal context, but that can also be explained by concomitant diseases or other medications. Information on post-discontinuation trends may be unavailable or inconclusive.
Unlikely	A clinical event or laboratory change with a temporal association that makes a causal relationship with the drug unlikely and for which an association with other drugs or concomitant diseases is a plausible explanation.
Conditional/Unclassifiable	A clinical event or laboratory change that has been reported as an adverse event but for which additional information is needed to adequately assess causality or for which the assessment process has not yet been completed.
Unclassifiable	A report that is suggestive of an adverse reaction but for which a causality assessment is not possible because the information is insufficient or contradictory and cannot be completed or confirmed.

In addition to spontaneous notification, there are other methods of pharmacovigilance, namely active pharmacovigilance, which have been developed through subsequent studies of drug authorization, publications in the medical literature, systematic database searches of suggestive events, and others. These methods have the same basic objective, which is to identify unknown adverse effects, generate alerts and suggest public health measures to reduce their frequency, and inform prescribers, other health professionals and regulatory authorities to take corrective actions [176].

I.5.1 Pharmacovigilance in Older People

Monitoring medications for ADRs in the geriatric population is imperative due to polypharmacy. Follow-up studies after post-authorization drugs to monitor ADRs are essential to improve the quality of life of this special population. This may reduce hospital readmissions, which in turn may reduce the economic burden on patients and society [42,156,158]. The majority of ADRs are preventable, highlighting the importance of improving the periodic review of medications and the study of ADRs, particularly in more vulnerable populations such as the elderly and patients with multiple comorbidities [132,167,172,192]. A strong pharmacovigilance system can conduct safety surveillance with processes, tools, and experts to monitor ADRs in medications taken by elderly patients. During this post-authorization surveillance, safety risks can be detected, especially in patients with comorbidity and polypharmacy who suffer from physiological changes associated with aging [20,143,156]. In addition, pharmacovigilance studies provide real-world insights into the use and safety of medications.

For all the reasons already mentioned, and due to the underrepresentation in clinical trials, the use of drugs in elderly has been considered a public health challenge. In 2011, EMA adopted several strategies aimed at improving benefit-risk assessment of drugs for this age group. Recognizing that older people are the main users of medicines, regulatory frameworks have been established to ensure that the use of newly approved medicines for this population is supported by relevant risk-benefit data. Additionally, it considers that the availability of information to patients and prescribers should be improved to support safer use of medicines. This is because, depending on patients' frailty and disability status, desirable outcomes and treatment options may vary. In fact, different patients assign different values to benefits and risks [161,193]. Therefore, relevant information on the safety profile, how risks can be avoided or minimized and how knowledge on the safety and efficacy of a particular medicinal product will be promoted must be included in the risk management plans submitted to the regulatory authorities when applying for a marketing authorisation. The development of this document is intended to provide an understanding of the safety issues in older adults and to plan how to reduce the possibility of suffering an ADR [143].

Thus, according to EMA, it is important to [193]:

- Provide clear information on interactions in the summary of product characteristics (SmPC) text for encouraging periodic medication review in chronic treatments;
- Inform on data available from elderly population;

- Provide specific information material for patients with cognitive/functional impairment;
- Encourage and improve reporting of ADR.

To improve the safety of medicines for this age group, EMA has also set up a Geriatric Expert Group to advise the agency and its Committee for Medicinal Products for Human Use on issues related to the elderly and to provide scientific advice to medicine developers [193].

I.5.2 Clinical Trials in Elderly

On average, older people are associated to 60% of the national burden of disease, but represent only 32% of participants in phase II and III clinical trials [143,194]. Elderly are typically excluded from phase I and II trials because they are at higher risk for unexpected toxicity [143].

Typically, older adults have a combination of barriers, including comorbidities, advanced age, economic constraints, communication problems (e.g., hearing difficulties that interfere with telephone interviews and visual impairment that interferes with survey writing), and physical immobility that limits transportation options [195]. Other barriers related to the patient include: non-understanding the benefits of the clinical trial, fear of adverse reaction, fear of losing the ability to make decisions about their treatment, no information about the availability of clinical trials [196]. In clinical trials, there are also barriers related to the investigator and the clinical trial to consider, such as fear of toxicities and lack of data on treatment tolerability, limited expectations for benefits, time needed to enrol and follow-up (e.g., to explain informed consent, perform follow-up visits for patients with cognitive, visual, hearing, speech, mobility impairment) [195,197]. In this context, the fear related to a possible ineligibility of the clinical trial due to comorbidities, cognitive impairment, physical disability and/or organ dysfunction and lack of funding for studies in elderly population, also can be a barrier [161,195].

For all these reasons, older adults remain underrepresented in clinical studies. Thus, the relative lack of data on efficacy and safety of many available medications in this population, particularly in frail older adults with multiple comorbidities, inevitably leads to off-label prescriptions [198].

Age-related biases in clinical research thus lead to uncertainty about the risks and benefits of new treatments for the elderly [199]. According to Herrera, et al. in phase I

trials, it is not essential to represent older adults with high-risk complications. However, adequate recruitment of older adults is essential in phase II and III clinical trials, as the goal is to confirm dosing, safety, adverse effects, and efficacy [195].

The 1994 E7 International Conference on Harmonisation guideline provided recommendations that apply to the geriatric population, with the guiding principle: "Medications should be studied in all age groups, including the elderly for whom they will have significant benefit. Patients enrolled in the clinical trial should be reasonably representative of the population that will later be treated with the drug" [33]. According to this guideline geriatric patients should be included in the phase III clinical trials (and in phase II at the choice of the sponsor) because only by including older patients in clinical trials is it possible to examine the presence of age-related differences, such as in adverse event rates, efficacy, and dose-response [33]. As this population is underrepresented in clinical trials, particularly those aged 75 or above, this guideline recommends having a significant number of older participants in trials (which can be estimated using epidemiological studies that target the disease that the drug is intended to treat) to assess the benefit-risk ratio of the drug in this age group. In fact, it is recommended to avoid excluding patients with concomitant diseases and patients in the older age range, 75 and above, when it is possible. How older the population likely to take the drug, more important it is to include the very old people in clinical trial [33,200].

When evaluating marketing authorisation applications, the Committee for Medicinal Products for Human Use considers that specific activities related to aspects such as comorbidities and monitoring of specific ADRs associated with elderly patients should be included in the risk management plan or as post-authorisation measures [201]. Thus, according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, clinical trials should be directed primarily to new molecular entities that are likely to have significant use in the elderly. This is important, either because the disease to be treated is characteristically a disease of old age (e.g., Alzheimer's disease) or because the population to be treated is known to include a substantial number of geriatric patients (e.g., hypertension). New formulations and new combinations of drugs should also be considered if there is a specific reason to believe that certain conditions common to the elderly (e.g., renal or hepatic failure, impaired cardiac function, concomitant diseases, or concomitant medications) are not already addressed in the current labelling. In cases of progressive impairment of renal or hepatic function or drug interactions, adequate assessment of pharmacokinetic profiles and pharmacodynamic endpoints is required [200].

The design of a clinical trial must also consider age-appropriate points, as inappropriate formulations and packaging can contribute to poor adherence, medication errors, and problems with safety and efficacy. In addition, considering the entire elderly population, the need for ease of administration, possible dose reduction, the impact of visual and motor impairments, and the likelihood of polypharmacy should be considered. If this is the case, protocols should also be designed to assess patients' ability to self-manage their medications [161].

Overall, the design of clinical trials and analysis should be tailored to the research objectives with outcomes for this specific population. A comprehensive geriatric assessment can be used as a criterion for randomization and outcomes in clinical trial design with specific endpoints such as effects on cognitive function, balance and falls, urinary incontinence, and/or weight loss, as appropriate. Patients participating in clinical trials must be reasonably representative of the population that will later be treated with the drug [161,194,195].

I.6 Strategies to Improve Elderly Patient Safety

Various types of interventions targeting patients, providers, or care systems have been used to reduce the risk of drug-related harm in older people. These interventions have gone using specialist professionals (through geriatric services, multidisciplinary teams or specialist drug reviews), different types of educational interventions, technological approaches (computerized decision support) and multi-layered approaches. One of the techniques used is medication reconciliation, a strategy used to identify discrepancies in prescribed medication regimens across care settings or at different times to inform prescribing decisions and prevent medication errors. This reconciliation is used to prevent medication errors such as omissions, duplications, dosing errors, or drug interactions and must be performed at each care transition (including changes in setting, service, professional, or level of care) when new medications are requested or existing orders are overwritten [17,20].

It was also considered the deprescribing (process of discontinuing medications), which should be done at the individual level when medications are no longer effective or useful, or when safer alternatives exist. It can be achieved in older people and may be associated with improved health outcomes without long-term negative effects. The deprescription process of discontinuation can involve any medication. The use of a validated tool or algorithm can assist in the implementation and execution of the deprescribing process [202]. It is important to minimize inappropriate prescribing and

unnecessary polypharmacy. A comprehensive geriatric assessment and the use of explicit prescribing criteria can be helpful in this regard [203].

To support ADR risk, a number of prediction tools have been published, three of which specifically related to ADRs: the GerontoNet ADR risk score [204], the Predicting adverse drug reactions in the hospitalised elderly [205], and the Development of a Risk Model for Adverse Drug Events in the Elderly [206]. The other tool titled “Risk factors for adverse drug events in hospitalized elderly patients: A geriatric score” was related to any adverse event [207]. However, any of these is universally accepted and any is routinely used in clinical practice [208]. All ADR prediction tools had weaknesses in terms of predictor definition and treatment variables [208].

In general, clinicians should consider potential ADRs as part of any differential diagnosis. New medications should be prescribed with a clear therapeutic goal in mind. Figure I.6 illustrates the principles to be considered in prescribing for this special population and the impact that they have in the choose of a drug. In addition, it is imperative to involve patients in decisions about their therapy, educate them about important ADRs and what to do if they occur [153].

In this scope, pharmacovigilance plays a key role in providing information about drug safety, improving patient care and safety in relation to the use of medicines and all medical and paramedical interventions. Additionally, it has a fundamental role in public health.

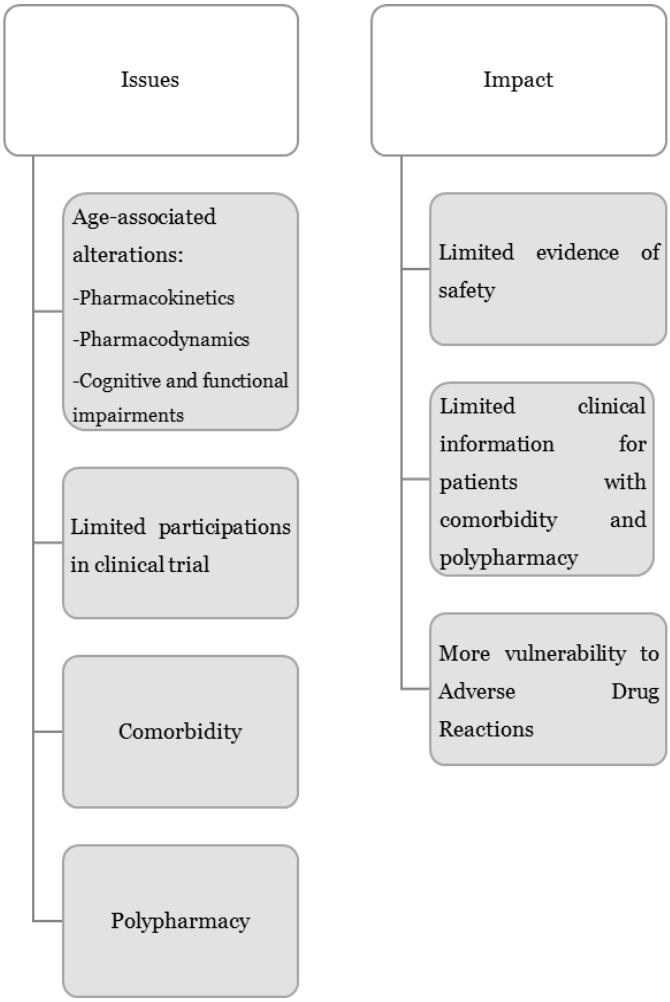

Figure I.6: Principles to be considered in prescribing for older patients and their impact

I.7 Aims of this Thesis

In Portugal, similarly to that is occurring in other countries, there has been an increase in average life expectancy and, consequently, in the number of elderly people. Given the role of pharmacovigilance in medicines safety, and as in Portugal there are still not many studies published in this area, for this population, it was considered to be opportune to characterize the suspected ADRs on elderly reported to the PPS. Pharmacovigilance allows the identification of problems related to drugs use, which are often only detected in the post-marketing phase. This is essential to prevent and minimize potential risks to patient's health. This work, through the study of ADRs, aims to minimize the risk of harms that may occur and prevent drug-related hospital admissions as well as the morbidity and mortality associated with drugs used in elderly,

contributing to reduce the impact of the global health problem related to ADRs and their consequences on the quality of life of geriatric population.

After a general study on the elderly suspected ADRs profile, and because diabetes *mellitus*, mostly type 2, is a common disease and its prevalence is expected to increase considerably in the future, in Portugal and in the World, it was considered important to perform a study for this specific older population. Particularly, elderly diabetic patients have been associated to a higher mortality and its complications are an important cause of morbidity and a reduced life expectancy. Consequently, the knowledge of ADRs and drugs involved in this population can contribute to minimize the risk of drug-related problems in elderly diabetic patients, and hospital admissions as well.

Additionally, the prevalence of rheumatic conditions is also increasing and, consequently, the use of NSAIDs as a drug therapy to relief pain associated to these conditions. Despite their good efficacy, NSAIDs must be used with caution in older people because of a high risk of potentially serious and life-threatening side effects. In this sense, it was also considered fundamental to monitor the NSAIDs safety profile in elderly people.

Therefore, the specific aims outlined for the implementation of this work were the following:

- To characterize the most prevalent suspected ADRs in elderly, in Portugal, spontaneously reported to PPS. The analysis was performed with the aim to understand the demographic data (age, sex), reported ADRs and whether or not they are expected, seriousness, evolution of cases, type of reporter and suspected drugs. In addition, in the cases with fatal outcome, ADRs involved and attributed causality were also analysed.

- To identify and analyse the suspected ADRs occurring in elderly diabetic patients. Similarly to the mentioned in the first point, the analysis was performed with the aim to understand the demographic data (age, sex), reported ADRs and whether or not they are expected, seriousness, evolution of cases, type of reporter and suspected drugs involved.

- To analyse the NSAIDs safety profile in elderly based on scientific evidence considering the data obtained through a comprehensive literature review of clinical trials and observational and interventional clinical studies that report data on NSAIDs safety in the elderly. In addition, it was performed an analysis of suspected ADRs sent to PPS. The aim was to conclude about the safety of

marketed NSAIDs in elderly, considering the studies available in the literature and the safety data collected in real world through the PPS.

Chapter II - Adverse Drug Reactions in Elderly: a Five-year Review of Spontaneous Reports to the Portuguese Pharmacovigilance System

The content of this chapter is included in the following publication:

Monteiro C, Duarte AP, Alves G. Adverse drug reactions in elderly: a five-year review of spontaneous reports to the Portuguese pharmacovigilance system. Expert Opin Drug Saf. 2021; 20(1):109-118. doi: 10.1080/14740338.2020.1849137

II.1 Introduction

In Portugal, as in other developed countries, there has been an increase in the average lifespan and, consequently, in the number of elderly people. In 2017, in Portugal, the aging index [i.e. the ratio of the number of elderly persons of an age when they are generally economically inactive (aged 65 and over) to the number of young persons (from 0 to 14)] was 155.4% [209].

Undoubtedly, in a population progressively older, the rate of elderly patients with multiple co-morbidities increases, which in turn leads to an increase of medication use and adverse drug reactions (ADRs) [129,210]. In 1993 the International Conference on Harmonization already considered older people as a 'special population' due to comorbidity, polypharmacy, markedly modified pharmacokinetics and higher vulnerability to ADRs [33]. Actually, ADRs can be considered a major healthcare problem with high costs in elderly, and it is a common cause of hospital admission and an important factor for morbidity and mortality [162,211–213]. A meta-analysis of eight observational studies reported that the proportion of hospital admissions related to ADRs in the elderly was four times higher than in younger persons [172]. In addition, due to the declining reserve capacity of many organs, the hospital admission of elderly patients may be more complex than the admission of the younger ones [172]. A review focusing on ADRs epidemiology in Europe indicates that approximately 3.6 % of all

hospital admissions are caused by ADRs, and up to 10 % of patients experience an ADR during their hospital stay [214]. A study based on an institutional database of the pharmacovigilance programme of Bellvitge University Hospital (Barcelona, Spain) concluded that one out of every 30 urgent hospital admissions of patients aged 65 years or more is related to ADRs [162]. Moreover, a meta-analysis performed to assess the relationship between ADRs and hospital admissions in the elderly, concluded that one in ten hospital admissions are due to ADRs [167]. Thus, given the data reported on this subject, it is indisputable that ADRs are a serious public health concern in the elderly.
With the purpose of knowing the Portuguese reality, we performed an analysis of the suspected ADRs spontaneously reported to the Portuguese Pharmacovigilance System (PPS) during a 5-year period, focusing mainly on those involving elderly patients, thus enabling the knowledge of the ADRs profile in this vulnerable population. In addition, a special emphasis was given to the cases of ADRs that led to a fatal outcome and to those that reported the appearance of unexpected ADRs.

II.2 Methods

II.2.1 Study Type, Setting and Data Source

The PPS was created in 1992 and is coordinated by INFARMED; since 2000 several regional pharmacovigilance units were created, which are also part of the PPS. They are responsible for collecting and processing spontaneous ADRs reports received from healthcare professionals, patients/consumers and marketing authorization holders. This was a retrospective study in which the spontaneous ADRs reports submitted to the PPS between 1 January 2013 and 31 December 2017 by healthcare professionals and patients/consumers (considered as direct reports) and also by marketing authorization holders (considered as indirect reports) were obtained and analysed. Although the main focus of this work was the analysis of the ADRs involving elderly patients, to provide a more complete overview of the spontaneous reporting rate to the PPS and to enable some comparisons all the reports received during the target study period were considered, which were then stratified, where appropriate, according to several variables such as age [young people (aged ≤ 17), adults (aged 18-64), older people (aged ≥ 65) and those where the age was not defined in the database], sex, and seriousness, and type of ADR. It should also be noted that, before data analysis, all duplicate and annulled reports, as well as the case studies identified, were discarded. Duplicate

reports were already identified by the authority according to the Guideline on Good Pharmacovigilance Practices, Module VI Addendum I [215].

II.2.2 Variables used of Analysis

As demographic variables, age and sex of the patients were those analysed most exhaustively. Regarding age, the groups defined were as follows: adults (aged 18-64) and elderly people (aged ≥ 65), with the last age group to be stratified into the three usual elderly subgroups (i.e. aged 65-74, aged 75-84, and aged 85 and over [162]). The cases were also stratified according to their seriousness and type of reporter. According to the definition of GVP, Module VI [151], a serious ADR is any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly/birth defect. We analyzed all cases with a fatal outcome, and the relationship between drug exposure and death following the criteria adopted by PPS, and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardised case causality assessment [216]. According to this method, which considers the clinical-pharmacological aspects of the case history and the quality of the documentation, reported cases were classified as certain, probable, possible, unlikely, conditional or unclassifiable [216].

The terminology used to code suspected ADRs was based on the Medical Dictionary for Regulatory Activities (MedDRA®). In this dictionary, medical terms are coded according to the Systems Organ Classes (SOC) affected. If in the same report there was more than one ADR belonging to the same SOC, that SOC was counted only once. It was also checked whether or not suspected ADRs found in our study were described in the Summary of Product Characteristics (SmPC) of the respective medicine. Suspected ADRs with fatal outcome were studied according to the Preferred Term (PT) belonging to the Important Medical Event (IME) terms list. The IME list is based on PT level coding in MedDRA dictionary [217]. The medicines involved were categorized by therapeutic group according to the WHO Anatomical Therapeutic Chemical (ATC) classification system [218]. As a given report may have more than one suspected drug involved, the total number of ATC codes considered may be greater than the number of reports analysed.

Data were analysed by means of descriptive statistics, using the Microsoft® Office® Excel® 365 software.

II.3 Results

II.3.1 Reporting Trends – Annual Evolution of Adverse Drug Reactions Reports

During the period studied (2013-2017), a total of 25572 ADRs reports were received by the PPS. Of these, 7.9 % (2008) occurred in young people (aged ≤ 17), 35.3 % (9037) in adults aged 18-64 and 16.4% (4204) were identified in elderly (aged ≥ 65); in addition, 40.4 % of the total number of ADRs reports received by PPS in this 5-year period did not mention the age of the patient (Figure II.1).

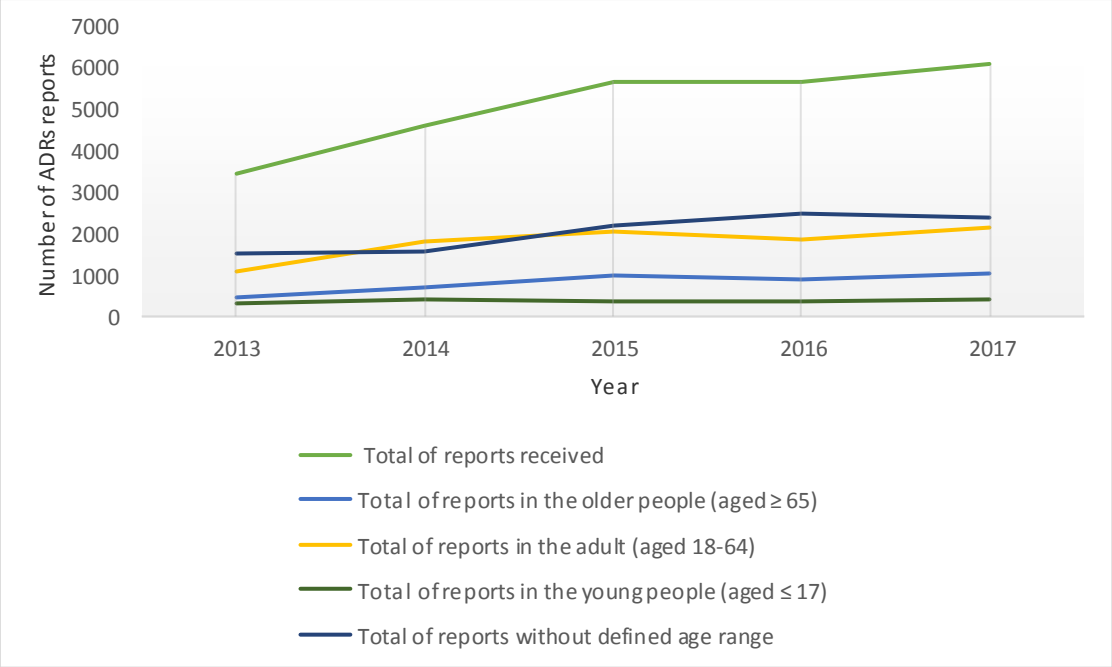

Figure II.1: Total number of suspected Adverse Drug Reactions (ADRs) reports versus ADRs reports in different age groups spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017, as well as those in which age was not mentioned.

II.3.2 Source of Adverse Drug Reactions Reports

Globally, during the target study period (2013-2017), 51.5 % of the reports were sent to the PPS by marketing authorization holders (indirect reports). Regarding the direct reports, the physicians were the healthcare professionals who submitted the highest number of suspected ADRs reports (20.7 %), followed by pharmacists (14.9 %) and

nurses (5.6 %) (Figure II.2). At this point, it should be noted that the ADRs reports submitted by consumers or other non-healthcare professionals already represent 4.1% of the total number of reports (Figure II.2).

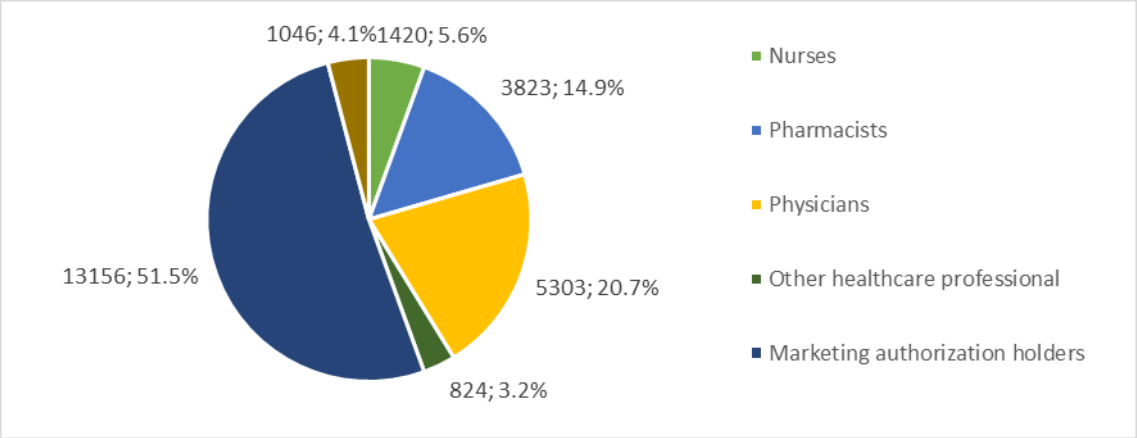

Figure II.2: Source of total suspected Adverse Drug Reactions reports spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017.

II.3.3 Demographic Data

For a deeper study of these ADRs reports in elderly and aiming to compare demographic data we also analysed the ADRs reports for adults aged 18-64. Thus, we started with 9073 reports and after discarding the duplicated and annulled reports we finalized with 8343 reports in the adults aged 18-64. Considering the age of 65 years and above, we started with 4204 notifications and after data cleaning the duplicates 3692 cases of suspected ADRs reports involving older people were considered as the total number of reports for analysis, which included a total of 13922 suspected ADRs associated.

In adults (aged 18-64), 61.1 % of the reports referred to female. A deep analysis of the serious ADRs independently of the age showed that the female sex was the most affected. In the group aged ≥ 65, most of suspected ADRs reported (58.1%) were observed in females (n=2145), 41.1% (n=1519) occurred in males and in 0.8% (n=28) of them the sex was not mentioned (Table II.1). Taking into account the different subgroups in which older people are usually stratified, approximately 55.3% (n=2040) of the ADRs reports analysed belong to the age subgroup of 65 to 74 years, followed by 35.3% (n=1305) belonging to the age subgroup of 75 to 84 years and 9.4% (n=347) referring to individuals aged 85 and over.

Table II.1: Number of Adverse Drug Reactions (ADRs) reports versus serious/non serious ADRs by age group and sex spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017

	Age group			
Sex	18-64		≥65	
	Serious n	Non-serious n	Serious n	Non-serious n
Female	3239	1857	1398	747
Male	2061	955	1040	479
Not identified	223	8	20	8
Total	5523	2820	2458	1234

Globally, regarding the occurrence of a fatal outcome, the male sex was the one with the most cases of suspected ADRs [51.0% (n=73) for people aged ≥ 65 and 47.1% (n=81) for adults aged 18-64]. However, in the subgroups aged 75-84 and aged 85 and above, female was the sex with most fatal outcome (Table II.2).

Table II.2: Number of Adverse Drug Reactions reports with fatal outcome by age group spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017

	Age group			
Sex	18-64 n (%)	65-74 n (%)	75-84 n (%)	≥ 85 n (%)
Female	75 (43.6%)	33 (44.6%)	28 (50.0%)	7 (53.8%)
Male	81 (47.1%)	41 (55.4%)	26 (46.4%)	6 (46.2%)
Not identified	16 (9.3%)	0 (0%)	2 (3.6 %)	0 (0%)
Total	172	74	56	13

II.3.4 Elderly Patients: Data Analysis

II.3.4.1 Adverse Drug Reactions Seriousness and Outcome

Overall, 66.6% (n=2458) of the reports were considered serious ADRs in elderly patients (aged ≥ 65). Figure II.3 shows all suspected ADRs reports *versus* the serious cases per year in the elderly.

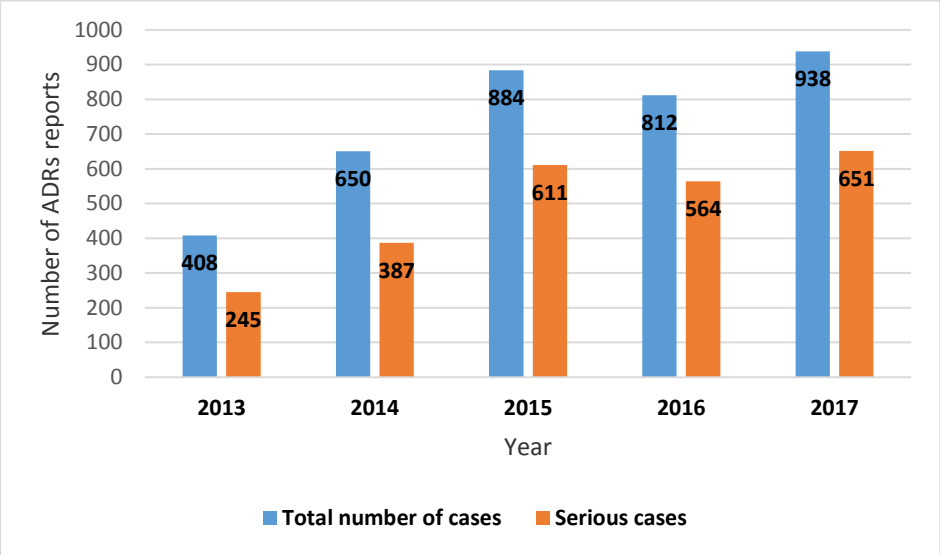

Figure II.3: All suspected Adverse Drug Reactions (ADRs) reports *versus* the serious cases per year spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017 for people aged 65 years or older.

Among the 2458 cases of serious ADRs reported, 837 (34.0%) led to hospitalization and in 143 (5.8%) of them a fatal outcome occurred. Considering the total of 3692 cases, the majority of the patients recovered completely (56.7%, n=2092) and only 0.6% (n=23) recovered with sequelae.

II.3.4.2 System Organ Class Involved in Adverse Drug Reactions

Among the 3692 cases of suspected ADRs reported in older people, we found 7169 SOC involved. Most of the reported ADRs referred to general disorders and administration site conditions (15.3%) and to the skin and subcutaneous tissue complaints (15.0%) (Figure II.4).

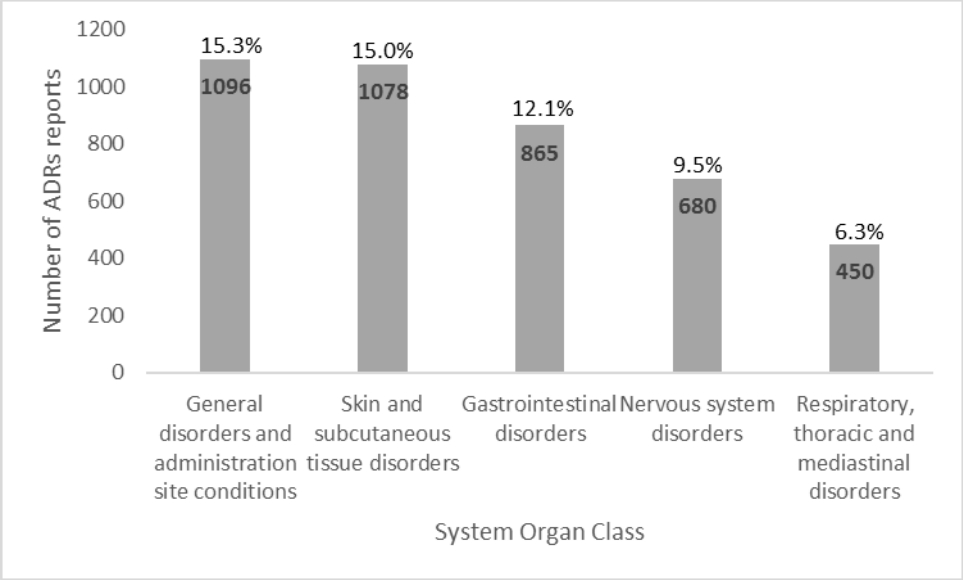

Figure II.4: System Organ Classes affected by suspected Adverse Drug Reactions (ADRs) spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017 for people aged 65 years or older: the five most frequent.

The suspected ADRs most associated with a fatal outcome belong to general disorders and administration site conditions (18.5%) and infections and infestations (11.6%). Among the 143 cases with a fatal outcome, we found 227 ADRs that included MedDRA terms belonging to the IME list. Cardio-respiratory arrest, pneumonia, sepsis, and pancytopenia were the most reported ADRs of the IME list. Table II.3 shows the suspected ADRs with fatal outcome belonging to the IME list and the corresponding SOC.

Table II.3: Suspected Adverse Drug Reactions (ADRs) with fatal outcome belonging to the Important Medical Events (IME) list and corresponding System Organ Class (SOC) spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017 for people aged 65 years or older

SOC	n	ADRs (number) belonging to the IME list
General disorders and administration site conditions	67	Multiple organ dysfunction syndrome (n=3), Sudden death (n=1)
Infections and infestations	42	Bacterial sepsis (n=1), Brain abscess (n=1), Bronchopulmonary aspergillosis (n=1), Cerebral aspergillosis (n=1), Cryptococcosis (n=2), Infected skin ulcer

		(n=1), Meningococcal sepsis (n=1), Oesophageal candidiasis (n=1), Pneumonia (n=9), Pneumonia bacterial (n=1), Pneumonia viral (n=1),Progressive multifocal leukoencephalopathy (n=2), Pseudomembranous colitis (n=2), Pulmonary toxicity (n=1), Respiratory tract infection (n=4), Scedosporium infection (n=1), Sepsis (n=7), Septic arthritis staphylococcal (n=1), Septic shock (n=2), Strongyloidiasis (n=1), Urosepsis (n=1)
Nervous system disorders	29	Altered state of consciousness (n=3), Cerebellar haematoma (n=1), Cerebral artery occlusion (n=2), Cerebral haemorrhage (n=2), Cerebrovascular accident (n=2), Coma (n=2), Depressed level of consciousness (n=1), Encephalopathy (n=1), Epilepsy (n=1), Haemorrhagic stroke (n=2), Hemianopia (n=1), Hemiparesis (n=2), Hydrocephalus (n=1), Hypoxic-ischaemic encephalopathy (n=1), Intraventricular haemorrhage (n=1), Ischaemic cerebral infarction (n=1), Ischaemic stroke (n=2), Neuroleptic malignant syndrome (n=1), Posterior reversible encephalopathy syndrome (n=3), Serotonin syndrome (n=1), Subarachnoid haemorrhage (n=1)
Respiratory thoracic and mediastinal disorders;	25	Acute respiratory distress syndrome (n=1), Acute respiratory failure (n=1), Cyanosis central (n=1), Epiglottic oedema (n=1), Haemothorax (n=1), Hypoxia (n=1), Interstitial lung disease (n=2), Laryngeal oedema (n=1), Pneumonia aspiration (n=1), Pulmonary embolism (n=1), Pulmonary haemorrhage (n=1), Pulmonary hypertension (n=1), Pulmonary infarction (n=1), Respiratory arrest (n=1), Respiratory depression (n=1), Respiratory distress (n=2), Respiratory failure (n=4)
Cardiac disorders	23	Acute coronary syndrome (n=1), Acute myocardial infarction (n=1), Atrial fibrillation (n=2), Bradycardia (n=1), Cardiac arrest (n=2), Cardiac failure (n=2), Cardio-respiratory arrest (n=10), Congestive cardiomyopathy (n=1), Endocarditis noninfective (n=1), Myocardial infarction (n=1), Pericardial effusion (n=1), Prinzmetal angina (n=1)
Blood and lymphatic system disorders	22	Agranulocytosis (n=1), Bone marrow failure (n=1), Febrile neutropenia (n=3), Leukopenia (n=2), Neutropenia (n=2), Pancytopenia (n=6), Thrombocytopenia (n=2)
Gastrointestinal disorders	22	Ascites (n=3), Diarrhoea haemorrhagic (n=1), Duodenal perforation (n=1), Haematemesis (n=2), Haematochezia (n=2), Intra-abdominal haematoma (n=3), Melaena (n=2), Oedematous pancreatitis (n=1), Peritoneal haemorrhage (n=1), Retroperitoneal haematoma (n=3), Small intestinal haemorrhage (n=1), Upper gastrointestinal haemorrhage (n=1)
Vascular disorders	18	Abdominal wall haematoma (n=1), Deep vein thrombosis (n=1), Haemorrhage (n=2), Hypovolaemic shock (n=2), Retroperitoneal haematoma (n=1), Shock (n=4), Shock haemorrhagic (n=1)

Injury, poisoning and procedural complications	16	Femoral neck fracture (n=1), Subdural haematoma (n=2)
Renal and urinary disorders	14	Acute kidney injury (n=2), Anuria (n=2), Hydronephrosis (n=2), Pyelonephritis (n=1), Ureteric stenosis (n=1), Urogenital haemorrhage (n=1), Renal impairment (n=3), Chronic kidney disease (n=2), Renal failure (n=2), Renal injury (n=1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	Acute myeloid leukaemia (n=1), Chondrosarcoma (n=1), Hepatic neoplasm (n=1), Lung adenocarcinoma (n=1), Lung neoplasm malignant (n=1), Metastatic malignant melanoma (n=1), Rectal cancer (n=1), Squamous cell carcinoma of lung (n=1), Thyroid cancer (n=1)
Metabolism and nutrition disorders	8	Hyperkalaemia (n=1), Lactic acidosis (n=2)
Skin and subcutaneous tissue disorders	8	Angioedema (n=2), Drug reaction with eosinophilia and systemic symptoms(n=1), Toxic epidermal necrolysis (n=1)
Immune system disorders	7	Anaphylactic reaction (n=2), Anaphylactic shock (n=4)
Psychiatric disorders	7	Dependence (n=1)
Hepatobiliary disorders	6	Acute hepatic failure (n=1), Hepatic failure (n=1), Hepatic mass (n=1), Hepatitis toxic (n=1), Hepatocellular injury (n=1)
Eye disorders	2	Pupil fixed (n=1)

n=number of occurrences related to the SOC

II.3.4.3 Drugs Involved in Adverse Drug Reactions

In the 3692 cases of suspected ADRs reported in people aged ≥ 65, we found 4241 ATC codes involved. Figure II.5 shows the five most frequent ATC codes. Antineoplastic agents were the most represented group of drugs (n=578, 13.6%) followed by the antibacterials for systemic use (n=397, 9.4%).

In the cases with a fatal outcome, antineoplastic and antithrombotic agents were the most represented pharmacotherapeutic groups of suspected drugs involved (25.0% and

13.6% respectively) (Table II.4). In the group of antineoplastic agents, the other antineoplastic agents (43.6%) and the alkylating agents (23.6%) were the pharmacological subgroups most represented. Regarding the antithrombotic agents, those belonging to the heparin group (36.7%) and the direct factor Xa inhibitors (36.7%) were the most frequently involved.

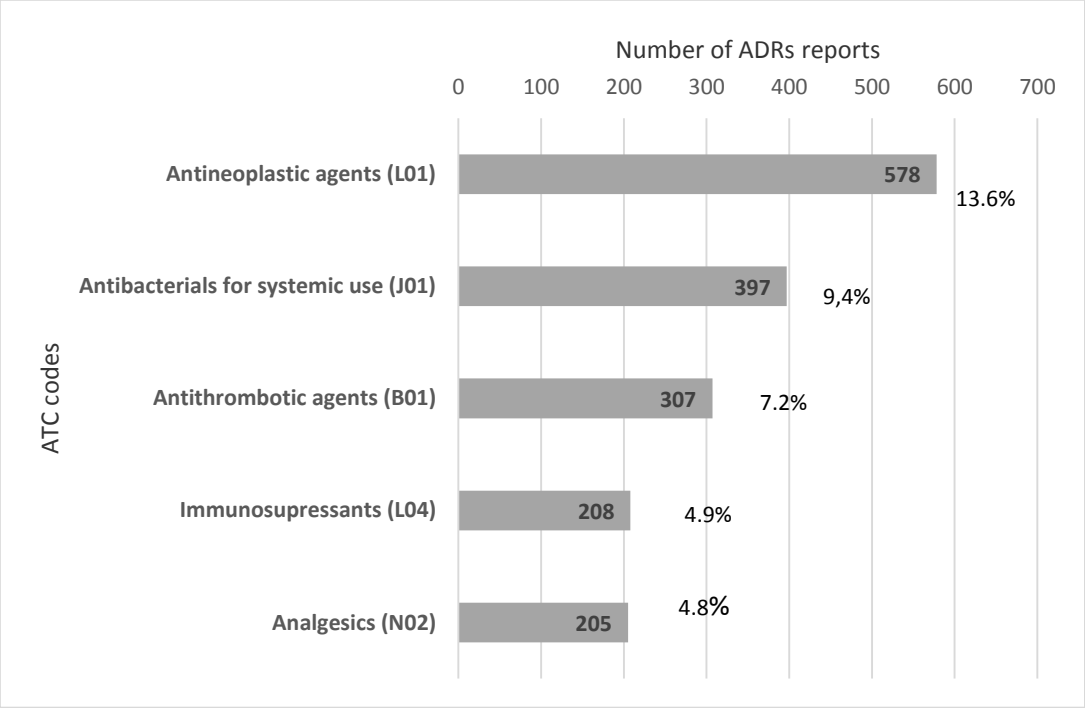

Figure II.5: Anatomical Therapeutic Chemical (ATC) Classification System code involved in suspected Adverse Drug Reactions (ADRs) spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017 for people aged 65 years or older: the five most frequent.

Table II.4: Anatomical Therapeutic Chemical (ATC) Classification System code and the chemical substance involved in a fatal outcome (frequency ≥ 10), spontaneously reported to the Portuguese Pharmacovigilance System from 2013 to 2017 for people aged 65 years or older

ATC code	Chemical substance	Number of occurrences
L01 antineoplastic agents	cyclophosphamide, temozolomide, bortezomib, vincristine, doxorubicin, azacitidine, decitabine, pemetrexed, fluorouracil, cisplatin, cabazitaxel, docetaxel, paclitaxel, trabectedin, bevacizumab, carboplatin, erlotinib, everolimus, idelalisib, pazopanib, oxaliplatin, rituximab, sorafenib, sunitinib, topotecan, vismodegib, ibrutinib, fludarabine, chlorambucil	55
B01 antithrombotic agents	clopidogrel, enoxaparin, rivaroxaban, warfarin, dabigatran etexilate, acetylsalicylic acid, apixaban	30
H02 corticosteroids for systemic use	prednisolone, dexamethasone, methylprednisolone, prednisone	17
L04 immunosuppressants	adalimumab, alemtuzumab, golimumab, methotrexate, pirfenidone, tocilizumab, mycophenolic acid, ciclosporin, etanercept	17
J05 antivirals for systemic use	sofosbuvir and ledipasvir, ribavirin, ritonavir atazanavir, ganciclovir, tenofovir	12
J01 antibacterials for systemic use	cefazolin, meropenem, ceftazidime, sulfamethoxazole and trimethoprim, levofloxacin, vancomycin	11

II.3.4.4 Fatal Outcome and Causality Assessment

According to the WHO system for standardized case causality assessment [216], only 2 cases were classified as certain and the drugs involved were ketamine and temozolomide. Among the remaining reports, 25 were classified as probable, 50 as possible, 10 as unlikely, 1 as unclassified, and 55 cases had not causality attributed.

II.3.4.5 Causality Assessment for the Adverse Drug Reactions Non-described in the Summary of Product Characteristics

In our study most of the ADRs reported were expected (97.4%), since they were described in the respective SmPC of the suspected medicine. In the sequence of a deep analysis of the ADRs non-described in the SmPC, in terms of causality assessment, it was found that 49.4% were classified as probable, 33.6% as possible, 8.3% as unclassifiable, 5.1% as unlikely and 3.6% as certain.

II.4 Discussion

Many studies available in the literature have analysed the risk of ADRs in the elderly and their seriousness, but retrospective studies on spontaneous ADRs reported using national pharmacovigilance databases are few for this age group [219–222].

During the 5-year period covered by our analysis, reporting of suspected ADRs in the elderly showed a slight tendency to increase and represents nearly 16.4% of all collected ADRs reports. This slight increase also occurred in other age groups (Figure II.1). These results perhaps reflect an increasing awareness of the reporters and the efforts performed by the pharmacovigilance system, as well as the demographic distribution of the Portuguese population [223]. Despite the increasing number of elderly people, the number of adults remains higher than that of the elderly, which explains the difference between the numbers of reports in the different age groups. On the other hand, a high number of reports the age of the patient is not defined, which may help to explain the value found for ADRs reports in the elderly.

Most cases were reported by healthcare professionals, and similarly to other countries, medical doctors are the main reporters [224–227].

The studies concerning ADRs have shown that women are affected twice more than men [159], which can be due to a combination of pharmacokinetic and pharmacodynamic factors [228]. On the other hand, the higher reporting rate for females can also be explained by a higher use of drugs in the female population when compared to the male population and by the fact that women are more prone to seek healthcare services [229]. For these reasons, their ADRs might potentially be detected earlier. However, male ADRs reports are usually more seriousness than female ADRs [229], which is in agreement with our results. In fact, in our study, the majority of ADRs involved women, but in the cases where a fatal outcome occurred the number of suspected ADRs observed was similar for both male and female, with 73 and 68 cases

respectively. On the other hand, a study in Portugal showed that the chronic use of medications was more prevalent in older people and in women [230]. In addition, women tend to live longer than men [223]. These facts may explain why we detected more ADRs reported for women. The advanced age and the comorbidity were other risk factors for ADRs and ADRs-related admissions in hospital [169]. Elderly' age was mostly between 65 and 74 years old, reflecting the demographic data in Portugal [223].

Overall, 66.6% (n=2458) of the reports were serious ADRs, and this may be partially explained because until 22 November 2017 the Marketing Authorization Holders only had to submit to the regulatory authorities the serious ADRs reports [151]. Moreover, healthcare professionals seem to be particularly sensitive to report serious adverse drug events, which may also explain the high incidence of serious cases that we found [231]. The results were similar to those of other studies from Tunisian National Centre of Pharmacovigilance, which evidenced that ADRs are frequent in older persons and are often serious [219,220]. In developed countries, ADRs are frequently a cause of hospitalization, morbidity and mortality [129,158]. Elderly patients often have high comorbidity, requiring many drugs and staying particularly vulnerable to ADRs [167], which also explains our data. Additionally, the poor quality or incomplete reports [232] explain the distribution of causality assessment. In fact, it is essential to describe as precisely as possible all clinical information about the patient, allowing the expert to make the most correct possible evaluation of the case. In pharmacovigilance, there is not just one possible cause for an adverse effect but several; each cause must be evaluated in the given context for probability [233]. In our study, most of the reported ADRs were expected, since they are described in SmPC. These results may be related to some of the reasons presented for the under-reporting, such as uncertainty about the drug causing the ADR or the fact that most of the healthcare professionals believe that serious reactions were well documented [232]. However, of the 2.6 % of the unexpected ADRs, almost half of them were considered by the authority as probable; thus, it was unlikely that they were attributed to diseases or other drugs, and there was a reasonable time relationship between the drug intake and the onset of the ADR. This information is very important because it allows the authority to evaluate the presence of possible safety signals in this population.

The most frequently reported ADRs were related to general disorders and administration site conditions, skin and subcutaneous tissue reactions and gastrointestinal disorders, as observed in other studies performed based on the Tunisian National Centre of Pharmacovigilance [220]. These results can be explained by the fact that those ADRs are adverse events that in general are more easily identified by patients and healthcare professionals [231]. In cases of fatal outcomes, the general

disorders and administration site conditions were the SOC most identified in reported ADRs, but infections and infestations were also frequently identified. These results may be related to the fact that elderly presents a progressive decrease in immune function and, consequently, increased susceptibility to infectious diseases [234]. Cardio-respiratory arrest, pneumonia, sepsis, and pancytopenia were the most reported ADRs of the IME list in our study. Infections and subsequent sepsis are an increasing cause of hospital admission and critical illness in the elderly with the mortality risk from sepsis increasing with age [235]. In this context, a study showed that the most common diseases diagnosed by emergency physicians were pneumonia [236]. Community-acquired pneumonia is a major public health problem in the elderly, being associated with high rates of readmission, morbidity, and mortality, with sepsis being a frequent complication [237]. Another study showed that if elderly patients suffer a cardiorespiratory arrest, the chance of survival and the functional outcome after in-hospital cardiopulmonary resuscitation is low to moderate [238], which may explain our results. In pancytopenia-ADR, one of the possible causes is the administration of antineoplastic agents. In our study, the suspected drugs associated with this specific ADR were cyclophosphamide, temozolomide, doxorubicin, and idelalisib. The immunosuppressant methotrexate and the antithrombotic agent rivaroxaban were the suspected drugs in other two cases. This ADR (pancytopenia) was described in corresponding SmPCs, except for rivaroxaban, being therefore an expected reaction. Several studies showed that antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, antineoplastic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for a high number of ADRs leading to hospital admission [234,235,239,240]. In an Italian spontaneous reporting database study, the ADRs with fatal outcome were associated with systemic anti-infective drugs followed by antineoplastic and immunomodulating agents, and nervous system drugs [225]. A study performed using the FDA Adverse Event Reporting System database showed that antineoplastic drugs were those more frequently reported as being associated with death [241]. Other studies, showed that antithrombotic agents, NSAIDs and contrast media were also involved [171,225,242]. An analysis of Italian Spontaneous Reporting Database concluded that the drugs most frequently involved in fatal outcomes were those with a narrow therapeutic range [225]. In our study, we found that antineoplastic agents were the most represented group of drugs (13.6%) associated with ADRs, followed by antibacterials for systemic use (9.4%). With a fatal outcome, antineoplastic and antithrombotic agents were the most represented pharmacotherapeutic groups of suspected drugs involved. These results are very similar to other reported studies [162,225,241,243–245]. On the other hand, to the best of our knowledge, the majority

of studies of ADRs in the elderly were performed in patients who have been hospitalized, making these results not directly comparable. However, the results with fatal outcome were similar to other studies that also showed that the antithrombotic agents and the antineoplastic agents are involved in serious ADRs [162,225,246]. Anticoagulants were the most frequently involved in spontaneous fatal reports in a German spontaneous reporting system [243] and in a Swedish study performed in the national database SWEDIS (Swedish Drug Information System) [244]. In an US study, antineoplastic and immunosuppressive agents were the drugs most frequently suspected in spontaneously reported death [245]. These are drugs generally with a low therapeutic index and they are included in lists of medicines most likely to be used in the elderly, and thus likely to be associated with ADRs [240]. It must also be taken into account the fact that the increase of life expectancy has augmented the incidence of cancer in elderly patients over the last few decades, and a wide range of side effects can be expected from systemic chemotherapy. The physiopathological changes that occur with aging (e.g. renal failure, cardiovascular impairment, metabolic problems) also make older persons more vulnerable to ADRs [246].

Despite some limitations, this study showed the importance of studying ADRs in the elderly based on the information available in pharmacovigilance databases. The main weaknesses involve the general under-reporting of ADRs, problems with assessment of ADRs and their seriousness. As proven by several studies, under-reporting is a general problem intrinsic to all spontaneous pharmacovigilance systems. It is estimated that less than 5–10% of ADRs are reported and sometimes the reports are of poor quality or incomplete [232]. On the other hand, the data related to the mortality must be carefully interpreted because a fatal outcome does not necessarily mean a causal relationship to the suspected medicinal product.

II.5 Conclusion

The physiological changes and comorbidities associated with aging change the response to drugs and the risk of adverse reactions. In fact, we found a considerable number of older people with ADRs and most of them were considered as serious, even being expected. Antineoplastic and antithrombotic agents were the suspected drugs most frequently associated with a fatal outcome. Therefore, in an attempt to improve ADRs recognition in older persons, the medication review should routinely be a part of the health care provided to these patients. In this context, the detection of preventable ADRs is an important starting point to improve drug safety in elderly. The fact that half

of the unexpected ADRs were considered as probably being related to the suspected drug, highlights the importance of reporting all ADRs, thus allowing the authorities to evaluate the presence of possible safety signals in this special subpopulation (i.e., in elderly).

Chapter III - Assessment of Suspected Adverse Drug Reactions in Elderly Patients with Diabetes *Mellitus* based on a Portuguese Spontaneous Reporting Database: Analysis of Reporting from 2008 to 2018

The content of this chapter is included in the following publication:

Monteiro C, Silvestre S, Duarte AP, Alves G. Assessment of suspected adverse drug reactions in elderly patients with diabetes mellitus based on a Portuguese spontaneous reporting database: analysis of reporting from 2008 to 2018. Expert Opin Drug Saf. 2021; 20(7):845-853. doi: 10.1080/14740338.2021.1928072.

III.1 Introduction

Diabetes *mellitus*, mostly type 2, is one of the most common chronic diseases and its prevalence is expected to increase considerably in the future, especially in developing countries [75]. In fact and as example, it is estimated that the prevalence of type 1 and type 2 diabetes *mellitus* (T2DM) between 2015 and 2030 in America will increase by 54%, with a rise of deaths and costs of 38% and 53% (to more than $622 billion of costs in 2030), respectively [247]. In addition, a projection of T2DM burden in Germany showed that case numbers will grow from 5 million (2.8 million diagnosed) in 2010 to a maximum of 7.9 million (4.6 million diagnosed) in 2037. In this study, it was also predicted that the annual costs of diabetes care will increase by 79% from €11.8 billion in 2010 to €21.1 billion in 2040 (€9.5 billion to €17.6 billion for diagnosed cases) [248]. In Portuguese population, the estimated prevalence of diabetes (type 2 and type 1) between the ages of 20 and 79 (7.7 million individuals) in 2018 was 13.6%. Therefore, more than 1 million Portuguese in this age group and over a quarter of people aged 60-79 have diabetes *mellitus* [73,249]. In fact, older adults are at higher risk for the development of diabetes *mellitus*, mainly T2DM, due to combined effects of increased insulin resistance and reduced pancreatic islet function with aging [250]. Moreover,

these patients have an increased risk of acute and chronic microvascular and macrovascular complications [250]. Therefore, diabetes *mellitus* in elderly patients is related to a higher mortality and its complications are an important cause of morbidity and of a reduced life expectancy [250,251].

Additionally to non-pharmacological measures, there are several drug classes and combinations of some of these that can be used to control blood glucose levels, such as biguanides, sulfonylureas, thiazolidinediones, acarbose, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium glucose cotransporter 2 (SGLT-2) inhibitors, as well as different pharmaceutical forms of human insulin and its analogues [252].

In addition to T2DM, polypharmacy, usually defined as the use of five or more drugs [253], is also more common in older population, which increases the probability of occurrence of drug-induced side effects and drug-drug interactions. In this context, age-related changes in pharmacokinetics (in particular reduced hepatic and renal elimination) and pharmacodynamics (e.g. increased sensitivity to some drugs) are responsible for the higher predisposition of elderly to drug-related adverse events [250].

In individuals using glucose-lowering medications the incidence of hypoglycaemia, the most common adverse event of these drugs, increases with age. In fact, polypharmacy, the delay of drug metabolism commensurate with renal failure, cognitive dysfunction and the diminished awareness of hypoglycaemia caused by a lack of autonomic signs, such as sweating and/or tachycardia, are responsible for severe hypoglycaemia in older adults and increased risk of death [254,255].

Clinical evidence for medication use in elderly patients is poor because many clinical trials exclude elderly population or they are underrepresented, either due to age or to the presence of one or more confounding comorbidities [250]. Therefore, medical decisions, including in diabetes *mellitus* therapy, are often made using evidence extrapolated from younger patients [250].

Due to the limited evidence to justify clinical decisions regarding optimal therapy in older patients and to minimize or prevent adverse drug reactions (ADRs) in this population, studies to analyse suspected ADRs in older patients are of high importance. Therefore, many studies in this scope can be found in the literature, involving, for instance, antidiabetic drugs [75,157,256]. However, retrospective studies on spontaneously reported ADRs using national pharmacovigilance data are very scarce and usually cover diabetic patients belonging to all age groups [251,257,258]. In fact, the knowledge of the most common medications and ADRs induced in elderly patients with diabetes is important to increase the safety of their use. For this, the databases

used in pharmacovigilance are important tools to increment this knowledge, and consequently to increase the drug's safety, having the advantage of identifying hazards associated with medicinal products used in real world context. Thus, this study intended to analyse the suspected ADRs in older patients with diabetes *mellitus* reported to the Portuguese Pharmacovigilance System (PPS) in an eleven-year period. In addition, it was assessed if they were known and preventable, the drugs mostly involved and the outcome of each case. With this type of knowledge, generated from real-world pharmacovigilance data, we intend to minimize the risk of harm that may occur and prevent drug-related hospital admissions as well as the morbidity and mortality associated to drugs used by elderly patients with diabetes.

III.2 Methods

III.2.1 Study Type, Setting and Data Source

An observational and retrospective analysis of suspected ADR reports in patients aged 65 years or older with diabetes *mellitus* received by PPS was performed.

PPS is coordinated by the Portuguese authority, INFARMED - National Authority of Medicines and Health Products, I.P. (Lisbon, Portugal). The present study analysed the reports received between 1 January 2008 and 31 December 2018 in which patients were taking at least one glucose lowering drug (concomitantly taken drugs were also considered). As there was no access to diagnosis data, it was assumed the presence of a glucose lowering drug as a proxy for diabetes. In this study, we included all the reports performed by healthcare professionals and patients (considered as direct reports) as well as by marketing authorization holders (considered as indirect reports) with the identified age range of 65 years or higher. After a deeper analysis of each report (searches based on similarities in patient, adverse reaction and medicinal product data), all duplicated and annulled reports were eliminated as well as the reports where the age of the patient was not defined (in some reports only the age range was defined). Duplicated reports were identified by the authority according to the Guideline on Good Pharmacovigilance Practices, Module VI Addendum I [215].

III.2.2 Parameters Used for Analysis

The reports were analysed in terms of sex and age groups of the involved patients, type of reporter, seriousness and type of ADRs according to the Preferred Term (PT) and System Organ Class (SOC) from the Medical Dictionary for Regulatory Activities (MedDRA®) terminology. If in the same report was detected more than one ADR belonging to the same SOC, that SOC was counted only once, as performed by other authors in a similar work [231].

Patient demographics concerning age were analysed using the following groups: 65-74, 75-84 and equal to or higher than 85 [162]. A serious adverse reaction, according to the definition of Good Pharmacovigilance Practices, Module VI [151], is any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly/birth defect. In this context, we also analysed all the reports with a fatal outcome and the relationship between exposure and death according to the criteria adopted by PPS and the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment [216]. According to this method, reports are classified as certain, probable, possible, unlikely, conditional or unclassifiable [216].

The medicines involved were categorized according to the WHO Anatomical Therapeutic Chemical (ATC) Classification system [218]. Each report corresponds to a single individual, but each individual report may correspond to more than one suspected ADR and more than one suspected drug. Therefore, the total number of ATC and ADRs may be higher than the number of reports. It was also checked whether or not suspected ADRs of our study were described in the Summary of Product Characteristics (SmPC) of the respective medicinal product. Finally, a more in-depth analysis of the MedDRA terms belonging to the Important Medical Event (IME) terms list [217] involving drugs used in diabetes was also performed.

Data were analysed by means of descriptive statistics, using the software Microsoft® Office® Excel® 365.

III.3 Results

III.3.1 Annual Evolution of Adverse Drug Reaction Reports (2008-2018)

During the eleven-year period studied, a total of 787 reports in elderly involving the use of drugs for diabetes *mellitus* were received by the PPS. After removal of all duplicated and annulled reports as well as reports with no defined age, we achieved 751 cases and a total of 2134 ADRs, with an average of 2.84 (range 1-14, Standard Deviation 2.32) ADRs per report and a median of 2 (Inter Quartile Range 1-4). In general, with the clear exception of 2017, there was an increase in reporting over the years (figure III.1).

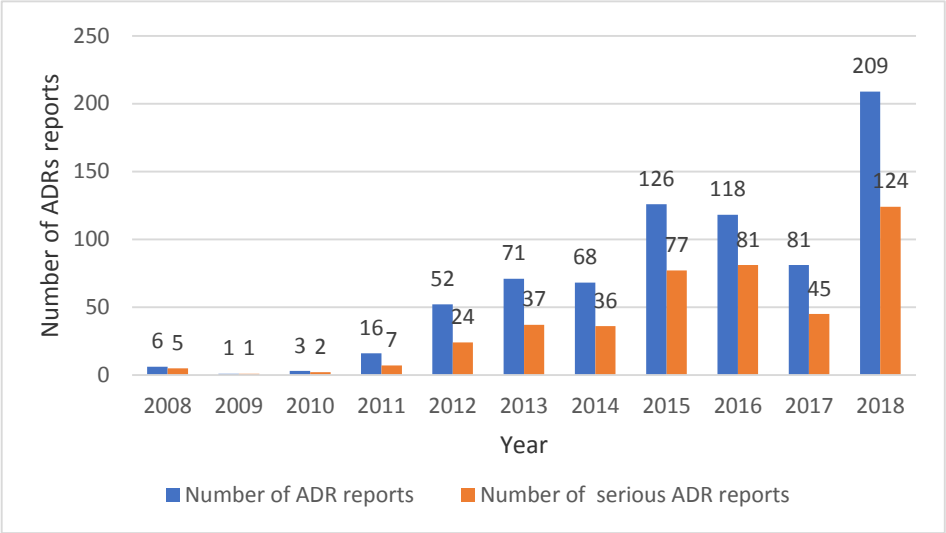

Figure III.1: Number of Adverse Drug Reactions (ADRs) reports versus serious ADRs spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older with diabetes *mellitus*

III.3.2 Sources of Adverse Drug Reactions Reports

Pharmacists were the health professionals that submitted the highest number of notifications (n=314, 41.8%), followed by physicians (n=234, 31.2%), marketing authorization holders (n=121, 16.1%), consumers (n=54, 7.2%), nurses (n=19, 2.5%) and other healthcare professionals (n=9, 1.2%). In our study, most of the reported ADRs were expected (85.1%), since they were described in the SmPC of the corresponding suspected drug involved. In addition, table S.1.1 in the appendix 1

described the ADRs according to PT classification classified as ‘not-labelled’ according to the SmPC.

III.3.3 Demographic Data

The majority of suspected ADRs were observed in females (n=393, 52.3%), 45.7% (n=343) of the cases refer to males and in 2% (n=15) of cases the gender was not identified. Near 54.0% (n=405) of the reports analysed belong to the age group of 65 to 74 years, followed by 36.7% (n=276) of the age group of 75 to 84 years and 9.3% (n=70) concerned patients aged 85 years or older.

III.3.4 Seriousness and Outcomes of Adverse Drug Reactions

Most of the reports were classified as serious (n=439, 58.5%). In Figure III.1 are indicated the serious cases and the number of ADRs per year. Among the 439 serious cases of suspected ADRs, 199 (45.3%) led to hospitalization and in 19 (4.3%) of them occurred a fatal outcome. However, the majority of patients completely recovered (63.9%, n=480).

III.3.5 Fatal Outcome and Causality Assessment

The causality assessment attributed by the regulatory authority was analysed in the 19 cases with fatal outcome. According to the WHO system for standardized case causality assessment [216], only 2 cases were classified as certain and the drugs involved were digoxin and levothyroxine; in the first case an elevated plasmatic digoxin level was reported, and in the second case phlebothrombosis and retroperitoneal haematoma was ascribed to levothyroxine. It is important to mention that these two fatal cases where not caused by drugs used to treat diabetes. Among the remaining reports, 3 were classified as probable and the other 14 were classified as possible, as unlikely, or had no causality attributed.

III.3.6 System Organ Class and Preferred Term involved in the Adverse Drug Reactions

In 751 cases, it was found 1517 involved SOC. Most of the reported ADRs referred to gastrointestinal disorders (13.7%) and to general disorders and administration site conditions (13.1%) (figure III.2).

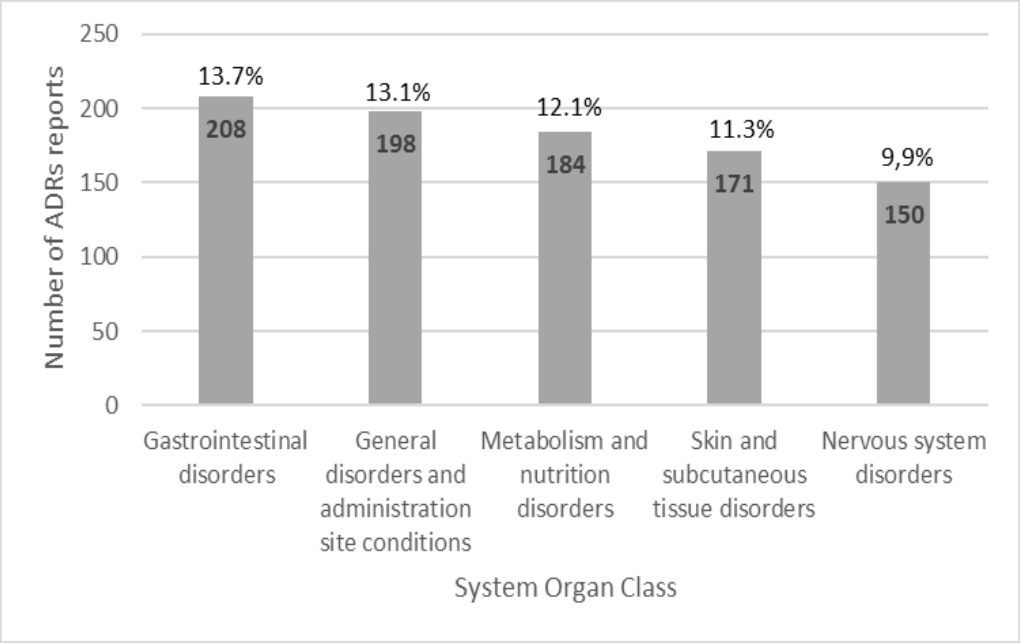

Figure III.2: System Organ Class affected by Adverse Drug Reactions (ADRs), spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older with diabetes *mellitus*: the five most frequent

Hypoglycaemia, lactic acidosis and diarrhoea were the most frequent ADRs reported in the total of the analysed reports (table III.1). Given the high diversity of ADRs we only considered in table III.1 the occurrences higher than 1%.

Table III.1: Suspected Adverse Drug Reactions most frequently reported (frequency ≥ 1%) according to Preferred Terms classification spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 in people aged 65 years or older with diabetes *mellitus*.

Preferred terms	Number of occurrences	%
Hypoglycaemia	57	2.67%
Lactic acidosis	56	2.62%
Diarrhoea	55	2.58%
Vomiting	50	2.34%
Nausea	45	2.11%
Dizziness	40	1.87%
Pruritus	34	1.59%
Fatigue	31	1.45%
Malaise	24	1.12%
Abdominal pain	22	1.03%
Dyspnoea	22	1.03%
Hypotension	22	1.03%
Others	1676	78.54%
Total	2134	100.00%

III.3.7 Drugs Involved in Adverse Drug Reactions

In 751 cases, we found 947 ATC codes (2nd level, therapeutic subgroup) involved in suspected ADRs. The five most frequent are presented in Figure III.3.

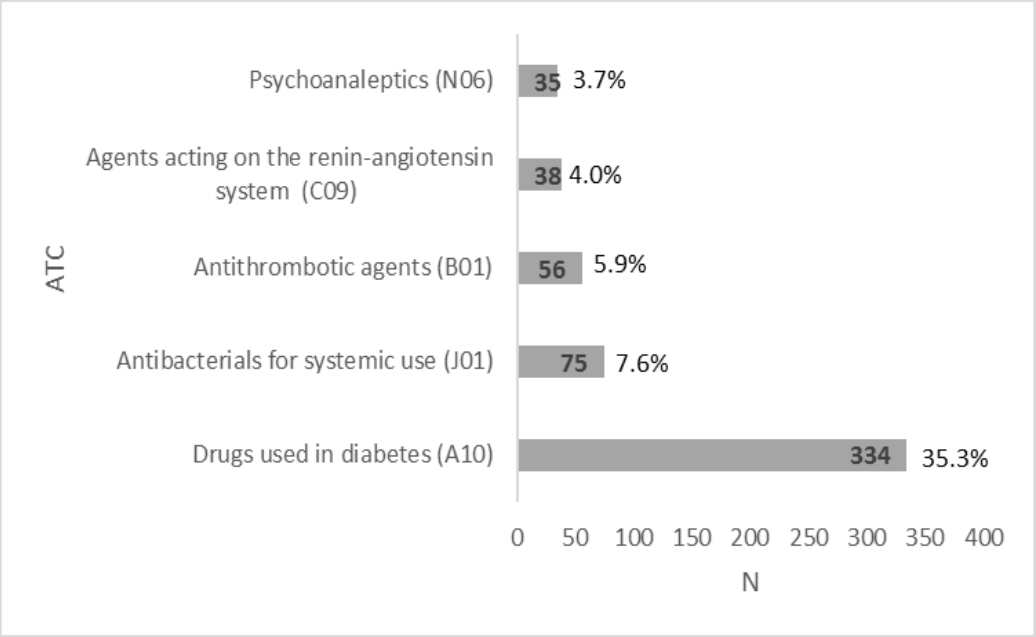

Figure III.3: Anatomical Therapeutic Chemical (ATC) code involved (2nd level, therapeutic subgroup) in Adverse Drug Reactions, spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older with diabetes *mellitus*: the five most frequent

Drugs used in diabetes *mellitus* were the most represented group (n= 334, 35.3%), followed by antibacterials for systemic use (n=75, 5.9%), antithrombotic drugs (n=56, 5.9%), agents acting on the renin-angiotensin system (n=38, 4.0%) and psychoanaleptics (n=35, 3.7%). The mostly reported therapeutic subgroup was also that corresponding to drugs used in diabetes, with 157 cases classified as serious. In this subgroup, metformin was considered the suspected drug in 76 cases (table III.2), with 5 fatal outcomes associated to it. In addition, metformin was the drug most associated to lactic acidosis. In 20 reports of hypoglycaemia insulin glargine was the only suspected drug involved and in additional 13 reports a sulfonylurea was the suspected drug.

In the 5 reports with fatal outcome associated to metformin, the suspected ADRs reported according to PT classification were lactic acidosis (n=4), renal failure (n=1), blood pH decreased (n=1), shock (n=2), respiratory failure (n=1), fatigue (n=1), metabolic acidosis (n=2), neurological symptom (n=1), toxicity to various agents (n=1), renal injury (n=1), hyperlactacidaemia (n=1), blood lactic acid increase (n=1), acute kidney injury (n=1) and hyperkalaemia (n=1). According to the WHO system for standardized causality assessment [216], the reports had not causality attributed.

Table III.2: Chemical substances belonging to A10 Anatomical Therapeutic Chemical group, considered the only suspected drug, and the number of occurrences, spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older with diabetes *mellitus*

Pharmacological subgroup	Chemical subgroup	Chemical substance (number of occurrences)
Insulins and analogues	Insulins and analogues for injection, fast-acting	Insulin glulisine (5), Insulin human (2)
	Insulins and analogues for injection, intermediate-acting combined with fast-acting	Insulin aspart (3), Insulin human (5) Insulin lispro (2)
	Insulins and analogues for injection, long-acting	Insulin glargine (25), Insulin detemir (2)
Blood glucose lowering drugs, excl. insulins	Biguanides	Metformin (76)
	Sulfonylureas	Gliclazide (10), Glimepiride (4) Glibenclamide (2)
	Combinations of oral blood glucose lowering drugs	Metformin and sitagliptin (14), Metformin and vildagliptin (11), Glibenclamide and metformin (5), Metformin and alogliptin (3), Glimepiride and pioglitazone (1), Metformin and dapagliflozin (1) Metformin and pioglitazone (1)
	Alpha-glucosidase inhibitors	Acarbose (2)
	Thiazolidinediones	Pioglitazone (4)
	Dipeptidyl peptidase 4 inhibitors	Linagliptin (6), Sitagliptin (6), Vildagliptin (5), Saxagliptin (2)
	Glucagon-like peptide-1 analogues	Exenatide (6), Liraglutide (4), Dulaglutide (2)
	Sodium-glucose co-transporter 2 inhibitors	Dapagliflozin (9), Empagliflozin (2) Canagliflozin (1)

Considering the IME list of the reported drugs from A10 ATC group, we found 137 ADRs belonging to the referred list and in 21 of these we found two or more A10 chemical substances involved (table III.3). The most reported ADR was lactic acidosis (n=48), with 44 reports associated to metformin. Concerning the renal system, we found 8 reports of acute kidney injury (5 of them associated with metformin as suspected drug), 4 of renal injury and 2 of renal failure, with metformin also involved. In addition, in 7 cases of urosepsis, metformin was considered the suspected drug in 6 of them (table III.3).

Table III.3: Suspected Adverse Drug Reactions (ADRs) belonging to the Important Medical Events (IME) list, corresponding System Organ Class (SOC), and chemical substance belonging to A10 Anatomical Therapeutic Chemical group, as the only suspected drug involved, spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older with diabetes *mellitus*.

SOC	ADRs (number) belonging to the IME list	Chemical substance, number of occurrences
Cardiac disorders	Aortic valve incompetence (1)	Insulin glargine (1)
	Cardiac arrest (1)	Metformin (1)
	Cardiac failure (1)	Metformin (1)
Gastrointestinal disorders	Autoimmune pancreatitis (1)	Metformin + Sitagliptin[b] (1)
	Haematochezia (1)	Metformin (1)
	Pancreatitis acute (3)	Sitagliptin (1), Empagliflozin (1), Linagliptin (1)
	Pancreatic failure (1)	Metformin + Sitagliptin[b] (1)
General disorders and administration site conditions	Terminal state (1)	Insulin lispro + Sitagliptin[b] (1)
Hepatobiliary disorders	Hepatitis (1)	Acarbose (1)
Immune system disorders	Anaphylactic reaction (3)	Insulin (human) (1), Liraglutide (1), Exenatide (1)
	Type I hypersensitivity (1)	Insulin detemir + Insulin (human)[b] (1)

Infections and infestations	Bacteraemia (1)	Insulin lispro + Sitagliptin[b] (1)
	Bacterial pyelonephritis (1)	Insulin lispro + Sitagliptin[b] (1)
	Escherichia urinary tract infection (1)	Insulin lispro + Sitagliptin[b] (1)
	Infected skin ulcer (1)	Insulin lispro + Sitagliptin[b] (1)
	Kidney infection (1)	Dapagliflozin (1)
	Parotid abscess (1)	Linagliptin (1)
	Pneumonia aspiration (1)	Insulin lispro + Sitagliptin[b] (1)
	Pyelonephritis acute (1)	Metformin (1)
	Urosepsis (7)	Dapagliflozin (1), Metformin (6)
Injury, poisoning and procedural complications	Craniocerebral injury (1)	Metformin (1)
	Femoral neck fracture (1)	Glibenclamide (1)
Metabolism and nutrition disorders	Diabetic ketoacidosis (1)	Dapagliflozin (1)
	Diabetes *mellitus* inadequate control (1)	Metformin (1)
	Euglycaemic diabetic ketoacidosis (1)	Dapagliflozin (1)
	Hyperkalaemia (5)	Metformin (2), Vildagliptin (1), Metformin + Sitagliptin + Dapagliflozin + Insulin (human)[b] (1), Dapagliflozin (1)
	Lactic acidosis (48)	Metformin and sitagliptin (1), Metformin and sitagliptin[a] + Metformin [b] (1), Metformin + Metformin and alogliptin[a] [b](1), Metformin (44), Metformin and vildagliptin[a] (1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Bladder cancer recurrent (1)	Pioglitazone (1)
	Bladder transitional cell carcinoma (1)	Pioglitazone (1)
	Inflammatory myofibroblastic tumour (1)	Metformin (1)

Nervous system disorders	Altered state of consciousness (3)	Glibenclamide (1), Gliclazide + Sitagliptin[b] (1), Metformin and sulfonylureas[a] (1)
	Cerebrovascular accident (1)	Insulin (human) + Insulin glargine[b] (1)
	Depressed level of consciousness (2)	Linagliptin + Insulin detemir[b] (1), Metformin
	Diabetic coma (1)	Glibenclamide (1)
	Hemiparesis (1)	Metformin (1)
	Loss of consciousness (2)	Metformin (1), Gliclazide (1)
	Neuropathy peripheral (1)	Insulin (human) + Insulin glargine [b] (1)
	Seizure (1)	Glimepiride (1)
Renal and urinary disorder	Acute kidney injury (8)	Metformin (5), Metformin and sitagliptin [a] (2), Metformin and vildagliptin [a] (1)
	Anuria (1)	Metformin and vildagliptin[a] (1)
	Prerenal failure (1)	Metformin (1)
	Pyelonephritis acute (1)	Metformin (1)
	Renal failure (2)	Metformin (2)
	Renal injury (4)	Dapagliflozin (1), Metformin (2), Metformin and sitagliptin[a] (1)
	Urinary retention (1)	Pioglitazone (1)
Respiratory, thoracic and mediastinal disorder	Acute pulmonary oedema (1)	Insulin glargine (1)
	Pneumonia aspiration (1)	Insulin lispro + Sitagliptin[b] (1)
	Pulmonary oedema (1)	Metformin and vildagliptin[a] (1)
	Respiratory distress (1)	Metformin (1)
	Respiratory failure (3)	Metformin (1), Metformin and vildagliptin[a] (1), Insulin lispro + Sitagliptin[b] (1)
Skin and subcutaneous tissue disorders	Dermatitis bullous (2)	Linagliptin (1), Metformin and vildagliptin[a] (1)
	Erythema multiforme (1)	Metformin (1)

	Infected skin ulcer (1)	Insulin lispro + Sitagliptin[b] (1)
	Lipodystrophy acquired (4)	Insulin glargine (1), Insulin (human) (1), Insulin detemir (1), Insulin lispro + Insulin (human) [b] (1)
	Pemphigoid (3)	Vildagliptin (1), Metformin and vildagliptin[a] (1), Linagliptin (1)
	Skin necrosis (1)	Insulin lispro + Sitagliptin[b] (1)
Vascular disorders	Shock (2)	Metformin (2)

[a] Fixed combinations of blood glucose lowering drugs (patient taking only a medication)

[b] Combinations of two or more different medications (patient taking different medication each one containing a chemical substance)

III.4 Discussion

Aiming to improve the knowledge on ADRs in older diabetic patients in real world context we performed an analysis of the reports sent to PPS during 11 years. In this study, most of the suspected ADRs were reported as serious and associated to drugs used in diabetes *mellitus*, despite being analysed all drugs taken by these patients. The majority of these ADRs, such as hypoglycaemia, are preventable. During the period of this study there was a trend toward an increase in reporting suspected ADRs in elderly with diabetes. This situation was expected considering that the prevalence of diabetes has also been increasing all over the world, including in Portugal [77,210]. Additionally, in developed countries, there has been an increase in the average lifespan and, consequently, in the number of elderly people [259]. Besides, the increase of reports perhaps also reflects an increasing awareness of reporters and the efforts performed by the national authority responsible for coordinating pharmacovigilance activities. Between 2016 and 2017 occurred a decrease of reports, however the number of reports does not necessarily reflect the frequency of a given ADR, because PPS does not receive reports for every adverse reaction that occurred [232].

Most ADRs were considered as serious and mainly involved females and individuals aged 65-74 years. Even though the prevalence of diabetes in Portugal in 2018 in men is significantly superior to women (16.4% *versus* 11.1%) [77], the studies concerning ADRs showed that women are affected twice more than men, which is due to a combination of pharmacokinetic and pharmacodynamic factors [159,228]. This may explain the fact that the majority of the reports of the present study involved female patients.

Additionally, these results are in agreement with others performed in Portugal, in which the majority of ADRs involved women and are serious [164,260,261]. In this context, it is important to mention that health professionals seem to be particularly sensitive to report only serious ADRs, which explains the high number of serious cases reported (58.5%) [231]. Most cases were reported directly by healthcare professionals, particularly pharmacists and physicians, similarly to which occurred in other studies [164,231,241,261].

A deeper analysis of all ADRs allowed concluding that most of the reported ADRs were expected because they are described in SmPC. In contrast, a study performed by Torre et al found a higher proportion of unlabelled ADR associated to DPP-4 inhibitors group [262]. However under-reporting is a general problem in pharmacovigilance [232], and unlabelled ADR they are not always reported, due to the doubts concerning the relationship with the drug. For this reason, intensive monitoring, in our perspective, allows the detection of these cases, which are not always reported to the PPS.

The most frequently reported ADRs were related to gastrointestinal disorders and to general disorders and administration site conditions. In many cases, the ADRs are related to antidiabetic therapy, aiming at achieving a strict glycaemic control. Of these, hypoglycaemia, lactic acidosis, diarrhoea, vomiting and nauseas were the most frequent ADRs reported in the total of the reports analysed, and were considered expectable. In fact, gastrointestinal adverse events are common with the use of oral antidiabetic drugs [75,263]. In addition, hypoglycaemia is a reaction associated to most drugs used in diabetes, and the risk of this event is elevated among elderly patients with this condition [75]. Actually, hypoglycaemia remains a critical concern to glycaemic control in elderly patients with diabetes. Thus, the predisposing factors to hypoglycaemia such as cognitive and renal impairment must be considered when setting glycaemic goals and eventually individualizing therapy in the elderly. Although elderly patients can reach glycaemic control with lifestyle modification, oral antidiabetic drugs and insulins are usually required due to the progression of the disease, and their use increases the risk of hypoglycaemia [74,80]. Additionally, changes in renal function are common in elderly and may affect drug elimination [80]. In fact, a decreased kidney function may lead to an increase of plasmatic concentrations of the glucose-controlling drugs with renal excretion. Furthermore, the loss of body mass connected with age and frailty syndrome can also lead to a relevant decrease on needed doses of antidiabetic medications [264]. In this context, ultra-long-acting basal insulins may present a lower risk of hypoglycaemia than the currently available basal insulin analogues, and therefore would be especially advantageous in elderly patients [264]. Despite this, in our study, we found several cases of hypoglycaemia associated to insulin glargine, a

long-acting insulin analogue. However, to more correctly evaluate a patient with diabetes it is necessary to take into account not only their chronological age, but also their biological age, physical fitness, intellectual capacity, occurrence of other chronic diseases, as well as the patient's motivation and support from family and friends [264], because it is important that the patient strictly fulfils the drug posology to control its glycaemic level. Unfortunately, these data are absent in the analysed cases. Other drugs associated to hypoglycaemic events found in our study were sulfonylureas, which were the only suspected drug class associated to 13 cases of this adverse event. This is a low-cost class of drugs, however the risk of hypoglycaemia with these agents may be problematic for older patients [250]. Alpha-glucosidase inhibitors, specifically targeting postprandial hyperglycaemia, have low hypoglycaemia risk, which makes them theoretically attractive for older patients. However, their relatively low efficacy as glucose-lowering agents and gastrointestinal intolerance may be limiting [250]. Reducing the risk of hypoglycaemia is particularly important in older patients who are at higher risk of hypoglycaemia unawareness or hypoglycaemia-associated complications such as falls and related fractures, or acute cardiovascular events [264]. In fact, a doubled rate of emergency department visits due to hypoglycaemia was observed on elderly when compared with the general population with diabetes [253].

When analysing the drugs potentially involved with lactic acidosis, metformin was found to be the most suspected. Actually, metformin constitutes the first line drug therapy for T2DM, which may partially explain our results. However, a review on metformin and its association with lactic acidosis showed that this drug rarely induces lactic acidosis when liver and kidneys are able to correctly process lactate [265]. In this review the authors emphasised that it is almost impossible to distinguish between lactic acidosis in a context of metformin accumulation (i.e. in acute kidney failure and voluntary intoxication) and lactic acidosis caused by systemic conditions (sepsis, cardiac failure, haemorrhage, etc.) in a patient taking metformin [265]. Kidneys have an important function in lactate homeostasis. Hence, impaired renal function can have a negative impact on lactate clearance, particularly when hepatic gluconeogenesis and lactate uptake by hepatocytes are also impaired, which explain the cases of hyperlactacidaemia [265]. In fact, the doses of this drug should be reduced if estimated glomerular filtration rate is 30–60 mL/min and it should not be used if estimated glomerular filtration rate is 30 mL/min or lower [266]. Therefore, as it was not possible to obtain information on the renal function, our results were inconclusive in this point. In this context, a study analysed lactic acidosis occurrences associated with metformin reported to the Australian Therapeutic Goods Administration and showed that the other underlying clinical conditions (such as renal impairment) or medications also

associated with risk of lactic acidosis were frequently reported in metformin-associated lactic acidosis (MALA) cases [257]. For this reason, metformin might also be unfairly implicated in these cases [257]. Even though high serum lactate levels are associated with increased mortality in septic shock patients, the mortality rate appeared to be significantly lower in those who were treated with metformin [266]. However, as lactate levels were not included in the ADRs analysed, it was not possible to relate this situation with deaths caused by septic shock in the present work. Additionally, diabetes is also associated to several complications such as suppression of cellular immunity, nephropathy, and fatty liver disease, which can lead to death, as shown in a study performed in United States from 1990 through 2010 [266]. Thus, the renal and urinary disorders found in this study may be the result of diabetes inappropriately controlled in elderly patients.

Another important drug used in diabetes is pioglitazone, which, in our study was identified in two reports of bladder tumours (recurrent bladder cancer and bladder transitional cell carcinoma). Concerning the association of pioglitazone and bladder cancer, a previous study showed the association between this drug use and the referred cancer [251]. The authors analysed this association through a spontaneous adverse event reporting system for antidiabetic drugs and they found a definite signal between pioglitazone and bladder cancer [251].

Considering the sodium-glucose co-transporter-2 inhibitors (SGLT2-Is), we found that dapagliflozin was associated to urosepsis, kidney infection, diabetic ketoacidosis, hyperkalaemia and euglycaemic diabetic ketoacidosis ADRs. In this context, a study showed that among antidiabetic drugs, SGLT2-Is are associated to a higher reporting of infections as well as metabolism, renal and reproductive adverse events, corroborating clinical trial evidence [258].

Evidence indicates that dipeptidyl peptidase-4 inhibitors are highly effective and safe in the elderly and that in the presence of mild, moderate and severe renal failure they improved glycaemic control with low risk of hypoglycaemia [267]. However, their use was associated to an increased risk of urinary tract infection in older patients [268]. This fact is in agreement with our results, since sitagliptin was connected to an Escherichia urinary tract infection, a bacterial pyelonephritis, a pneumonia aspiration, a bacteraemia, and an infected skin ulcer. However, it is important to take into account that infectious diseases are more frequent and/or serious in patients with diabetes *mellitus*, because the hyperglycaemic environment favours immune dysfunction (e.g., lead to damage of neutrophil function, reduction of antioxidant defences and humoral immunity) [269]. Diabetes is also responsible for micro- and macroangiopathies, neuropathy, for decreasing the antibacterial activity of urine, gastrointestinal and

urinary dysmotility and lead to a higher number of medical interventions in these patients [269]. Older adults with diabetes also have the highest rates of myocardial infarction, visual impairment, and end-stage renal disease of any age-group [270].
Overall, this research work showed the importance of studying ADRs in the elderly based on the information available in pharmacovigilance databases, including in patients with diabetes *mellitus*. However, it has some limitations, namely the fact that this study is descriptive and the ADRs are spontaneously reported; consequently, the true incidence of ADRs cannot be determined using these data. As proven by many studies, under-reporting is a general problem in pharmacovigilance [232], so we can speculate that a relevant number of ADRs is not reported to the PPS. Another limitation is the poor quality or incomplete reports, being more difficult to establish a definite relationship between the suspected drugs and the ADRs [216]. This fact explains the distribution of causality assessment. Hence, it is essential to describe as far as possible all clinical information concerning the situation, to allow the expert to perform a more correct evaluation of the case. Other limitations of this study are related to lack of other clinical information, including the confirmation of a definitive diagnosis of T2DM. However, as the main indication for these studied drugs is T2DM, and as this condition has higher prevalence in older patients, we can speculate that these drugs are being used for this condition.

III.5 Conclusion

The general prevalence of diabetes *mellitus* is increasing over the years and older adults are at higher risk for the development of this disease, mainly T2DM. Consequently, improvements in efforts to reduce the annual incidence of morbidities and premature deaths related to diabetes are urgent, particularly in elderly. This requires a comprehensive management of multiple health measures, including an increase in knowledge of safety and efficacy of antidiabetic drugs. However, studies in older individuals with diabetes are limited, but prescription drugs are a necessary component of the treatment of this disease. Therefore, the occurrence of ADRs, particularly the serious cases, must always be evaluated to establish more clearly the benefit-risk balance of the medication for each patient. With this purpose, in the present study it was performed a retrospective analysis of suspected ADRs in older patients with diabetes reported to the PPS. Hypoglycaemia, lactic acidosis and diarrhoea were the most frequent ADRs reported in the total of the analysed reports.

The majority of the suspected ADRs were serious and associated to hypoglycaemic drugs, being metformin the mostly reported. As most ADRs are preventable, preventive measures are important to minimize their occurrence. Therefore, the accurate identification of ADRs is an important starting point to improve drug safety in elderly. In this context, spontaneous reports are a key component of post marketing surveillance and a valuable resource that supports ongoing efforts to understand the public health burden of ADRs. More studies with the purpose of evaluating the safety of antidiabetics drugs in the older people should be performed, namely with metformin.

Chapter IV - Safety of Non-Steroidal Anti-Inflammatory Drugs in the Elderly: An Analysis of Published Literature and Reports Sent to the Portuguese Pharmacovigilance System

The content of this chapter is included in the following publication:

Monteiro C, Silvestre S, Duarte A.P, Alves G. Safety of Non-Steroidal Anti-Inflammatory Drugs in the Elderly: An Analysis of Published Literature and Reports Sent to the Portuguese Pharmacovigilance System. Int J Environ Res. Public Health 2022; 19(6):3541. doi: 10.3390/ijerph19063541

IV.1 Introduction

The use of non-steroidal anti-inflammatory drugs (NSAIDs) for a wide range of rheumatic conditions and other musculoskeletal disorders is increasing. This is in part due to the growing number of elderly patients who constitute the main users of these drugs [122,271]. Despite their relevant efficacy, NSAIDs must be used with caution in older people due to the high risk of potentially serious and life-threatening adverse effects [122]. NSAIDs constitute a group of therapeutic agents with diverse structural and pharmacological profiles but similar mechanism of action. They inhibit the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes that are involved in biosynthesis of inflammatory mediators such as prostaglandins, which also play a protective role in multiple physiological functions involving the gastrointestinal, renal and cardiovascular systems, among others [122,272]. Therefore, it is not surprising that NSAIDs trigger some important deleterious effects, and in older people they have been implicated in 23.5% of hospital admissions due to adverse drug reactions (ADRs) [273]. Although these drugs are generally associated with mild gastrointestinal adverse events on short-term use, more serious adverse events such as gastrointestinal ulceration or bleeding may arise under long-term use [274]. In fact, gastrointestinal toxicity can

occur with all NSAIDs, which may be of particular concern when treating older patients. However, gastrointestinal adverse events may be reduced by taking a concomitant gastroprotective agent [271]. In addition, older patients have usually other comorbidities, mostly cardiovascular diseases and/or decline in renal function, and for these reasons they frequently need to use other drugs that can potentially interact with NSAIDs and consequently increase the risk of cardiovascular, hematologic, and renal adverse events [271]. The main problematic drugs in this context include selective serotonin reuptake inhibitors, corticosteroids, digitalis glycosides, diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, clopidogrel, low-dose acetylsalicylic acid, warfarin, and other anticoagulant agents [122,131].

With the goal of reducing serious gastrointestinal adverse effects ascribed to conventional (i.e., COX-2-nonselective) NSAIDs, highly selective COX-2 inhibitors, called as coxibs, were introduced into clinical practice about 20 years ago. However, they have only limited benefit in reducing these untoward effects. In fact, the risk of serious cardiovascular and renal adverse effects remains as a major concern [63,122].

Consequently, it is important to perform a continuous monitoring of the safety of these drugs in older population by means of pharmacovigilance or other post-authorisation safety studies. In this context, the identification of preventable ADRs is an important starting point to improve drug safety in elderly [164]. Moreover, due to the comorbidities they often present, elderly patients do not always participate in clinical trials, and therefore treatment recommendations for this special population are usually based on the extrapolation of evidence obtained from clinical trials conducted in healthy and younger subjects [275,276]. Currently, there are already several recent reviews addressing the use of NSAIDs in elderly [123,277–280]; however, it is important to continue monitoring the NSAIDs safety in this special population, gathering real world evidence on the occurrence of serious ADRs, the impact of concomitant drugs, and the effect of gastroprotection use. For all these reasons, we intended to integrate the evidence from the most recent clinical studies and the reports of suspected ADRs received in a pharmacovigilance database.

In this context, we carried out a comprehensive literature review of clinical trials and observational and interventional clinical studies that report data on NSAIDs safety in the elderly. In addition, we intended to characterize in elderly patients the suspected ADRs associated with NSAIDs reported to the Portuguese Pharmacovigilance System (PPS) from 2008 to 2018. The overall aim was to conclude about the safety of NSAIDs in the elderly, considering in an integrated manner the available scientific literature and the real-world evidence obtained from pharmacovigilance activities. Secondarily,

we intended to compare the extent to which the drug safety documented in the literature is reflected in the safe use of these drugs by this population.

IV.2 Methods

IV.2.1 Comprehensive Review

A bibliographic search was performed in different databases (Pubmed, Web of Knowledge, Medline and Cochrane Collection Plus) to identify studies addressing the safety of NSAIDs in older patients (age ≥65). This search considered the period between January 1, 2005 to January 23, 2020 and was performed using the following terms: (adverse reaction OR adverse event OR safety OR pharmacovigilance) AND (non-steroidal anti-inflammatory) AND (elderly OR older people OR older patient OR older person OR geriatric OR older adult) AND (Humans [Mesh]) and the filters age ≥65 and articles related with clinical studies were applied. In the process to select the studies to be included in the review, the exclusion of all studies referring to NSAIDs that had already been removed from the market was considered. In fact, the objective of using only NSAIDs currently on the market and the fact that several reviews on this subject have already been published [122,131,271,274], were the reasons for the selection of the time period referred to. Thus, studies focused on rofecoxib and lumiracoxib were excluded [281,282].

Other criteria of exclusion were: review articles, pre-clinical *in vivo* studies, studies that did not describe drug-safety, studies with ambiguous design or methods, studies in which the analysed population included people under 65 years or the results were not presented by specific age (i.e., studies that involved young adults and elderly, but the results were presented in terms of average age), studies with ocular formulations, and studies where the results were not separated by specific drug.

Observational and interventional studies were considered. Only studies published in English were included.

The outcomes considered were related to the safety of NSAIDs in older people, with the description of ADRs associated, and the conclusion about which drug is safer in the older people.

IV.2.2 Analysis of Adverse Drug Reactions Reports Sent to Portuguese Pharmacovigilance System

An observational and retrospective analysis of suspected ADRs reported to the PPS was performed. The PPS is coordinated by the National Authority of Medicines and Health Products, I.P. (INFARMED).

In this analysis, it was considered only the reports involving one or more NSAIDs as suspected drug(s) in patients aged 65 or over, between the period of 2008 to 2018. Duplicates and reports that did not present the necessary information for ADRs characterization were excluded, namely those that did not mention age. The reports referring to eye drops or acetylsalicylic acid as antiplatelet agent were excluded. It is also important to note that each notification concerns a single case, but for each notification more than one suspected ADR and more than one implicated drug may be associated.

Initially, 367 reports were considered, of which 49 were duplicated, 6 did not mention age, 5 referring to eye drops and 46 involving acetylsalicylic acid at a low dosage, acting as an antiplatelet agent. Thus, 261 spontaneous reports involving patients aged ≥65 were included for analysis.

The suspected ADRs reports were grouped in terms of System Organ Class (SOC) of Medical Dictionary for Regulatory Activities (MedDRA) [283]. A deeper analysis of the SOCs gastrointestinal, renal and cardiac disorders considering the Preferred Term reactions (PT) of the MedDRA dictionary was performed; in addition, suspected ADRs that resulted in life-threatening, caused patient hospitalization or prolonged hospitalization were also analysed in detail. Concerning, these serious outcomes the concomitant drugs were analysed for gastrointestinal events occurred. In the reports with a fatal outcome, a deeper analysis in terms of each ADR was also performed. The relationship between exposure and death followed the criteria adopted by the PPS, and the World Health Organization-Uppsala Monitoring Center (WHO-UMC) system for case causality assessment [284]. According to this method, which considers the clinical-pharmacological aspects of the reported history and the quality of the documentation reported, the causality is classified as certain, probable, possible, unlikely, conditional or unclassifiable [284].

Considering the seriousness, the reports were grouped as serious or not serious. According to the Guidelines on Pharmacovigilance for Medicinal Products for Human Use, a serious ADR is defined as an adverse reaction that results in death or is life-threatening, causes patient hospitalization or prolonged hospitalization, permanent or significant disability, or birth defect(s) [151].

The descriptive statistical analysis of the data was performed using Microsoft Office Excel 365 Pro Plus.

IV.3 Results

IV.3.1 Comprehensive Review

From the literature we identified only 14 articles which were considered eligible for our analysis according to the criteria described in the methods. The years of the selected studies were 2019 (n=1), 2018 (n=2), 2017 (n=1), 2014 (n=1), 2013 (n=1), 2012 (n=3), 2010 (n=1), 2009 (n=1), 2008 (n=1), 2007 (n=1) and 2006 (n=1). Of the 14 studies included in the review, 9 were clinical trials and involved the NSAIDs naproxen, diclofenac, celecoxib and etoricoxib, and the other 5 were observational studies and included several NSAIDs. One of these studies showed the results for elderlies with more than 75 years old. Table IV.1 shows the type of study, the drugs involved, the number of patients and the outcomes for each study.

Table IV.1: Studies evaluating the safety of non-steroidal anti-inflammatory drugs (NSAIDs) in the elderly

Reference	Study design	Study population	Number of patients with ≥ 65 years old	Number of patients with <65 years old	Drugs compared/ route of administration	Outcomes
Dillon et al 2019 [272]	Retrospective observational study for AE reported to Food and Drug Administration's Adverse Events Reporting System	Patients with an NSAID as the primary suspect for an AE	n=1347	n= 0	Acetylsalicylic acid (ASA), naproxen, ibuprofen, diclofenac, celecoxib or other NSAID; oral	• 72.5 % of the AEs were associated to acetylsalicylic acid; • Predictors of gastrointestinal bleed: ➢ ASA ➢ Rivaroxaban ➢ Concurrent NSAID
Couto et al 2018 [285]	Four multicenter, multidose, randomized, parallel, double-blind, placebo-controlled studies	Patients with OA	n=229, placebo n=231	n=180, placebo n=178	Naproxen/placebo; oral	• Rate of AEs and gastrointestinal events comparable in the naproxen sodium and placebo groups (26% and 24% of patients, and 13% vs 10%, respectively); • Most common AEs were related to the gastrointestinal system and similar in two groups (dyspepsia, nausea, and diarrhea)
Chelly et al 2018 [286]	Three phase III trials (2 were randomized, placebo- and active controlled trials and 1 was open-label, multiple-dose safety	Patients with Acute Moderate-to-Severe Postoperative Pain	n= 411	n=878	One or more doses of HPbCD-diclofenac or placebo; injectable	• Incidence of AE similar in the groups; • Gastrointestinal disorders were the most common AE; • Higher incidence of acute renal failure in those aged ≥75 years (3.9%) than was observed in those aged <65 years (0.1%) or 65–74 years (0.4%)

	study)					
Bakhriansyah et al 2017 [287]	Case–control study with data obtained from the Dutch PHARMO Record Linkage System	Patients with a first hospital admission for risk of gastrointestinal perforation, ulcers, or bleeding (PUB)	Age ≥ 75 n=2890, control 2184	18-74 n= 1504, control 2890	Conventional NSAIDs or selective COX-2, alone or combined with PPI; route of de administration unknown	• Selective COX-2 inhibitors combined with PPIs had the lowest risk of PUB followed by selective COX-2 inhibitors and conventional NSAIDs with PPIs; • Risk of PUB was lower for those aged ≥75 years taking conventional NSAIDs with PPIs compared with younger patients with conventional NSAIDs; • Risk of PUB, for those aged ≥75 years taking selective COX-2 inhibitors, was higher compared with younger patients
Hirayama et al 2014 [288]	Prospective, nonblinded, non-randomized, comparative observational study performed in hospitals and general practice clinics	Patients with OA or RA	Celecoxib (n=5591), other NSAIDs (n=5057)	Celecoxib (n=1767), other NSAIDs (n=1692)	Celecoxib/ Others NSAIDS (Loxoprofen, Etodolac, Meloxicam, Lornoxicam, Diclofenac, Zaltoprofen, Other); route of administration unknown	• No apparent increase in cardiovascular risk in the celecoxib group compared with the conventional NSAID group.

Chelly et al 2013 [289]	Multicenter, open-label, repeated dose, multiple-day, single-arm safety study	Patients with acute moderate-to-severe pain following major surgery	n=367	n=604	HPbCD diclofenac; injectable	• Elevated incidences of renal AEs (acute renal failure, decreased urinary output) in patients >75 years of age and in those with significant pre-existing renal impairment.
Kellner et al 2012 [290]	Prospective, double blind, randomized, parallel-group, multicenter, international study	Patients with OA and/or RA	n=2446	n=0	Celecoxib or diclofenac slow release 75 mg plus omeprazole 20 mg once a day; route of administration unknown	• Incidence of gastrointestinal events in the celecoxib group was lower compared with the diclofenac group; • Incidence of moderate-to-severe abdominal symptoms and discontinuation of treatment due to gastrointestinal AEs were lower in the celecoxib group; • Celecoxib was shown to be superior to a conventional NSAID plus a PPI in reducing the risk of clinical outcomes across the entire gastrointestinal tract.
Roth et al 2012 [291]	Seven multicenter, randomized, blinded, Phase III clinical trials	Patients ≥75 years with a primary diagnosis of OA in the knee or hand	n=280	n=0	TDiclo solution 1.5% [w/w] in 45.5% dimethyl sulfoxide; placebo (topical lotion consisting of 2.33% or 4.55% dimethyl sulfoxide); and control (topical	• Skin or subcutaneous tissue were the most AE reported; • Few patients (18%) reported gastrointestinal AE (constipation, diarrhoea, and nausea were the most common AE); • Cardiovascular and renal/urinary AE were rare, and group differences were not detected.

					lotion consisting of 45.5% dimethyl sulfoxide); topical	
Baraf et al 2012 [292]	Five randomized, double-blind, placebo-controlled trials	Patients with mild to moderate OA of the knee and hand	n=538	n=888	Diclofenac sodium gel (DSG) or placebo (vehicle gel); topical	• Similar and low rates of AEs in DSG-treated patients aged ≥ 65 and <65 years
Laine et al 2010 [293]	Three double-blind randomized trials	Patients OA or RA	n=14227	n=20474	Etoricoxib or diclofenac; oral	• Predictors of clinical events and complicated events: ➢ age ≥65 ➢ prior event ➢ low-dose ASA ➢ corticosteroid • Predictors of discontinuation due to dyspepsia: ➢ prior dyspepsia ➢ prior event ➢ age ≥ 65 years • No significant difference for etoricoxib vs. diclofenac in the complicated upper gastrointestinal events

Turajane et al 2009 [294]	Hospital-based retrospective cohort study	Patients with knee OA	n=1030	n=0	Conventional NSAIDs (diclofenac, diflunisal, sulindac, piroxicam, indomethacin, loxoprofen, meloxicam, nimesulide, and naproxen) or two coxibs (celecoxib and etoricoxib); oral	• Incidence of gastrointestinal and cardiovascular events was lower for coxibs than for conventional NSAIDs; • Patients with advanced age and higher drug exposure time had a significantly increased risk of gastrointestinal events; • The use of gastroprotective agents significantly decreased gastrointestinal risks; • Factors that significantly increase the risk of cardiovascular events: ➢ females ➢ age > 80 years ➢ drug exposure time
Laine et al 2008 [295]	Three randomized, double-blind, clinical trials	Patients with OA or RA	n=14396	n=20305	Etoricoxib) or diclofenac; oral	• There is not a statistically significant decrease in lower gastrointestinal clinical events with the COX-2 selective inhibitor etoricoxib versus the traditional NSAID diclofenac • The major risk factors of lower gastrointestinal events are: ➢ a prior gastrointestinal event ➢ age >65 years
Rahme et al 2007 [296]	Retrospective cohort study using Quebec government	Patients ≥65 who filled a prescription for	n=332491	n=0	Conventional NSAID only, celecoxib only,	• Celecoxib without ASA was less likely than conventional NSAID without ASA to be associated with gastrointestinal

	databases	celecoxib or a conventional NSAID			conventional NSAID and low-dose ASA, celecoxib and ASA; oral	hospitalization • Celecoxib and ASA was also less likely to be associated with gastrointestinal hospitalization than conventional NSAID and ASA • Gastrointestinal hospitalization rates were similar for celecoxib and ASA and conventional NSAID without ASA
Cannon et al 2006 [297]	Three randomised, double-blind clinical trials	Patients with OA or RA	n=14396	n=20305	Etoricoxib or diclofenac; oral	• Rates of thrombotic cardiovascular events are similar for etoricoxib and for diclofenac • Rates of upper gastrointestinal clinical events (perforation, bleeding, obstruction, ulcer) were lower with etoricoxib than with diclofenac • Rates of complicated upper gastrointestinal events were similar for etoricoxib and diclofenac

AE: adverse event; ASA: acetylsalicylic acid; COX-2: cyclooxygenase-2: DSG: diclofenac sodium gel; HPbCD-diclofenac: hydroxypropyl-b-cyclodextrin-diclofenac; NSAID: non-steroidal anti-inflammatory drug; NSAIDs: non-steroidal anti-inflammatory drugs; OA: osteoarthritis; PPI: proton pump inhibitor; PUB: gastrointestinal perforation, ulcers, or bleeding; RA: rheumatoid arthritis; TDiclo: diclofenac sodium topical solution 1.5% (w/w) in 45.5% dimethyl sulfoxide

IV.3.1.1 Main Points Evidenced by the Literature Review

A summary analysis of the studies collected by the search strategy applied in this comprehensive review is presented in Table IV.1.

Overall, the studies analysed showed that patients treated with COX-2-selective NSAIDs had a lower risk of adverse gastrointestinal events than those treated with conventional NSAIDs [286], and the concomitant use of gastroprotective agents also lowered the possibility of suffering from the referred adverse effects [287,290]. However, it was also demonstrated that the risk of gastrointestinal events was higher in persons aged ≥75 years taking COX-2-selective NSAIDs when compared with younger patients [287]. On the other hand, a study comparing etoricoxib with diclofenac in patients with osteoarthritis or rheumatoid arthritis showed that there was no significant difference between etoricoxib and diclofenac in the development of complicated upper gastrointestinal events [293]. However, a prior lower gastrointestinal tract event and older age significantly increase this risk [293,295]. Advanced age (aged ≥75) and patients with pre-existing renal impairment also rise the incidence of relevant renal adverse events, such as acute renal failure or decreased urinary output [286,289].

Additionally, the concomitant use of other drugs by older individuals can increase the risk of gastrointestinal bleeding, mainly those controlling haemostasis, such as acetylsalicylic acid (ASA), rivaroxaban, clopidogrel and warfarin [272]. However, the use of low-dose ASA for cardiovascular protection was less likely to be associated with hospitalization when concomitantly taken with celecoxib than with conventional NSAIDs [296].

A study concluded that the rates of thrombotic cardiovascular events in patients with arthritis taking etoricoxib are similar to those in patients on diclofenac after long-term use of these drugs [297]. However, for the same drugs the rates of upper gastrointestinal events were lower with etoricoxib than with diclofenac, but similar for complicated upper gastrointestinal tract events [297].

The incidence of gastrointestinal and cardiovascular adverse events was lower with coxibs than with conventional NSAIDs and celecoxib was associated to a lower incidence of these events than etoricoxib. Despite the advanced age and drug exposure time can increase cardiovascular events [294], a study concluded that there was no apparent rise in cardiovascular risk in the celecoxib group when compared with the conventional NSAID group in patients with rheumatoid arthritis or osteoarthritis [288].

On the other hand, and as expected, it was evidenced that a topical formulation of diclofenac is well tolerated in persons aged 75 years or older [291,292].

IV.3.2 Adverse Drug Reactions Reports Sent to Portuguese Pharmacovigilance System

In our study we found 261 reports associated to NSAIDs, for people aged 65 years or older. The number of reports associated to NSAIDs, are presented in Figure IV.1.

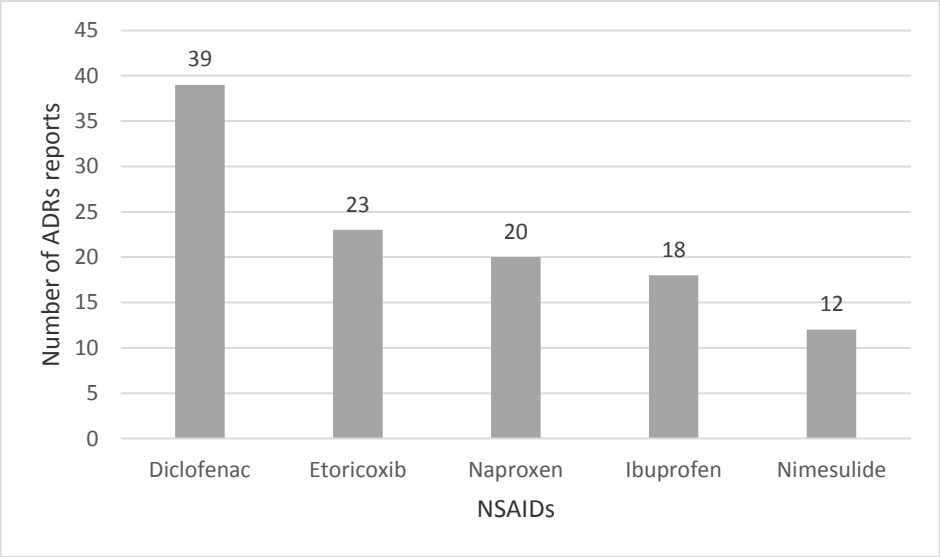

Figure IV.1: Single non-steroidal anti-inflammatory drugs (NSAIDs) involved in suspected Adverse Drug Reactions (ADRs) reports spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older: the top five

The mostly reported NSAIDs as a single suspected drug associated to ADRs were diclofenac (39 reports) followed by etoricoxib (23 reports).

In 180 reports (69.0%) only one NSAID was referred as the suspected drug, but in 71 reports (27.2%) a NSAID was associated to other drug classes, and in 10 reports (3.8%) associations between NSAIDs were detected. Most suspected ADRs occurred in females (64.7%, n=169) and a high percentage the suspected ADRs were serious (71.3%, n=186). Nearly 59.8% (n=156) of the reports analysed belong to the age group of 65 to 74 years, followed by 31.8% (n=83) of the age group 75 to 84 years and 8.4% (n=22) concerned patients aged 85 years older. The SOC “skin and subcutaneous tissue

disorders" was the mostly reported, followed by "general disorders and administration site conditions" and "gastrointestinal disorders" (figure IV.2).

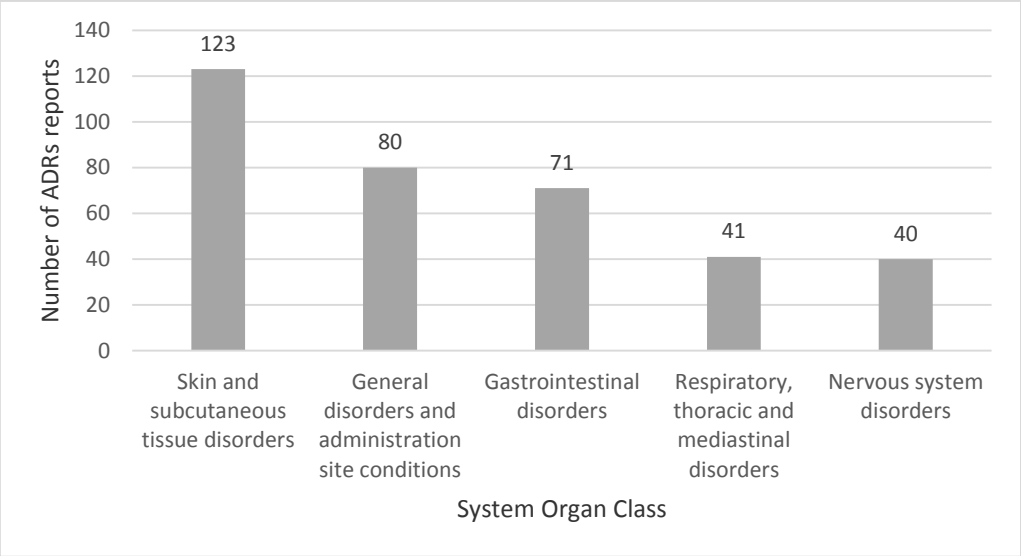

Figure IV.2: System Organ Classes affected by suspected Adverse Drug Reactions (ADRs) reports spontaneously reported to the Portuguese Pharmacovigilance System from 2008 to 2018 for people aged 65 years or older: the top five

A deeper analysis of the SOC "gastrointestinal disorders" showed that 66.2% (n=47) reports were serious, 1 resulted in death, 6 were life-threatening and 11 caused patient hospitalization or prolonged hospitalization. Among the reports associated to life-threatening adverse events that caused patient hospitalization or prolonged hospitalization, gastrointestinal haemorrhage mainly occurred in patients who had taken 2 or more NSAIDs and/or anticoagulant agents. Ibuprofen and diclofenac were the drugs most commonly associated with gastrointestinal events (Table IV.2). The gastroprotection only was presented in 5 reports, but in 5 reports the concomitant drugs were unknown.

Table IV.2: Non-steroidal anti-inflammatory drugs and other drug classes associated with serious gastrointestinal events that resulted in life-threatening adverse events, caused patient hospitalization or prolonged hospitalization

Suspected drugs	Number of occurrences	Preferred terms	Concomitant drugs
Aceclofenac	1	Melaena, Duodenal ulcer, Gastric ulcer	Unknown
Acetylsalicylic acid + diclofenac[b]	1	Gastrointestinal haemorrhage	Unknown
Dabigatran etexilate + etoricoxib + amiodarone [b]	1	Melaena, Haematochezia	Furosemide + glyceryl trinitrate + tramadol and paracetamol[a, b]
Dexketoprofen	1	Vomiting	Paracetamol + tramadol + etoricoxib + pregabalin [b]
Diclofenac	2	Tongue oedema, Diarrhoea, Melaena, Gastric haemorrhage, Erosive oesophagitis	Unknown
Diclofenac + colchicine [b]	1	Diarrhoea, Nausea, Dyspepsia, Vomiting, Abdominal pain upper	Salbutamol
Escitalopram + ibuprofen [b]	1	Gastric ulcer, Rectal injury, Abdominal pain, Decreased appetite, Rectal haemorrhage, Haematemesis	Metamizole + acetylsalicylic acid + sucralfate + pravastatin and fenofibrate[a] + citicoline + furosemide + etoricoxib + ferrous sulfate + midazolam + spironolactone [b]
Etoricoxib	1	Abdominal distension	Amiodarone + pantoprazole + diazepam + levomepromazine [b]
Ibuprofen + nimesulide [b]	1	Haematochezia	Omeprazole + alprazolam + pravastatin + amitriptyline + acetylsalicylic acid 100 mg + gabapentin + potassium clorazepate + metamizole [b]
Ibuprofen	1	Lip oedema	Unknown

Imidapril + ketoprofen [b]	1	Tongue oedema	Cobamamide + lansoprazole + atorvastatin + furosemide + finasteride + gliclazide + acetylsalicylic acid 100mg + allopurinol + rilmenidine + idebenone [b]
Indomethacin	1	Gastrointestinal haemorrhage	Ibuprofen +clopidogrel [b]
Metformin and vildagliptin[a] + acemetacin [b]	2	Vomiting, Diarrhoea	Simvastatin + furosemide +perindopril + amlodipine and indapamide[a] + sertraline + trazodone + codeine + lorazepam + omeprazole + magnesium + allopurinol [b]
Proglumetacin + metamizole [b]	1	Diarrhoea, Nausea	Pregabalin
Ribavirin + sofosbuvir and ledipasvir[a] + ibuprofen [b]	1	Duodenal ulcer haemorrhage	Unknown

[a] Fixed combination of drugs (patient taking only a medication)

[b] Combinations of two or more different medications (patient taking different medication each one containing a chemical substance)

From a deeper analysis of the SOC “renal and urinary disorders” identified in 19 reports, it was found that 17 were serious, 1 resulted in death, 2 in life-threatening adverse events and 7 caused patient hospitalization or prolonged hospitalization. In these reports, only 2 patients were aged <74 years. Ibuprofen and naproxen were the drugs most associated with renal injury or renal failure, but 3 of these patients were diabetic. The patient that suffered aggravated chronic kidney disease associated to diclofenac had clinical history of chronic kidney disease (Table IV.3). The SOC “cardiac disorders” only had 7 reports associated, but 6 were serious, 2 resulted in death, 1 was life-threatening and 1 led to hospitalization (Table IV.3). A deeper analysis of the reports of these 2 patients (1 was life-threatening and 1 was hospitalized) allowed to conclude that they had clinical history of arterial hypertension.

Table IV.3: Non-steroidal anti-inflammatory drugs and other classes of drugs associated to serious renal events and cardiac disorders where occurred adverse reactions that resulted in life-threatening adverse events, caused patient hospitalization or prolonged hospitalization

System Organ Classes	Preferred term	Suspected drugs
Renal and urinary disorders	Acute renal failure	Etoricoxib + ciprofloxacin [b]
	Tubulointerstitial nephritis	Ibuprofen
	Renal injury	Metformin + ibuprofen [b]
	Renal failure chronic aggravated	Diclofenac + colchicine [b]
	Haematuria	Warfarin + diclofenac [b]
	Renal failure acute	Ibuprofen
	Chronic kidney disease	Naproxen
	Acute renal insufficiency	Naproxen + metformin and vildagliptin [a, b]
	Tubulointerstitial nephritis	Carvedilol + ibuprofen + allopurinol + carvedilol [b]
Cardiac disorders	Tachycardia, blood pressure increased	Etofenamate + diclofenac + thiocolchicoside [b]
	Cardio-respiratory arrest	Acetylsalicylic acid

[a] Fixed combination of drugs (patient taking only a medication)

[b] Combinations of two or more different medications (patient taking different medication each one containing a chemical substance)

A deeper analysis of the serious reports with fatal outcome was also performed. The patients died in 7 cases and the drugs involved were naproxen and dabigatran etexilate, strontium ranelate and etoricoxib, ASA, diclofenac and ibuprofen, diclofenac and thiocolchicoside and diclofenac combinations and allopurinol (Table IV.4).

Table IV.4: Adverse Drug Reactions (ADRs) and suspected drugs associated with a fatal outcome

Drugs	ADR Preferred Term (PT)
Naproxen + dabigatran etexilate [b]	Melaena, Gastrointestinal haemorrhage
Strontium ranelate + etoricoxib [b]	Fatigue, Pulmonary hypertension, Pneumonia, Respiratory failure
Acetylsalicylic acid	Cerebrovascular accident
Acetylsalicylic acid	Hypotension, Acute respiratory failure, Tracheobronchitis, Cardiac failure, Prinzmetal angina
Diclofenac + ibuprofen [b]	Acute kidney injury
Diclofenac + thiocolchicoside [b]	Blood pressure immeasurable, Bronchospasm, Respiratory distress, Hypotension, Hypoxia, Oxygen saturation decreased, Sinus tachycardia, Rash, Hyperhidrosis
Diclofenac combinations + allopurinol [b]	Thermal burn

[b] Combinations of two or more different medications (patient taking different medication each one containing a chemical substance)

Only in two of these reports a single NSAID was involved as suspected drug and in the remainder reports the NSAID was associated to another drug. However, after evaluation of the reports according to the WHO system for standardised causality assessment of cases as described in methods, melaena and gastrointestinal haemorrhage were considered as probably related to the use of dabigatran etexilate. In the other reports, only the combination of strontium ranelate and etoricoxib and the combinations of diclofenac and thiocolchicoside were considered as possible causative agents of the respective adverse reaction. For the remaining reports, the causality assessment was not presented.

IV.4 Discussion

Considering the analysis of data obtained from the literature review and from the suspected ADRs reported to PPS in order to assess the safety use of NSAIDs in older

patients we concluded that, in general, coxibs showed to be safer than conventional NSAIDs [272,287,290,294,298]; however, clinical monitoring of the risks and potential adverse events (mainly gastrointestinal effects) should be mitigated with reduction of concomitant drugs use, if possible, and use of gastroprotection. Regarding the reports sent to the PPS, in 69.0% of them only a single NSAID was the suspected drug, and the majority of reports were considered serious, associated to the female gender and belonging to the age group of 65 to 74 years, similar to the observed in other analogous studies [164,260,261]. Even though etoricoxib was one of the 5 most reported drugs to the PPS, the more classical diclofenac, naproxen, ibuprofen and nimesulide remained the mostly reported drugs. Despite ASA was not in the five most reported, we found two fatal outcomes associated to this drug, and in one of them the patient suffered a cerebrovascular accident. In this context, a meta-analysis demonstrated a trend towards increased risk of haemorrhagic stroke and a 50% relative risk increase of major gastrointestinal bleeding in ASA users [299]. In addition, the gastrointestinal bleeding risk increased when taking ASA and rivaroxaban with other NSAIDs. Therefore, it is important to reduce NSAIDs use by older adults, especially ASA, and avoid rivaroxaban in older persons taking NSAIDs [272].

Additionally, the concomitant use of NSAIDs and proton pump inhibitor (PPIs) reduced the gastrointestinal perforation, ulcers, or bleeding [287]. In fact, when compared with the use of isolated conventional NSAIDs, the risk of gastrointestinal perforation, ulcers, or bleeding was lower for those aged ≥75 years taking conventional NSAIDs with PPIs [287]. Another study concluded that the incidence of gastrointestinal events was lower for coxibs than for conventional NSAIDs and that celecoxib was associated to a lower incidence than etoricoxib [294]. However, patients with advanced age and higher drug exposure time had a significantly increased risk of gastrointestinal events, which can be reduced with the use of gastroprotective agents [294]. In general, the discontinuation of the treatment due to adverse events is higher with conventional NSAIDs [290]. Prior dyspepsia or upper gastrointestinal events and age ≥65 years were associated to an increased risk of developing dyspepsia, severe enough to led to NSAIDs discontinuation [293]. In fact, a study showed that the risk of an upper gastrointestinal clinical event with NSAID use is not statistically significant when comparing the COX-2-selective inhibitor etoricoxib with the traditional NSAID diclofenac, but this risk increases with a prior gastrointestinal event [295]. Our analysis of the reports showed that the drug with most reports was a conventional NSAID and the SOC "gastrointestinal disorders" was one of the most reported. Additionally, the gastrointestinal haemorrhage (which includes the cases of melaena reported) occurred in patients with concomitant treatments and not all patients had appropriate

gastroprotection. Despite it was already clearly demonstrated that antiplatelets, anticoagulants and the concomitant use of NSAIDs increase the risk of gastrointestinal bleeding [122,123,277], we found in our study that several patients were taking combinations of these drug families. In this context, ibuprofen, which is considered safe in this population due to its short half-life, in some reports was associated with other drugs that increase gastrointestinal adverse events [277]. Indeed, it is recommended to prescribe gastroprotective agents to older patients taking NSAIDs [279]. In fact, the STOPP/START criteria, used for medication review in the elderly, considered that NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis increased the risk of peptic ulcer disease [146], so it is essential that these patients take gastroprotective agents in certain specific circumstances, and in real-world, this is not always the case.

Among elderly arthritis patients, the incidence of gastrointestinal intolerability was lower with celecoxib than with naproxen, ibuprofen, or diclofenac. In general, the elderly patients that discontinued NSAIDs use due to gastrointestinal intolerability were using naproxen or ibuprofen [300]. In fact, analysing the reports to the PPS, the drugs most reported were diclofenac, naproxen, ibuprofen and nimesulide. In this context there were, also, reported to PPS associated to these drugs diarrhoea, nausea, vomiting and abdominal pain, as non-serious ADRs, and serious ADRs, as gastrointestinal haemorrhages.

Gastrointestinal events, including bleeding and ulceration, increase in frequency and seriousness with increasing age [301]. Old patients receiving NSAIDs are also more susceptible to renal side effects, including renal vasoconstriction and increased tubular sodium reabsorption that may cause fluid retention, oedema and worsening of congestive cardiac failure [301]. In this context, most NSAIDs can also contribute to worsening of chronic renal failure, particularly in patients with co-existing renal damage or patients taking diuretics or angiotensin converting enzyme inhibitors [301]. Concerning our data, the patients that suffered renal disorders were diabetics, a major risk factor for kidney disease [302] or had clinical history of chronic renal failure and the majority also had age ≥74. The results were in agreement with the literature that refer that advanced age (aged ≥75) and patients with pre-existing renal impairment rise the incidence of relevant renal adverse events [286,289]. Despite this, in our study, the estimated glomerular filtration rate is not available. However, the STOPP/START criteria consider that the use of NSAID's if estimate glomerular filtration rate < 50 ml/min/1.73m^2 increase the risk of deterioration in renal function [146].

In our study using data from PPS, the reports with fatal outcome (Table IV.4) associated to diclofenac users included blood pressure immeasurable and hypotension.

Despite these ADRs were associated to the diclofenac and thiocolchicoside, the adverse events are in agreement with three phase III clinical trials that studied one or more doses of hydroxypropyl-b-cyclodextrin-diclofenac or placebo in older patients with acute moderate-to-severe postoperative pain [286]. These authors concluded that the incidences of postoperative anaemia, constipation, and hypotension increased significantly across the age groups [286]. In fact, it was evidenced that NSAIDs administration may produce an increase in a mean arterial blood pressure of 5 mmHg [303]. Also, with respect to diclofenac, the relative risks were similar in the diclofenac and placebo groups for all studied SOC categories and preferred terms [286]. The SOC category of 'Gastrointestinal disorders' were the most common, and this was driven predominantly by cases of nausea and constipation [286]. In our study we also found acute kidney injury in one report associated to this drug. In this context, Chelly et al. found a significantly higher incidence of acute renal failure in those aged ≥75 years [286]. Other study showed that intravenous (IV) hydroxypropyl-b-cyclodextrin-diclofenac is safe and well tolerated, however elevated incidences of relevant renal adverse events (acute renal failure, decreased urinary output) were again observed in patients >75 years as well as in those with significant pre-existing renal impairment [289]. A meta-analysis performed by Ungprasert et al. demonstrated that exist an elevated acute kidney injury risk in patients taking conventional NSAIDs [125].

A study performed by Couto et al. concluded that naproxen can be relatively safe in younger and older patients [285]. The ADRs most described for this drug were related to the gastrointestinal system, but the study also showed that there was no significant differences in adverse event between groups, regardless of age [285]. In our analysis of ADR reported to PPS, in the fatal outcome associated to this drug, the patient suffered melena and haemorrhage, which is expected due to its mechanism of action [274]. However, the patient was also taking dabigatran etexilate, whereby the authority considered that the ADRs reported were related to this drug. Despite dabigatran is considered an anticoagulant with a good safety profile, its use also requires considerable caution, particularly in elderly, high bleeding risk patients, patients with decreased renal function and those on complex drug regimens [299]. Among patients receiving antithrombotic therapy after myocardial infarction, the use of NSAIDs was associated with an increased risk of bleeding and thrombotic events, even after short-term treatment [304]. Another study concluded that in elderly patients receiving cardiovascular protection with low-ASA and pain control with NSAIDs, celecoxib may be safer with regards to gastrointestinal toxicity than conventional NSAIDs [296].

Concerning the cardiovascular risk for serious adverse events (such as myocardial infarction, angina pectoris heart failure) a study showed that there was no apparent

increase in cardiovascular risk in the celecoxib group when compared with the NSAID group in patients with rheumatoid arthritis or osteoarthritis with a higher risk of cardiovascular disease [288]. In addition, a retrospective cohort study concluded that the incidence of serious cardiovascular events was lower for coxibs than for NSAIDs and celecoxib was associated to a lower incidence than etoricoxib [294]. However, the female gender, advanced age, and drug exposure time significantly affected cardiovascular events [294]. Another study for etoricoxib *versus* diclofenac for cardiac events, cerebrovascular events, and peripheral vascular events did not show any discernible difference between treatment groups [297]. The same study concluded that the rates of thrombotic cardiovascular events in patients with arthritis on etoricoxib are similar to those in patients on diclofenac with long-term use of these drugs [297]. The most serious cardiovascular disorders, in our study, were found in patients who were taking other drugs and had clinical history of hypertension, so most predisposed for these events.

Although topical NSAIDs are considered safer and well-tolerated in older patients than oral NSAIDs (fewer severe gastrointestinal events), a substantial proportion of older adults reports systemic adverse events with topical agents [280]. The most common adverse event for topical diclofenac involved the skin or subcutaneous tissue [291]. Actually, the SOC most reported to the PPS was skin disorders. In fact, NSAIDs use are one of the leading causes of hypersensitivity reactions to drugs by nonspecific or by specific immunological mechanisms [305]. In fact, these drugs may be responsible for exacerbated respiratory disease, cutaneous disease, urticaria/angioedema or anaphylaxis [306], which can explain the ADRs associated to the fatal outcome for diclofenac and for ASA and the fact that the SOC “skin and subcutaneous” was the mostly reported.

Concerning the fatal outcome associated to strontium ranelate and etoricoxib, where the ADRs reported were fatigue, pulmonary hypertension, pneumonia, respiratory failure we only suspect that they maybe be related with other comorbidities. In this context an increased risk for cardiac events with strontium ranelate was also described [307]. However, the fatigue can be explained by other diseases. It is also important to mention that elderlies present a progressive decrease in immune function and, consequently, increased susceptibility to infectious disease, namely pneumonia [234].

Despite some limitations, this study performed an assessment of the safety of NSAIDs in the elderly. The main weakness refers to the diversity of different studies selected for the review, which difficult the comparisons between them. Data were obtained from clinical trials or observational studies where patients had different inclusion and exclusion criteria. Different doses of NSAID were tested, and not all studies had a

placebo group. The outcomes measured in each trial were also different, which may bias the results. Additionally, data related to the PPS must be interpreted cautiously, as a fatal outcome does not necessarily imply a causal relationship with the suspected drug. The lack of information in most reports, makes it is impossible to perform a correct causality assessment and attribute an ADR to a drug. It is also important to mention that several health professionals believe that if the ADR is known for some drug it is not necessary to report it [183,308]. This point can explain the few reports associated to NSAIDs in the PPS and also the relatively low number of reports with gastrointestinal events.

IV.5 Conclusion

The use of NSAIDs as a drug therapy for a wide range of conditions is increasing, in part due to the increase of elderly population, raising the risk of adverse events. Therefore, a selection of an appropriate NSAID taking in consideration the risk-benefit factors is very important in the elderly. The advanced age and the use of other concomitant drugs were associated to an increased risk of adverse events. In addition, the use gastroprotective agents, that can decrease some of these risks, is not always observed in real-world. For all NSAIDs it is important an evaluation of the renal function because with age ≥75 it was observed an increase of acute renal failure occurrences, increasing the adverse events risk.

The results showed, that even the NSAID toxicity is well understood, their safe use need to be monitored in clinical practice, so it is urgent to increase the appropriateness of the medication regimen to improve the quality of pharmacotherapy of this special population.

Chapter V - General Discussion

Considering that each of the chapters presented in this thesis that involve research work have already been discussed in each specific chapter, this section has been prepared with the aim of discussing in an integrated and comprehensive manner the various topics dealt with in the previous chapters. Therefore, this section provides a critical overview of the main topics that comprise the general research conducted to achieve the main objectives proposed in the work plan leading to this thesis.

In Portugal, as in many other countries, the average life expectancy is increasing, whereby the challenge is to ensure that elderly can live with the highest possible life quality [309]. Overall, with increasing age, the number of comorbidities also increases, which leads to a higher consumption of medicines and, consequently, to a higher prevalence of drug-related problems. In order to improve the knowledge in this field and thus contribute to the safety of medicines, we conducted some studies focused on elderly Portuguese population, which were included in the present thesis.

In a study carried out by us in elderly residents of a nursing home or outpatients (Appendix 2), it was possible to note that most patients actually had multiple comorbidities, with diseases of the circulatory system being the most common, followed by endocrine, nutritional and metabolic diseases, as well as mental and behavioural disorders. Hypertension, dyslipidaemia, and dementia were found to be the most prevalent diseases, which is consistent with those referred to this age group [3,5,35]. Several elderly diabetic patients were also found in this study. In two studies conducted in Belgrade related to the most common diseases, diabetes *mellitus* was the eighth along with diseases of the circulatory system and diseases of the mental and behavioural systems [310,311]. When evaluating the number of medications that each consumer took, the average number of drugs prescribed was 7.6, with the majority of elderly taking more than 5 drugs. This was expected given the fact that polypharmacy is associated with this age group. In Germany, polypharmacy currently affects approximately 42% of people over 65 years, and the trend continues to increase [312]. In a study conducted in Portugal, polypharmacy was present in 62.3%, with an average of 5.5 ± 2.7 drugs per user [313].

With polypharmacy, multiple drug-related problems can occur, namely ADRs and/or use of PIMs. In the aforementioned study carried out by our team (Appendix 2), due to lack of information on clinical records, it was not possible to evaluate the ADRs associated with the medication use. However, we were able to evaluate the presence of PIMs and we found polymedicated patients with multiple comorbidities and with a

high number of PIMs, similarly to other studies [140,314,315]. In fact, most elderly patients evaluated were taking at least one or more PIMs, as described in other countries [140,316–320]. Despite the relatively small sample size of our study, these findings are important because, according to the literature, PIMs, ADRs and polypharmacy are frequently observed in patients discharged from hospital and increase the risk of unplanned readmission to hospital [315]. Therefore, with a reduction in the number of PIMs, it is possible not only to reduce the number of hospital readmissions, but also to reduce health care costs [321,322].

In fact, a retrospective matched cohort study concluded that PIMs led to an increase of health care costs and it is influenced by the number of prescribed drugs [321]. Another study involving a comprehensive geriatric assessment concluded that with a reduction of polypharmacy prevalence, PIMs decreased and the monthly saved total per capita cost of PIMs was US$12.8 [323].

In a study conducted at the Gerontology Center Belgrade, in addition to benzodiazepines as the most common PIMs, sulfonylureas and non-selective NSAIDs were also found as PIMs and frequently associated with adverse events in the same patients [310]. Other studies found an association between PIMs and NSAIDs [311,324]. In fact, in a cross-sectional study with 400 elderly patients of a geriatric center, the use of PIMs was high, with NSAIDs being the most commonly used drugs and diclofenac was the drug associated with a higher number of PIMs [325]. In this study, a high percentage of patients were also taking oral hypoglycaemic agents [325].

In this scope, it is important to emphasize that ADRs are closely associated with inappropriate prescribing and polypharmacy in the elderly. Therefore, by reducing the number of PIMs, it can be possible to improve the safety profile of medication in this age group. In general, ADRs are a serious and growing public health concern, especially in the elderly [207,326]. ADRs can be clinically and economically significant because there is a causal relationship between adverse drug events and serious negative outcomes, especially hospitalizations and mortality. In this ambit, hospitalizations of older adults due to ADRs are a growing problem [207,326]. In fact, approximately one in four patients admitted to hospital has at least one PIM prescribed, and up to 20% of all inpatient deaths are attributed to potentially preventable ADRs [327]. In addition, one in three community-dwelling older people taking at least five medications experience an ADR, 95% of which are predictable and approximately 28% are preventable [158,327]. These adverse effects include postural hypotension, delirium, immobility, and falls leading to fractures, which are associated with significant mortality and morbidity. Several studies have identified independent risk factors for adverse effects in elderly patients: specific drug classes (cardiovascular drugs, opioids,

anti-inflammatory drugs, anticoagulants, antibiotics, diuretics, antineoplastics, antidepressants, sedative-hypnotics, cardiac glycosides, steroids); disease states (heart failure, chronic lung disease, diabetes, cancer, renal failure, liver disease, dementia); patient characteristics (advanced age, female gender, multiple comorbidities, noncompliance, alcohol abuse); and factors of healthcare system (multiple prescribers and poor communication between prescribers, among others) [327–330].

Considering the available literature, the studies of this thesis were made to understand the reality in Portugal, contributing to increase the knowledge about the use of drugs in elderly. First, through a general study of reported ADRs to the PPS in elderly, and then specifically in elderly people with diabetes *mellitus*. Diabetes has increased in Portugal and these patients have a higher risk of suffering from adverse side effects [72,249]. Given the high prevalence of patients with musculoskeletal disorders and the fact that several studies have associated the use of NSAIDs with PIMs [122,325,331,332], it was considered to acquire a higher level of information about the safer NSAIDs for this age group, based on the scientific evidence and results of suspected ADRs reported to PPS [164]. In fact, several studies reported that most ADRs are serious and lead to hospitalisation or prolonged hospitalisation, which in turn leads to an increase in health care costs. Therefore, it is urgent to take measures to prevent its occurrence [157,162,173,239].

In our studies using data from PPS, most ADR reports were serious. The results are similar to those of other studies, namely from the Tunisian National Centre of Pharmacovigilance, showing that ADRs are frequent in the elderly and are often serious [219,220]. The most frequently reported ADRs were those related to general disorders and administration site conditions, skin and subcutaneous tissue reactions, and gastrointestinal disorders, as observed in other studies [25,220]. Among the fatal cases, general disorders and administration site conditions were the SOC most reported, but infections and infestations were also frequently identified. These results may be related to the fact that elderly patients have a progressive decline in immune function and consequently an increased susceptibility to infectious diseases [234]. Cardio-respiratory arrest, pneumonia, sepsis, and pancytopenia were the most reported ADRs of the IME list in our study. Infections and subsequent sepsis are an increasing cause of hospitalisation and critical illness in the elderly, with the risk of death from sepsis increasing with age [235]. In pancytopenia ADR, one of the possible causes is the administration of antineoplastic agents. Several studies have shown that antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, antineoplastic agents, and NSAIDs are responsible for a high number of ADRs leading to hospitalisation [42,235,239–241]. In an Italian spontaneous reporting database study, adverse effects

with fatal outcomes were associated with anti-infectives agents for systemic use, followed by antineoplastic and immunomodulatory agents as well as CNS system drugs [225]. In general, the drugs most frequently involved in fatal outcomes were those with a narrow therapeutic range [225]. These studies corroborate the results of our first study performed with data of the PPS, where the antineoplastic agents were the most represented group of drugs (13.6%) associated with ADRs, followed by antibacterial agents for systemic use (9.4%). In the reports with a fatal outcome, antineoplastic and antithrombotic agents were the most represented pharmacotherapeutic groups of suspected drugs. These results are largely consistent with the findings of other studies [162,225,241,243–246]. Overall, these are drugs with a low therapeutic index, which are included in the lists of drugs most likely to be used in the elderly and therefore likely to be associated with ADRs [240]. It must also be considered that the increase of life expectancy has increased the incidence of cancer in elderly patients in recent decades and a wide range of side effects can be expected with systemic chemotherapy. In addition, it is important to consider that in diseases such as cancer, the risk-benefit ratio on drug use must always be considered. The drugs used have many known risks, but the benefit in disease evolution is higher than the risk for most patients. In our initial analysis, analgesics were among the top 5 ATC groups involved, but in the overall analysis of fatal outcome cases, they were not the most reported suspected drugs.

In our study performed in diabetic elderlies, most of the suspected adverse effects associated with drugs used in diabetes *mellitus* were also serious, although all drugs taken by these patients were analysed. In addition, most ADRs induced by those drugs, such as hypoglycaemia, are preventable. This is a concern given the therapeutic goals for glycaemic control. In elderly, diabetes is associated with a high comorbidity burden and an increased prevalence of geriatric syndromes in addition to vascular complications [78]. Due to the heterogeneity of older people with diabetes and the differences in their functional status, comorbidities, and life expectancy, therapeutic interventions and glycaemic targets should be individualised considering each patient [78,333]. In frail elderly patients, the presence of competing comorbidities also means that life expectancy and quality of life may be reduced and older people with diabetes and dementia may have difficulty of performing self-care tasks [78]. In fact, diabetes self-care (taking diabetes medications, exercising regularly, following a recommended diet plan, measuring blood glucose, and inspecting feet) has been shown to worsen once dementia develops [78,334]. In this context, all these aspects can be considered in these patients to prevent the risk of hypoglycaemia associated with these medications. Therefore, the initial diagnostic assessment should be comprehensive and include screening for these syndromes, especially cognitive and physical dysfunction. Because

of the heterogeneity of older adults with diabetes, treatment plans must be individualized, with varying glycaemic goals. Globally, quality of life must be the focus of treatment plans.

The most frequently reported ADRs in diabetic patients were related to gastrointestinal disorders and general disorders and administration site conditions. In many cases, the adverse effects were related to antidiabetic therapy aimed at tight control of blood glucose levels. Of these, hypoglycaemia, lactic acidosis, diarrhoea, vomiting, and nausea were the most frequent ADRs reported in all reports analysed and were expected. Indeed, gastrointestinal adverse events are common when taking oral antidiabetic drugs [75,263]. In addition, hypoglycaemia is a reaction associated with most medications used in diabetes, and the risk for this event is increased in elderly patients with this condition [75]. Therefore, predisposing factors for hypoglycaemia such as cognitive and renal impairment must also be considered when setting glycaemic targets and eventually the individualized therapy in elderly can be required. Although elderly patients can achieve glycaemic control through lifestyle modification, progression of the disease usually requires oral antidiabetic drugs and insulin therapy, the use of which increases the risk of hypoglycaemia [74,80]. Moreover, changes in renal function are common in elderly and may interfere with drugs excretion [80]. Furthermore, the loss of body mass associated with age and frailty syndrome may also lead to a relevant reduction in the required doses of antidiabetic drugs [264]. Reducing the risk of hypoglycaemia is particularly important in elderly patients, who are at higher risk of not perceiving hypoglycaemia or suffering hypoglycaemia-related complications such as falls and associated fractures or acute cardiovascular events [264]. In fact, hypoglycaemia is a frequent reason of the hospital admissions observed in the elderly [75,83,264,335].

In this context, in the analysis of drugs potentially associated with lactic acidosis, metformin was the most frequently involved suspected drug. However, a review on metformin and its association with lactic acidosis showed that this drug rarely induces lactic acidosis when the liver and kidneys are able to correctly process lactate [265]. Since it was not possible to obtain information on renal function in our study, this type of relationship was not assessed. However, the changes in renal function associated with age should be considered when prescribing metformin. In fact, the dose of this drug should be reduced if the estimated glomerular filtration rate is 30-60 mL/min, and it should not be used if the estimated glomerular filtration rate is 30 mL/min or less [266].

Additionally, diabetes *mellitus* is also associated with various complications such as suppression of cellular immunity, nephropathy, and fatty liver disease, which can lead

to death, as shown in a study conducted in the United States from 1990 to 2010 [266]. Thus, renal and urinary tract diseases found in our study could be the result of an inadequate control of diabetes in elderly patients. However, it is important to consider that infectious diseases are more frequent and/or severe in patients with diabetes *mellitus*, since the hyperglycaemic environment favours immune system dysfunction (e.g., by damaging neutrophil function, reducing antioxidant defences and humoral immunity) [269]. Diabetes is also responsible for microangiopathies, macroangiopathies, neuropathy, reduction in urinary antibacterial activity, gastrointestinal and urinary dysmotility, and leads to a higher number of medical interventions in these patients [269]. Older adults with diabetes also have the highest rates of myocardial infarction, visual impairment, and end-stage renal disease of any age-group [270]. However, in order to better evaluate a patient with diabetes, it is necessary to consider not only their chronological age, but also their biological age, physical fitness, intellectual abilities, the presence of other chronic diseases, as well as the patient's motivation and support from family and friends [264]. Moreover, it is important that the patient strictly adheres to the prescribed medication regimen to control its blood glucose levels.

Given the high prevalence of patients with musculoskeletal disorders that lead to the use of NSAIDs it was considered fundamental to characterize the NSAIDs safety profile in elderly. Considering the analysis of data obtained from the literature review and from the suspected ADRs reported to PPS, we concluded that coxibs are generally safer than conventional NSAIDs [272,287,290,294,298]. Regarding the reports sent to PPS, in 69.0% of the reports, only one NSAID was the suspected drug, and the majority of reports were classified as serious, similarly to that has been observed in other studies [164,260,261]. The NSAIDs most reported were diclofenac, etoricoxib, naproxen, ibuprofen, and nimesulide. The incidence of gastrointestinal events was lower for coxibs than other NSAIDs, and celecoxib was associated with a lower incidence than etoricoxib [294]. However, patients with advanced age and prolonged drug use had a significantly increased risk of gastrointestinal events (even for the coxibs), but this can be reduced by the use of gastroprotective agents [294]. The risk of a gastrointestinal clinical event with NSAID use appears to be high, mainly in patients with a previous gastrointestinal event and in older patients [295]. In fact, gastrointestinal events, including bleeding and ulceration, increase in frequency and severity with age [301]. In the analysis performed in the PPS database, the gastrointestinal haemorrhage (which includes the cases of melaena reported) occurred in patients with concomitant treatments and not all patients had appropriate gastroprotection. Despite it was already clearly demonstrated that antiplatelets, anticoagulants and the concomitant use of

NSAIDs increase the risk of gastrointestinal bleeding [122,123,336], we found in our study that several patients were taking combinations of these drug classes. Indeed, it is recommended to prescribe gastroprotective agents to older patients taking NSAIDs [279]. In fact, the STOPP/START criteria, used for medication review in the elderly, consider that the use of a NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis increased the risk of peptic ulcer disease [146], so it is essential that these patients take gastroprotective agents in certain specific circumstances, and in real-world, this is not always the case.

Considering that renal dysfunction, including renal vasoconstriction and increased tubular sodium reabsorption, can lead to fluid retention and edema, worsening the congestive heart failure [301], it should also be highlighted that most NSAIDs may contribute to the worsening of chronic renal insufficiency, especially in patients with concomitant renal impairment or in patients taking diuretics or angiotensin-converting enzyme inhibitors [301]. For this reason, the STOPP/START criteria consider that the use of NSAIDs increases the risk of deterioration in renal function if the estimated glomerular filtration rate is < 50 ml/min/1.73m^2 [146].

In addition, it is important to consider that the use of NSAIDs is one of the main causes of hypersensitivity reactions to drugs through nonspecific or specific immunological mechanisms [305]. In fact, these drugs may be responsible for the exacerbation of respiratory diseases, skin diseases, urticaria/angioedema, or anaphylaxis [306], and in our study SOC skin and subcutaneous have been reported most frequently for this kind of drugs.

In general, advanced age and use of other concomitant medications were associated with an increased risk of gastrointestinal events. With all NSAIDs, it is important to monitor renal function because the incidence of acute renal failure increases with age ≥75 years, which increases the risk of adverse events. Several studies suggested that celecoxib may be a drug of choice for this population, as the gastrointestinal and cardiovascular events were lower with this drug compared to etoricoxib or conventional NSAIDs [287,290,294,296,298].

In all studies conducted for this thesis, we found a higher prevalence of adverse effects in women compared to men. This is because women tend to live longer and are more prone to physical or psychological complaints [223,320]. In fact, a study in Portugal showed that chronic medication use is more common in the elderly and in women [230]. The studies on ADRs have shown that women are affected twice as often as men [159], which may be due to a combination of pharmacokinetic and pharmacodynamic factors [228]. Additionally, the higher reporting rate in women can also be explained by the fact that they usually take more medicines and are more likely to seek medical care

compared to the male population [229]. For these reasons, their ADRs may also be detected earlier. However, ADRs reported by men tend to be more serious than those reported by women [229], which is consistent with our results.

Even though the prevalence of diabetes *mellitus* in Portugal in 2018 was higher in men than in women (16.4% versus 11.1%) [77], the studies on ADRs showed that women are affected twice as often as men [159,228].

In general, most of the reported ADRs were expected as they are described in the SmPC. These results could be related to some of the reasons given for underreporting, such as uncertainty about the drug causing the ADR [232]. In this context, it is important to mention that healthcare professionals seem to be particularly concerned about reporting only serious ADRs, which explains the high number of serious cases reported [231]. Most cases were reported directly by healthcare professionals, particularly pharmacists and physicians, similarly to what was found in other studies [164,231,241,261]. In addition, unlabelled ADRs are not always reported due to doubts about the association with the drug and the adverse events, therefore some ADRs are not always reported to PPS, being a limitation. Another limitation is that our study was descriptive and the ADRs were reported spontaneously, consequently, the true incidence of ADRs cannot be determined from these data [164,337,338] .

Despite this, studies with spontaneously reported data provide us with real-world information and allow scientists and professionals to consider comorbidities and concomitant medications that are not always present in clinical trials. However, lack of reporting, poor quality or incomplete reports difficult in establishing a clear relationship between suspected drugs and the suspected ADRs [216]. In addition, the lack of other clinical information, namely confirmation of a definitive diagnosis and renal function information, such as creatinine clearance values, contributes to the fact that it is not always possible to establish a definitive causal relationship between the drug and the ADR that occurred. Moreover, poor quality or incomplete reports [232] do not allow the expert to evaluate the case as correctly as possible. In pharmacovigilance, there is not only one possible cause of an adverse effect, but several; each cause must be evaluated for its probability in the given context [233]. Therefore, it is important to mention that all clinical information is useful because it allows the authority to evaluate the presence of possible safety signals.

Finally, mortality data must be interpreted carefully, because a fatal outcome does not necessarily imply a causal relationship with the suspected drug.

Chapter VI - Conclusion & Future Perspectives

The high prevalence of polymedication and ADRs in elderly patients is a major public health concern and, therefore, it is urgent to improve the instructions for a safer use of medications in this special population and to reduce, as far as possible, the complexity of pharmacotherapeutic regimens. For this, it is important to have reports with high quality clinical information and concomitant medications to allow a consistent assessment of causality and to identify and address safety signals. As most ADRs are serious and expectable, medication review should be a part of routine healthcare interventions targeting these patients, in order to detect ADRs as soon as possible, or even prevent them. Prevention should be considered the only way to improve medication safety in the elderly. It is important to give a special attention to drugs with a narrow therapeutic index, such as antineoplastic and antithrombotic agents. In diabetics, the use of hypoglycaemic drugs should be regularly monitored mainly due to the risk of hypoglycaemia. On this point, information on renal function should be also provided in all reports.

In summary, the most relevant key findings brought from all the research work carried out in the scope of the present thesis were:

- Most of the suspected ADRs reported were serious and expected, so can be preventable, whereby preventives measures are important to minimize their occurrence.
- The majority of the suspected ADRs reported in elderly patients with diabetes were serious and associated with hypoglycaemic drugs, being metformin the most implicated.
- The pharmacovigilance data analysed also showed that the monitoring of NSAIDs use in elderly remains essential to mitigate the associated risks, especially in those patients with comorbidities and under polytherapy. Although the NSAIDs toxicity is well understood, serious gastrointestinal ADRs occurred mostly in patients taking more than one NSAID and/or another concomitant drug that increases the incidence of these events. So, the safe use of NSAIDs needs to be monitored in clinical practice.

Hence, it is important to raise awareness among the general population and especially among healthcare professionals to report any suspected ADR, but also to provide the

maximum level of clinical information about the patient who suffered the adverse event.

Moreover, prescribing medicines in the future is likely to become an act supported by screening tools to inform doctors of PIMs and clinically relevant ADRs. As EMA intends, there is an urgent need to specify in the SmPC the adverse effects to which elderly patients are more susceptible.

Despite some limitations, all studies in this thesis have shown the importance of investigating adverse effects in the elderly based on the information available in pharmacovigilance databases, including in patients with diabetes *mellitus* and in the older patients taking NSAIDs. In the future, similar studies should be performed with focus on other relevant medical conditions and/or other important drug classes. Thus, the work described in this thesis represents a relatively small but important contribution to the drug safety in the elderly and highlights the importance of ADRs reporting and the role of pharmacovigilance.

References

1. WHO. Relatório Mundial de Envelhecimento e saude. Available from: https://apps.who.int/iris/bitstream/handle/10665/186468/WHO_FWC_ALC_15.01_por.pdf?sequence=6 (Accessed 10 July 2021).

2. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549–62.

3. Ageing and health. Available from:https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (Accessed 16 March 2022).

4. Kalache A, Gatti A. Active ageing: a policy framework. In: Second United Nations World Assembly on Ageing. 2002. p. 1–60.

5. World Population Ageing 2019 Highlights. World Population Ageing 2019. United Nations. 2019. 64 p.

6. Veríssimo M. Geriatria fundamental saber e praticar. 2014. 59–64, 119–136, 263–274, 291-296,353-364 p.

7. Kowal P, Dowd JE. Definition of an older person. Proposed working definition of an older person in Africa for the MDS Project. Geneva: World Health Organization; 2001.

8. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly." Geriatr Gerontol Int. 2006;6(3):149–58.

9. Alterovitz SSR, Mendelsohn GA. Relationship goals of middle-aged, young-old, and old-old internet daters: An analysis of online personal ads. J Aging Stud. 2013;27(2):159–65.

10. Pordata. Available from: https://www.pordata.pt/Europa/%c3%8dndice+de+envelhecimento-1609. (Accessed 18 August 2021).

11. Pordata. Available from: https://www.pordata.pt/DB/Portugal/Ambiente+de+Consulta/Tabela

(Accessed 03 February 2022).

12. GEP. Relatório De Portugal - Terceiro Ciclo De Revisão E Avaliação Da Estratégia De Implementação Regional (Ris) Do Plano Internacional De Ação De Madrid Sobre O Envelhecimento (Mipaa). 2017;40.

13. Pordata. Available from: https://www.pordata.pt/Glossario (Accessed 20 August 2021).

14. OCDE. European Observatory on Health Systems and Policies, Portugal: Country Health Profile 2019. Available from: https://www.oecd.org/portugal/portugal-country-health-profile-2019-85ed94fc-en.htm (Acessed 1 July 2021). Ocde. 2019;

15. OECD; Systems, E. O. o. H.; Policies, Portugal: Country Health Profile 2017. 2017. Available from: https://www.oecd.org/portugal/portugal-country-health-profile-2019-85ed94fc-en.htm (Accessed 1 July 2021).

16. Burrage DR, Lonsdale E V., Lonsdale DO, Baker E. Prescribing for elderly people. Br J Hosp Med. 2014;75(8):C119–21.

17. Coleman JJ. Drugs and the Elderly. In: Mann's Pharmacovigilance, 3th ed:John Wiley & Sons. 2014. p. 639–58.

18. Kane RL, Ouslander JG AI. Clinical implications of the aging process. In: Essentials of Clinical Geriatrics, 5th ed New York: McGrawHill. 2004. p. 3–15.

19. EJ. M. Physiology of aging. In: Tallis R, Fillit H, eds Brocklehurst's Textbook of Geriatric Medicine, 6th ed London: Churchill Livingstone. 2003. p. 292–9.

20. Martin U, George C. Drugs and the Elderly. In: Pharmacovigilance: John Wiley & Sons Ltd. 2002. 77–96 p.

21. Starner C, Gray S, Guay D, Hajjar S, Hanlon J. Geriatrics. In: Pharmacoterapy a pathophysiologic approach, 8th ed New York: McGrawHill. 2011. p. 57–65.

22. Timiras M, Luxenberg J. Pharmacology and Drug Management in the Elderly. In: Physiological Basis of Aging and Geriatrics,4th ed. 2007. p. 355–61.

23. Cusack BJ. Pharmacokinetics in Older Persons. Am J Geriatr Pharmacother. 2004;2(4):274–302.

24. McLean A, Couteur DGLE. Aging Biology and Geriatric Clinical Pharmacology. Pharmacol Rev. 2004;56(2):163–84.

25. Dubrall D, Just KS, Schmid M, Stingl JC, Sachs B. Adverse drug reactions in older adults: A retrospective comparative analysis of spontaneous reports to the German Federal Institute for Drugs and Medical Devices. BMC Pharmacol Toxicol. 2020;21(1):1–20.

26. Scibona P, Angriman F, Vazquez C, Ferreyro BL, Perelsztein AG, Simonovich VA, et al. Individualization of drug therapy in older people. Rev Clin Gerontol. 2014;24:145–57.

27. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2003;57(1):6–14.

28. Massoud L, Agha H Al, Taleb M. Pharmacokinetic and pharmacodynamic changes in elderly people. WJPMR. 2017;3(11):14–23.

29. Ryan DJ, O'Sullivan F, Jackson SHD. Prescribing medicines for older patients. Med (United Kingdom). 2016;44(7):433–7.

30. Turnheim K. When drug therapy gets old: Pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003;38(8):843–53.

31. Bowie MW, Slattum PW. Pharmacodynamics in Older Adults: A Review. Am J Geriatr Pharmacother. 2007;5(3):263–303.

32. Timiras P. Physiological Basis of Aging and Geriatrics. 4th ed. CRC Press. 2007. 355–360 p.

33. ICH Expert Working Group. ICH Harmonised Tripartite Guideline.Studies in Support of Special Populations : Current. 1993;(June).

34. Van den Akker M, Bunhx F, Knottnerus J. Comorbidity or multimorbidity: what's in a name? A review of the literature. Eur J Gen Pr. 1996;2:65–70.

35. 10-facts-on-ageing-and-health. Available from: https://www.who.int/news-room/fact-sheets/detail/10-facts-on-ageing-and-health. (Accessed 16 july 2021).

36. McLean G, Gunn J, Wyke S, Guthrie B, Watt GCM, Blane DN, et al. The

influence of socioeconomic deprivation on multimorbidity at different ages: A cross-sectional study. Br J Gen Pract. 2014;64(624):440–7.

37. DALYs definition. Available from: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/158 (Accessed 23 August 2021).

38. Xue QL. The Frailty Syndrome: Definition and Natural History. Clin Geriatr Med. 2011;27(1):1–15.

39. Pesante-Pinto JL. Clinical Pharmacology and the Risks of Polypharmacy in the Geriatric Patient. Phys Med Rehabil Clin N Am. 2017;28(4):739–46.

40. Berrut G, De IA, Baeyens J, Bergman H. Promoting acess to innovation for frail old persons. J Nutr Heal Aging. 2013;17(8).

41. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol. 2013;69(3):319–26.

42. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - The elderly. Br J Clin Pharmacol. 2015;80(4):796–807.

43. Toren A, Fowler RA. Eligibility Criteria of Randomized Controlled. 2015;297(11):1233–40.

44. Jaul E, Barron J. Age-Related Diseases and Clinical and Public Health Implications for the 85 Years Old and Over Population. Front Public Heal. 2017;5(December):1–7.

45. Picard N, Nouaille Y, Charmes J-P, Laroche M-L, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? Br J Clin Pharmacol. 2006;63(2):177–86.

46. Bloch F, Thibaud M, Dugué B, Brèque C, Rigaud A. Psychotropic Drugs and Falls in the Elderly People : Updated Literature Review and Meta-Analysis. J Aging Health. 2011;23(2):329–46.

47. Frels C, Williams P, Narayanan S, Gariballa S. Iatrogenic causes of falls in hospitalised elderly patients: a case-control study. Postgr Med J. 2002;78:487–9.

48. Hartikainen S, Lo E, Louhivuori K. Medication as a Risk Factor for Falls : Critical

Systematic Review. J Gerontol. 2007;62(10):1172–81.

49. Sabzwari SR, Qidwai W, Bhanji S. Polypharmacy in elderly: A cautious trail to tread. J Pak Med Assoc. 2013;63(5):624–7.

50. Pilleron S, Sarfati D, Janssen-heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. IJC. 2019;144:49–58.

51. Sneha S, Simhadri K, Subeesh V, Sneha. Predictors of adverse drug reactions in geriatric patients: An exploratory study among cancer patients. South Asian J cancer. 2019;8(3):130–3.

52. Korc-Grodzicki B, Boparai MK LS. Prescribing for older patients with cancer. Clin Adv Hematol Oncol. 2014;12(5):309–18.

53. Shrestha S, Shrestha S, Khanal S. Polypharmacy in elderly cancer patients: Challenges and the way clinical pharmacists can contribute in resource-limited settings. Aging Med. 2019;2(1):42–9.

54. Lavan AH, O'Mahony D, Buckley M, O'Mahony D, Gallagher P. Adverse Drug Reactions in an Oncological Population: Prevalence, Predictability, and Preventability. Oncologist. 2019;24(9):e968–77.

55. Collerton J, Davies K, Jagger C, Kingston A, Bond J, Eccles MP, et al. Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. BMJ. 2009;399:1–11.

56. Butt DA, Harvey PJ. Benefits and risks of antihypertensive medications in the elderly. JOIM. 2015;278:599–626.

57. Fick DM, Semla TP, Steinman M, Beizer J, Brandt N, Dombrowski R, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674–94.

58. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;14(370):173–84.

59. Wilmot KA, Khan A, Krishnan S, Eapen DJ. Statins in the Elderly : A Patient-

Focused Approach. Clin Cardiol. 2015;38(1):56–61.

60. Munshi MN, Maguchi M, Segal AR. Treatment of type 2 diabetes in the elderly. Curr Diab Rep. 2012;12(3):239–45.

61. Soe K, Sacerdote A, Karam J, Bahtiyar G. Management of type 2 diabetes mellitus in the elderly. Maturitas. 2011;70(2):151–9.

62. Musculoskeletal conditions. Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions (Accessed 06 March 2022).

63. Kean WF, Rainsford KD, Kean IRL. Management of chronic musculoskeletal pain in the Elderly: Opinions on oral medication use. Inflammopharmacology. 2008;16(2):53–75.

64. Causes-of-death-among-americans-aged-65-and-older. Available from: https://www.silverbook.org/fact/in-2004-the-leading-causes-of-death-among-americans-aged-65-and-older-were-heart-disease-1418-deaths-18 per-100000/ (Accessed 16 August 2021).

65. Causes of deaths for people who were 70 years and older, World, 2019. Available from: https://ourworldindata.org/grapher/causes-of-death-in-70-year-olds. (Accessed 24 April 2022).

66. Broeiro-Gonçalves P. Morbilidade em Idosos Dependentes ao Cuidado das Equipas Domiciliárias da Rede Nacional de Cuidados Continuados Integrados na Região de Lisboa e Vale do Tejo: Estudo Transversal Observacional. Acta Med Port. 2017;30(7–8):546.

67. Retrato da Saúde 2018. Available from: “https://www.sns.gov.pt/wp-content/uploads/2018/04/RETRATO-DA-SAUDE_2018_compressed.pdf”. (Accessed 16 August 2021).

68. Costa FL da. Como Adoecem os Portugueses - saúde, estilos de vida. Vol. 53. 2020. 1689–1699 p.

69. IDF DIABETES ATLAS 10th edition 2021. Avaialble from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. (Accessed 24 April 2022).

70. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global

and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.

71. Barreto M, Kislaya I, Paula A, Joa A, Boavida M, Antunes L, et al. Prevalence , awareness , treatment and control of diabetes in Portugal : Results from the first National Health examination Survey (INSEF 2015). Diabetes Res Clin Pr. 2018;140:271–8.

72. Raposo JF. Diabetes: Factos e Números 2016, 2017 e 2018. Rev Port Diabetes. 2020;15(1):19–27.

73. Sociedade Portuguesa de Diabetologia. Diabetes: factos e números - OS ANOS DE 2016, 2017 E 2018. 1-64.

74. Chang AM, Halter JB. Aging and insulin secretion. Am J Physiol Endocrinol Metab. 2003;289(4):E7–12.

75. Mordarska K, Godziejewska-zawada M. Diabetes in the elderly. Menopause Rev. 2017;16(2):38–43.

76. Colman E, Katzel LI, Rogus E, Coon P, Muller D, Goldberg AP. Weight loss reduces abdominal fat and improves insulin action in middle-aged and older men with impaired glucose tolerance dietary and weight loss program hyperglycemic clamp protocol. Metabolism. 1995;44(11):1502–8.

77. Sociedade Portuguesa de Diabetologia. Diabetes: Factos e Números – O Ano de 2015. 2016. 1–67 p.

78. Abdelhafiz AH, Sinclair AJ. Management of type 2 diabetes in older people. Diabetes Ther. 2013;4(1):13–26.

79. Valiyeva E, Russell LB, Miller JE, Safford MM. Lifestyle-Related Risk Factors and Risk of Future Nursing Home Admission. Arch Intern Med. 2006;166:985–90.

80. Moghissi E. Management of Type 2 Diabetes Mellitus in Older Patients : Current and Emerging Treatment Options. Diabetes Ther. 2013;4:239–56.

81. Schernthaner G, Grimaldi A, Mario U Di, Drzewoski J, Kempler P, Kvapil M, et al. GUIDE study : double-blind comparison of once-daily gliclazide MR and

glimepiride in type 2 diabetic patients. Eur J Clin Investig. 2004;34(June):535–42.

82. Prado M, Francisco P, Barros M. Diabetes in the elderly : drug use and the risk of drug interaction. Cien Saude Colet. 2016;21(11):3447–58.

83. Pathak RD, Schroeder EB, Seaquist ER, Zeng C, Lafata JE, Thomas A, et al. Severe hypoglycemia requiring medical intervention in a large cohort of adults with diabetes receiving care in U.S. integrated health care delivery systems: 2005-2011. Diabetes Care. 2016;39(3):363–70.

84. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012;1:1–15.

85. Nanjan MJ, Mohammed M, Kumar BRP, Chandrasekar MJN. Bioorganic Chemistry Thiazolidinediones as antidiabetic agents : A critical review. Bioorg Chem. 2018;77:548–67.

86. Mima A. Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Non-Diabetic Chronic Kidney Disease. Adv Ther. 2021;38(5):2201–12.

87. Alicic RZ, Neumiller JJ, Johnson EJ, Dieter B, Tuttle KR. Sodium – Glucose Cotransporter 2 Inhibition and Diabetic Kidney Disease. Diabetes. 2019;68(February):248–57.

88. Tanwani LK. Insulin therapy in the elderly patient with diabetes. Am J Geriatr Pharmacother. 2011;9(1):24–36.

89. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: Risk of hypoglycemia and strategies for care. JAGS. 2012;60(8):1564–70.

90. Marks J. Insulin analogues. Postgrad Med. 2002;112(5 Suppl Designer):8–12.

91. Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with Type 1 diabetes. Diabet Med. 2003;20(8):626–34.

92. Mooradian AD. Special considerations with insulin therapy in older adults with diabetes mellitus. Drugs and Aging. 2011;28(6):429–38.

93. Dunn CJ, Plosker GL. Insulin lispro: A pharmacoeconomic review of its use in

diabetes mellitus. Pharmacoeconomics. 2002;20(14):989–1025.

94. Sebastião É, Christofoletti G, Gobbi S, Hamanaka ÁYY. Atividade física e doenças crônicas em idosos de Rio Claro-SP. Motriz, Rio Claro. 2008;14(4):381–8.

95. Antonio da Silva N, Carolina de Oliveira Silva Montandon A, Vasconcelos da Silva Prado Cabral M. Doenças osteoarticulares degenerativas periféricas Peripheral degenerative joint diseases. Einstein. 2008;6(Supl 1):21–8.

96. Andrade, F. A., Pereira, L. V. & Sousa F. Mensuração da dor no idoso. Rev Latino-am Enferm. 2006;14(2):271–6.

97. Wieland HA, Michaelis M, Kirschbaum BJ, Rudolphi KA. Osteoarthritis - An untreatable disease? Nat Rev Drug Discov. 2005;4(4):331–44.

98. Swedberg JA SJ. Osteoarthritis. Am Fam Physician. 1992;45(2):557-68.

99. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip and Knee. Arthritis Rheumatol. 2020;72(2):220–33.

100. Artrite reumatoide. Available from: https://spreumatologia.pt/artrite-reumatoide/(Accessed 24 August 2021).

101. Narváez J. Tratamiento de la artritis reumatoide. Med Clin (Barc). 2016;147(4):176–80.

102. Benjamin O, Bansal P, Goyal A, et al. Disease Modifying Anti-Rheumatic Drugs (DMARD) [Updated 2021 Jul 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507863/.

103. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The Diagnosis of Osteoporosis. J Bone Miner Res. 1994;9(8):1137–41.

104. Srivastava M, Deal C. Osteoporosis in elderly: Prevention and treatment. Clin Geriatr Med. 2002;18(3):529–55.

105. Hughes B, Harris S, Krall E, G D. Effect of Calcium and Vitamin D

supplementation on Bone Density in Men and Women 65 years of age or Older. N Engl J Med. 1997;10:670–6.

106. U A Liberman, S R Weiss, J Bröll, H W Minne, H Quan, N H Bell, J Rodriguez-Portales, R W Downs Jr, J Dequeker MF. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med. 1995;333(22):1437–43.

107. Wehling M. Non-steroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: Management and mitigation of risks and adverse effects. Eur J Clin Pharmacol. 2014;70(10):1159–72.

108. Dray A, Urban L, Dickenson A. Pharmacology of chronic pain. Trends Pharmacol Sci. 1994;15:190–7.

109. Schwan J, Sclafani J, Tawfik V. Chronic Pain Management in the Elderly. Anesth Clin. 2019;37(3):547–60.

110. Ray AD. Inflammatory mediators of pain. Br J Anaesth. 1995;75:125–31.

111. Widgerow AD. Cellular resolution of inflammation - Catabasis. Wound Repair Regen. 2012;20:2–7.

112. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006;8(2):1–6.

113. Frenzel L, Hermine O. Mast cells and inflammation. Jt Bone Spine. 2013;80(2):141–5.

114. Francischetti I, Moreno J, Scholz M, Yoshida W. Leukocytes and the inflammatory response in ischemia-reperfusion injury. Rev Bras Cir Cardiovasc 2010; 2010;25(4):575–84.

115. Sallusto F, Baggiolini M. Chemokines and leukocyte traffic. Nat Immunol. 2008;9(9):949–52.

116. Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil Function: From Mechanisms to Disease. Rev Bras Cir Cardiovasc 2010; 2012;30:459–89.

117. Coleman R, Smith W, Narumiya S. International Union of Pharmacology Classification of Prostanoid Receptors : Properties, Distribution , and Structure of the Receptors and Their Subtypes. Pharmacol Rev. 1994;46(2):205–29.

118. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci U S A. 1993;90(24):11693–7.

119. Bacchi S, Palumbo P, Sponta A, Coppolino MF. Clinical Pharmacology of Non-Steroidal Anti-Inflammatory Drugs : A Review. Antiinflamm Antiallergy Agents Med Chem. 2012;11:52–64.

120. Mantzoukis D, Pitsariotis T, Dourakis SP, Archimandritis AJ, Alexopoulou A, Deutsch M, et al. Adverse drug reactions as a cause of hospital admissions: A 6-month experience in a single center in Greece. Eur J Intern Med. 2008;19(7):505–10.

121. Infomed. Available from: https://extranet.infarmed.pt/INFOMED-fo/pesquisa-avancada.xhtml (Accessed 06 February 2022).

122. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging Dis. 2018;9(1):143–50.

123. Pilotto A, Sancarlo D, Addante F, Scarcelli C, Franceschi M. Non-steroidal anti-inflammatory drug use in the elderly. Surg Oncol. 2010;19(3):167–72.

124. Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf. 2009;8(6):669–81.

125. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015;26(4):285–91.

126. Shimp L. Safety Issues in the Pharmacologic Management of Chronic Pain in the Elderly. In: Pharmacoterapy vol 18, number 6. 1998. p. 1313–22.

127. Schmidt M, Lamberts M, Olsen AS, Fosbøll E, Niessner A, Tamargo J, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs : review and position paper by the working group for Cardiovascular

Pharmacotherapy of the European Society of Cardiology. Eur Heart J. 2016;16:1–11.

128. Mccarberg BH. NSAIDs in the older patient: Balancing benefits and harms. Pain Med (United States). 2013;14(SUPPL1):43–4.

129. Petrovic M, Cammen T Van Der, Onder G. Adverse Drug Reactions in Older People. Drug Aging. 2012;29(6):453–62.

130. Dovjak P. Polypharmacy in elderly people. Wiener Medizinische Wochenschrift. 2022;172:109–13.

131. Vandraas KF, Spigset O, Mahic M, Slørdal L. Non-steroidal anti-inflammatory drugs: Use and co-treatment with potentially interacting medications in the elderly. Eur J Clin Pharmacol. 2010;66(8):823–9.

132. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7(1):11–22.

133. Tesfaye Z, Nedi T. Potential drug – drug interactions in inpatients treated at the Internal Medicine ward of Tikur Anbessa Specialized Hospital. Drug Healthc Patient Saf. 2017;9:71–6.

134. Snowden A. Medication management in older adults: a critique of concordance. Br J Nurs. 2016;17(2):114–9.

135. Laroche M, Charmes J, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly ? Br J Clin Pharmacol. 2006;63(2):177–86.

136. Gallagher P, Baeyens J, Topinkova E, Madlova P, Cherubini A, Gasperini B, et al. Inter-rater reliability of STOPP (Screening Tool of Older Persons ' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria amongst physicians in six European countries. Age Ageing. 2009;603–6.

137. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet. 2007;370(14):173–84.

138. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the Risk of Adverse Drug Events in Older Adults. AFP. 2013;87(5):331–6.

139. Paci J, Alfaro M, Alonso F, San- Martín M. Prescripción inadecuada en pacientes polimedicados mayores de 64 años en atención primaria. Aten Primaria. 2015;47(1):38–47.

140. Silva C, Ramalho C, Luz I, Monteiro J, Fresco P. Drug-related problems in institutionalized, polymedicated elderly patients : opportunities for pharmacist intervention. Int J Clin Pharmacol. 2015;37:327–34.

141. Galli TB, Reis WCT, Andrzejevski VMS. Potentially inappropriate prescribing and the risk of adverse drug reactions in critically ill older adults. Pharm Pract (Granada). 2016;14(4):1–7.

142. Montastruc F, Duguet C, Rousseau V, Bagheri H, Montastruc JL. Potentially inappropriate medications and adverse drug reactions in the elderly: A study in a PharmacoVigilance database. Eur J Clin Pharmacol. 2014;70(9):1123–7.

143. Gomes D, Gomes E, Ribeiro-Vaz I, Herdeiro MT, Roque F. Pharmacovigilance in Older Adults. In: Intech [Internet]. 2021. p. 1–15. Available from: https://www.intechopen.com/books/advanced-biometric-technologies/liveness-detection-in-biometrics

144. Turner G, Clegg A. Best practice guidelines for the management of frailty : a British Geriatrics Society , Age UK and Royal College of General Practitioners report. Age Ageing. 2014;43:744–7.

145. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to RightTreatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.

146. O´Mahony D, O´Sullivan D, Byrne S, O´Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people : version 2. Age Ageing. 2014;0:1–6.

147. Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: A randomised controlled study. Drugs and Aging. 2014;

148. Salbu RL, Feuer J. A Closer Look at the 2015 Beers Criteria. J Pharm Pract. 2017;30(4):419–24.

149. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: A list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015;71:861–75.

150. Monteiro C, Canário C, Ribeiro MÂ, Duarte AP, Alves G. Medication evaluation in Portuguese elderly patients according to beers, stopp/start criteria and EU(7)-PIM list – an exploratory study. Patient Prefer Adherence. 2020;14:795–802.

151. EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). Available from: https://www.ema.europa.eu/documents/regulatory-procedural-guidel.

152. Edwards IR, Aronson JK. Adverse drug reactions : definitions , diagnosis , and management. Lancet. 2000;356(7):1255–9.

153. Rohilla A, Yadav S. Adverse drug reactions: An Overview. IJPR. 2013;03(01):10–2.

154. Aronson JK, Ferner RE. Joining the DoTS : new approach to classifying adverse drug reactions. BMJ. 2003;327(November):1222–5.

155. Cressman AM, Petrovic V, Piquette-Miller M. Inflammation-mediated changes in drug transporter expression/activity: Implications for therapeutic drug response. Expert Rev Clin Pharmacol. 2012;5(1):69–89.

156. Nagaraju K, Manasa S, Manjunath R. Pharmacovigilance study in geriatric population. Asian J Pharm Clin Res. 2015;8(2):395–9.

157. Lattanzio F, Laino I, Pedone C, Corica F, Maltese G, Salerno G, et al. Geriatric conditions and adverse drug reactions in elderly hospitalized patients. J Am Med Dir Assoc. 2012;13(2):96–9.

158. Lazarou J, Pomeranz BH, Corey PN. Incidence of Adverse Drug Reactions in Hospitalized Patients. Jama. 1998;279(15):1200–5.

159. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol. 2001;2(6):349–51.

160. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57–65.

161. Furlan G, Caduff-Janosa P, Sottosanti L, Cappello E, Valdiserra G, Tuccori M. Drug Safety in Geriatric Patients: Current Status and Proposed Way Forward. Drug Saf. 2020;43(9):853–66.

162. Pedrós C, Formiga F, Corbella X, Arnau JM. Adverse drug reactions leading to urgent hospital admission in an elderly population: Prevalence and main features. Eur J Clin Pharmacol. 2016;72(2):219–26.

163. Farmacovigilância. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso humano/ farmacovigilancia (Accessed 26 August 2021).

164. Monteiro C, Duarte AP, Alves G. Adverse drug reactions in elderly: a five-year review of spontaneous reports to the Portuguese Pharmacovigilance System. Expert Opin Drug Saf. 2021;20(1):109–18.

165. Coronavirus disease (COVID-19) pandemic. Available from: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/novel-coronavirus-2019-ncov (Accessed 06 March 2022).

166. Geer MI, Koul PA, Tanki SA, Shah MY. Frequency, types, severity, preventability and costs of Adverse Drug Reactions at a tertiary care hospital. J Pharmacol Toxicol Methods. 2016;81:323–34.

167. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73:759–70.

168. Rottenkolber D, Schmiedi S, Rottenkolber M, Farker K, Al E. Adverse drug reactions in Germany: direct costs of internal medicine hospitalizations. Pharmacoepidemiol Drug Saf. 2011;20:626–34.

169. Nair NP, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions – the need for a prediction tool. Clin Interv Aging. 2016;11:497–505.

170. Pirmohamed M, James S, Meakin S, Green C, Scott AK W, TJ et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18, 820 patients. BMJ. 2004;329:15–9.

171. Marengoni A, Pasina L, Concoreggi C, Martini G, Brognoli F, Nobili A, et al. Understanding adverse drug reactions in older adults through drug-drug

interactions. Eur J Intern Med. 2014;25(9):843–6.

172. Beijer HJM, De Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): A meta-analysis of observational studies. Pharm World Sci. 2002;24(2):46–54.

173. Sousa-pinto B, Marques B, Lopes F, Freitas A. Frequency and Impact of Adverse Events in Inpatients : A Nationwide Analysis of Episodes between 2000 and 2015. J Med Syst. 2018;42:1–9.

174. Pharmacovigilance-overview. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview. (Accessed 18 August 2021).

175. Uppsala Monitoring Centre. Available from: https://www.who-umc.org/about-us/who-we-are/ (Accessed 18 August 2021).

176. Pego A, Al E. Farmacovigilância em Portugal: 25 anos. 2018. 55–62 p.

177. Ministério da Saúde. Despacho Normativo nº107/92 [Internet]. Diário da República n.º 146/1992, Série I-B de 1992-06-27. 1992. p. 3060–3060. Available from: https://dre.pt/application/file/98865

178. Canedo F, Rodrigues H. Editorial Restruturação do Sistema Nacional de Farmacovigilância Unidades Regionais de Farmacovigilância. Bol Farm. 2017;21(2):1–4.

179. União Europeia. Diretiva 2012/26/UE do Parlamento Europeu e do Conselho de 25 de outubro de 2012 que altera a Diretiva 2001/83/CE no que diz respeito à farmacovigilância. J Of da União Eur [Internet]. 2012;2012(4):1–4. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2012_26/dir_2012_26_pt.pdf

180. European Medicines Agency. Human Medicines Division EMA pharmacovigilance system manual. 2021;31(March):1–28.

181. Biagi C, Montanaro N, Buccellato E, Roberto G, Vaccheri A, Motola D. Underreporting in pharmacovigilance: an intervention for Italian GPs (Emilia – Romagna region). Eu J Clin Pharmacol. 2013;69:237–44.

182. Hazell L, Shakir SAW. Under-Reporting of Adverse A Systematic Review. Drug

Saf. 2006;29(5):385–96.

183. Lopez-Gonzalez E, Herdeiro M, Figueira A. Determinants of Under-Reporting of Adverse Drug Reactions. A Systematic Review. Drug Saf. 2009;32(1):19–31.

184. European Medicines Agency. EMA. Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-ix-signal-management-rev-1_en.pdf. Eur Med Agency. 2017;44(April):1–6.

185. Beninger P. Signal Management in Pharmacovigilance : A Review of Activities and Case Studies. Clin Ther. 2020;42(6):1110–29.

186. Benefit-risk management. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk- management-plans. (Accessed 12 September 2021).

187. Gehlbach SH. Interpreting the Medical Literature 5rd ed. New York: McGraw-Hill, Inc. 2006.

188. Edwards IR. Causality Assessment in Pharmacovigilance : Still a Challenge. Drug Saf. 2017;40(5):365–72.

189. Arimone Y, Miremont-salame G, Moore N, Fourrier-re A. Comparison of Three Methods (Consensual Expert Judgement, Algorithmic and Probabilistic Approaches) of Causality Assessment of Adverse Drug Reactions. Drug Saf. 2010;33(11):1045–54.

190. Macedo AF, Marques FB, Ribeiro CF. Can Decisional Algorithms Replace Global Introspection in the Individual Causality Assessment of Spontaneously Reported ADRs ? Drug Saf. 2006;29(8):697–702.

191. Causality assessment. Available from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf (Accessed 01 February 2022).

192. Desnoyer A, Guignard B, Lang PO, Desmeules J, Vogt-Ferrier N, Bonnabry P. Prescriptions médicamenteuses potentiellement inappropriées en gériatrie: quels outils utiliser pour les détecter? Press Medicale. 2016;1–14.

193. European Medicines Agency. EMA geriatric medicines strategy. Eur Med Agency. 2015;44(February 2011):1–3.

194. Guidance for including elderly patients in clinical trials | Cambridge Cognition Available from: https://www. cambridgecognition.com/blog/entry/guidance-for-including-elderlypatients- in-clinical-trials. (Accessed 26 August 2021).

195. Herrera AP, Snipes SA, King DW, Torres-Vigil I, Goldberg DS, Wenberg AD. Disparate inclusion of older adults in clinical trials: priorities and opportunities for policy and practice change. Am J Public Health. 2010;100(SUPPL. 1):105–12.

196. Moreno-john G, Fleming CM, Nápoles-springer A. Ethnic minority older adults participating in clinical research: developing trust. J Aging Heal. 2004;16(5):93–123.

197. Lee SD, Gazmararian JA. Health Literacy and Social Support Among Elderly Medicare Enrollees in a Managed Care Plan. JAG. 2006;25(4):324–37.

198. Mangoni AA, Jansen PA, Jackson SHD. Under-representation of older adults in pharmacokinetic and pharmacodynamic studies: A solvable problem? Expert Rev Clin Pharmacol. 2013;6(1):35–9.

199. Watts G. Why the exclusion of older people from clinical research must stop. BMJ. 2012;344(7858):3–5.

200. Stegema S. Patient Reported Outcomes in Clinical Trials and Practice with Older Patients. In: Developing Drug Products in na Aging Society From Concept to Prescribing, 1st ed:Springer. 2016. p129-138.

201. Medicines-older-people. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/medicines-older-people#geriatric-medicines-strategy-section. (Accessed 18 August 2021).

202. Frank C, Weir E. Deprescribing for older patients. CMAJ. 2014;186(18):1369–76.

203. Lavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly patients with multimorbidity. Clin Interv Aging. 2016;11:857–66.

204. Onder G. Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older. Am Med Assoc 2010.

2015;170(13):1142–8.

205. Tangiisuran, B. (2009) Predicting adverse drug reactions in the hospitalised elderly. PhD thesis,University of Sussex, Brighton.

206. McElnay JC, McCallion CR, Al-Deagi F, Scott MG. Development of a risk model for adverse drug events in the elderly. Clin Drug Investig. 1997;13(1):47–55.

207. Trivalle C, Burlaud A, Ducimetière P. Risk factors for adverse drug events in hospitalized elderly patients: A geriatric score. Eur Geriatr Med. 2011;2(5):284–9.

208. Stevenson JM, Williams JL, Burnham TG, Prevost AT, Schiff R, Erskine SD, et al. Predicting adverse drug reactions in older adults; A systematic review of the risk prediction models. Clin Interv Aging. 2014;9:1581–93.

209. National Institute of Statistic. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0001272&xlang=pt&contexto=bd&selTab=tab2 (Accessed 10 January 2019).

210. Shi S, Mörike K, Klotz U. The clinical implications of ageing for rational drug therapy. Eur J Clin Pharmacol. 2008;64(2):183–99.

211. Wu C, Bell CM, Wodchis WP. Incidence and Economic Burden of Adverse Drug Reactions among Elderly Patients in Ontario Emergency Departments. Drug Saf. 2012;35(9):769–81.

212. Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing. 2000;29(1):35–9.

213. Ma J, Wang Y, Gao M, Meng Q, Liu J. Adverse drug reactions as the cause of emergency department admission of patients aged 80 years and older. Eur J Intern Med. 2012;23(6):e162–3.

214. Bouvy JC, Bruin ML De, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe : A Review of Recent Observational Studies. Drug Saf. 2015;437–53.

215. EMA. Guideline on good pharmacovigilance practices (GV) Module VI-

addendum-I-duplicate-management-suspected. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-a.

216. Worl Heath Organization. The Uppsala Monitoring Centre, Uppsala. Available from: https://www.who-umc.org/. (Accessed 04 September 2019).

217. Important medical event terms list (MedDRA version 21.1) Available from: https://www.ema.europa.eu/en/documents/other/important-medical-event-terms-list-version-meddra-version-221_en.xls important-medical-event-terms. (Accessed 25 September 2019).

218. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2018. Available from: https://www.whocc.no/atc_ddd_index/. (Accessed 30 August 2019).

219. Lakhal M, El Aïdli S, Charfi R, Zaïem A, Daghfous R, Sraïri S, et al. Serious Adverse Drug Reactions in Older Adults Notified to Pharmacovigilance. Therapie. 2012;67(5):465–70.

220. Lakhal M, Charfi R, Daghfous R, Zaïem A, El Aïdli S, Sraïri S, et al. Adverse Drug Reactions in Older Adults: a Retrospective Study from Pharmacovigilance. Therapie. 2012;67(5):471–6.

221. Michenot F, Somme A, Bagheri H, Lapeyre M, Montastruc JL. Adverse drug reactions in patients older than 70 years during the heat wave occurred in France in summer 2003: a study from the French PharmacoVigilance Database. Pharmacoepidemiol Drug Saf. 2006;15(August):735–40.

222. Chisaki Y, Aoji S, Yano Y. Analysis of Adverse Drug Reaction Risk in Elderly Patients Using the Japanese Adverse Drug Event Report (JADER) Database. Biol Pharm Bull. 2017;40(6):824–9.

223. National Institute of Statistics. Available from : https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0001223&xlang=pt&contexto=bd&selTab=tab2. (Accessed 30 January 2019).

224. Giofre C, Scicchitano F, Palleria C, Mazzitello C, Ciriaco M, Gallelli L, et al. Pharmacovigilance and drug safety in Calabria (Italy): 2012 adverse events

analysis. J Pharmacol Pharmacother. 2013;4((Suppl 1)):S55-60.

225. Leone R, Sottosanti L, Luisa Iorio M, Santuccio C, Conforti A, Sabatini V, Moretti U VM. Drug-related deaths: an analysis of the Italian spontaneous reporting database. Drug Saf. 2008;31(8):703–13.

226. Kopečná E, Descikova V, Vlček J, Mladá J. Adverse drug reaction reporting in the Czech Republic 2005-2009. Int J Clin Pharm. 2011;33(4):683–9.

227. Scicchitano F, Giofrè C, Palleria C, Mazzitello C, Ciriaco M, Gallelli L, et al. Pharmacovigilance and drug safety 2011 in Calabria (Italy): Adverse events analysis. J Res Med Sci. 2012;17(9):872-5.

228. Anderson GD. Gender differences in pharmacological response. Int Rev Neurobiol. 2008;83:1–10.

229. Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine. 2019;17:100188.

230. Ferreira R. Consumo crónico de medicamentos na população de um centro de saúde. Rev Port Med Geral e Fam. 2007;23(2):125–32.

231. Marques J, Ribeiro-Vaz I, Pereira AC, Polónia J. A survey of spontaneous reporting of adverse drug reactions in 10 years of activity in a pharmacovigilance centre in Portugal. Int J Pharm Pract. 2014;22(4):275–82.

232. Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.

233. Edwards I. Considerations on causality in pharmacovigilance. Int J Risk Saf Med. 2012;24(1):41–54.

234. Fülöp T, Larbi A, Dupuis G PG. Ageing, autoimmunity and arthritis: Perturbations of TCR signal transduction pathways with ageing - a biochemical paradigm for the ageing immune system. Arthritis Res Ther. 2003;5(6):290–302.

235. Mukherjee K, Burruss S, Brooks S, Addison M. Managing Infectious Disease in the Critically Ill Elderly Patient. Curr Geriatr Reports. 2019;8(3):pp 180–193.

236. Ittisanyakorn M, Ruchichanantakul S, Vanichkulbodee A, Sri-on J. Prevalence and factors associated with one-year mortality of infectious diseases among elderly emergency department patients in a middle-income country. BMC Infect Dis. 2019;662:1–10.

237. Cill C, Domined C, Ielpo A, Ferrer M, Gabarrús A, Battaglini D, et al. Risk and Prognostic Factors in Very Old Patients with Sepsis Secondary to Community-Acquired Pneumonia. J Clin Med. 2019;8(961):1–12.

238. Gijn M, Fijns D, Gund E, Munster B, Hamaker M. The chance of survival and the functional outcome after in-hospital cardiopulmonary resuscitation in older people : a systematic review. Age Ageing. 2014;43(April):456–63.

239. Suh DC, Woodall BS, Shin SK H-DSE. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother. 2000;34(12):1373-9.

240. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol. 2004;57(2):121–6.

241. Sonawane KB, Cheng N, Hansen R. Serious Adverse Drug Events Reported to the FDA : Analysis of the FDA Adverse Event Reporting System 2006-2014 Database. J Manag Care Spec Pharm. 2018;24(7):682–90.

242. Tarekegn M, Leanne A, Colin C. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries : A Review of Prevalence and Contributing Factors. Drug Saf. 2016;39(9):847–57.

243. Tiaden JD, Wenzel E, Berthold HK M-OB. Adverse reactions to anticoagulants and to antiplatelet drugs recorded by the German spontaneous reporting system. Semin Thromb Hemos. 2005;31(4):371–80.

244. Wester K, Jönsson A, Spigset O HS. Spontaneously reported fatal suspected adverse drug reactions: a 10-year survey from Sweden. Pharmacoepidemiol Drug Saf 2007. 2007;16(2):173–80.

245. Chyka P. How many deaths occur annually from adverse drug reactions in the United States? Am J Med. 2000;109:122–30.

246. Baldo P, Fornasier G, Ciolfi L, Sartor I, Francescon S. Pharmacovigilance in oncology. Int J Clin Pharm. 2018;40(4):832–41.

247. Rowley WR, Bezold C, Arikan Y. Diabetes 2030: Insights from Yesterday, Today, and Future Trends. Popul Health Manag. 2017;20(1):6–12.

248. Waldeyer R, Brinks R, Rathmann W, Giani G, Icks A. Projection of the burden of Type 2 diabetes mellitus in Germany : a demographic modelling approach to estimate the direct medical excess costs from 2010 to 2040. Diabet Med. 2013;30:999–1008.

249. Gardete- Correia L, Boavida JM, Raposo JF, Mesquita AC, Fona C, Carvalho R, et al. First diabetes prevalence study in Portugal : PREVADIAB study. Diabet Med. 2010;27:879–81.

250. Kirkman M, Briscoe V, Clark N, Florez H, Haas L, Halter J, et al. Diabetes in Older Adults. Diabetes Care. 2012;35:2650–64.

251. Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting. Diabetes Care. 2011;34:1369–71.

252. Srinivasan BT, Davies M. Glycaemic management of type 2 diabetes. Med (United Kingdom). 2019;47(1):32–9.

253. Kuijpers MAJ, Marum RJ Van, Egberts ACG, Jansen PAF, Oldy T. Relationship between polypharmacy and underprescribing. BJCP. 2007;65(1):130–3.

254. Desouza C, Bolli G, Fonseca V. Hypoglycemia, Diabetes, and Cardiovascular Events. Diabetes Care. 2010;33(6):1389–94.

255. Bonds DE, Miller ME, Bergenstal RM, Al E. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ. 2010;340(b4909):1–9.

256. Ghouse J, Isaksen JL, Skov MW, Lind B, Svendsen JH, Kanters JK, et al. Effect of diabetes duration on the relationship between glycaemic control and risk of death in older adults with type 2 diabetes. Diabetes Obes Metab. 2019;1–12.

257. Huang W, Castelino RL, Peterson GM. Adverse event notifications implicating metformin with lactic acidosis in Australia. J Diabetes Complications. 2015;29(8):1261–5.

258. Raschi E, Parisotto M, Forcesi E, Placa M La, Marchesini G, Ponti F De. Adverse events with sodium-glucose co-transporter-2 inhibitors: A global analysis of international spontaneous reporting system. Nutr Metab Cardiovasc Dis. 2017;27(12):1098–107.

259. National Institute of Statistic. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&contecto=pi&indOcorrCod=0008258&selTab=tab0 (Accessed 30 December 2020).

260. Sousa J, Monteiro C, Taborda-Barata L. Biological therapy-associated adverse reactions in asthma: analysis of reporting to the Portuguese pharmacovigilance system pharmacovigilance system Biological therapy-associated adverse reactions in asthma : analysis of reporting to. Expert Opin Drug Saf. 2020;19(1):99–106.

261. Gonçalves C, Monteiro C, Santos JL. Suspected Adverse Drug Reactions From Corticosteroids: J Clin Pharmacol. 2020;60(10):1367–75.

262. Torre C, Guerreiro J, Longo P, Raposo JF, Leufkens H, Martins AP. Intensive monitoring of adverse drug events associated with the use of new glucose-lowering drugs : results from an inception cohort study in Portugal. Diabet Med. 2019;37:648–56.

263. Handelsman Y, Chovanes C, Dex T, Giorgino F, Skolnik N, Souhami E, et al. Efficacy and safety of insulin glargine/lixisenatide (iGlarLixi) fixed-ratio combination in older adults with type 2 diabetes. J Diabetes Complications. 2019;33(3):236–42.

264. Chelliah A, Burge MR. Hypoglycaemia in Elderly Patients with Diabetes Mellitus Causes and Strategies for Prevention. Drugs Aging. 2004;21(8):511–30.

265. Lalau J, Pharmd FK, Protti A, Christensen MM, Broe ME De, Wiernsperger N. Metformin-associated lactic acidosis (MALA): Moving towards a new paradigm. Diabetes Obes Metab. 2017;19:1502–12.

266. Lipska K, Bailey C, Inzucchi S. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care. 2011;34:1431–7.

267. Gomez-Peralta F, Abreu C, Gomez-Rodriguez S, Barranco R, Umpierrez G. Safety and Efficacy of DPP4 Inhibitor and Basal Insulin in Type 2 Diabetes : An

Updated Review and Challenging Clinical Scenarios. Diabetes Ther. 2018;9:1775–89.

268. Nishi T, Yasui M, Imatoh T, Saito Y, Une H, Babazono A. Association between dipeptidyl peptidase - 4 inhibitors and urinary tract infection in elderly patients : A retrospective cohort study. Pharmacoepidemiol Drug Saf. 2018;27:931–9.

269. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus : A review of pathogenesis. Indian J Endocrinol Metab. 2012;16:27–36.

270. Gregg E, Yanfebg L, Wang J, Burrows NR, Ali MK, Ch B, et al. Changes in Diabetes-Related Complications in the United States, 1990–2010. N Engl J Med. 2014;370(16):1514–23.

271. Cooper C, Chapurlat R, Al-Daghri N, Herrero-Beaumont G, Bruyère O, Rannou F, et al. Safety of Oral Non-Selective Non-Steroidal Anti-Inflammatory Drugs in Osteoarthritis: What Does the Literature Say? Drugs and Aging. 2019;36(s1):15–24.

272. McDonald DD. Predictors of gastrointestinal bleeding in older persons taking nonsteroidal anti-inflammatory drugs: Results from the FDA adverse events reporting system. J Am Assoc Nurse Pract. 2019;31(3):206–13.

273. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–46.

274. Bahadur S, Keshri L, Pathak K. Adverse Drug Reactions and Safety Considerations of NSAIDs: Clinical Analysis. Curr Drug Saf. 2011;6(5):310–7.

275. Hughes CM, Cadogan CA, Patton D, Ryan CA. Pharmaceutical strategies towards optimising polypharmacy in older people. Int J Pharm. 2016;502(2):360–5.

276. Carroll CB, Zajicek JP. Designing clinical trials in older people. Maturitas. 2011;68(4):337–41.

277. Barkin RL, Beckerman M, Blum SL, Clark FM, Koh EK, Wu DS. Should Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) be prescribed to the older adult? Drugs Aging. 2010;27(10):775–89.

278. Modig S, Elmståhl S. Kidney function and use of nonsteroidal anti-inflammatory

drugs among elderly people: a cross-sectional study on potential hazards for an at risk population. Int J Clin Pharm. 2018;40(4):870–7.

279. Medlock S, Eslami S, Askari M, Taherzadeh Z, Opondo D, de Rooij SE, et al. Co-prescription of gastroprotective agents and their efficacy in elderly patients taking nonsteroidal anti-inflammatory drugs: A systematic review of observational studies. Clin Gastroenterol Hepatol. 2013;11(10):1259-1269.e10.

280. Makris U. Adverse Effects (AEs) of Topical NSAIDs in Older Adults with Osteoarthritis (OA): a Systematic Review of the Literature. J Rheumatol. 2010;37(6):1236–43.

281. Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. CMAJ. 2004;171(9):1027–8.

282. EMA. European Medicines Agency recommends withdrawal of the marketing authorisations for lumiracoxib-containing medicines. Doc. Ref. EMEA/CHMP/579301/2007 PRESS. 13 December 2007. Available from: https://www.ema.europa.eu/en/news/european-medicines-agency.

283. Introductory Guide MedDRA Version 22.1, (September 2019). Available from: https://www.meddra.org/sites/default/files/guidance/file/000354_intguide_22.1.pdf. (Accessed 28 February 2020).

284. Worl Heath Organization. The Uppsala Monitoring Centre, Uppsala. Available from: https://www.who-umc.org/. (Accessed 04 march 2020).

285. Couto A, Troullos E, Moon J, Paredes-Diaz A, An R. Analgesic efficacy and safety of non-prescription doses of naproxen sodium in the management of moderate osteoarthritis of the knee or hip. Curr Med Res Opin. 2018;34(10):1747–53.

286. Chelly JE, Lacouture PG, Reyes CRD. Safety of Injectable HPβCD-Diclofenac in Older Patients with Acute Moderate-to-Severe Postoperative Pain: A Pooled Analysis of Three Phase III Trials. Drugs and Aging. 2018;35(3):249–59.

287. Bakhriansyah M, Souverein PC, de Boer A, Klungel OH. Gastrointestinal toxicity among patients taking selective COX-2 inhibitors or conventional NSAIDs, alone or combined with proton pump inhibitors: a case–control study. Pharmacoepidemiol Drug Saf. 2017;26(10):1141–8.

288. Hirayama A, Tanahashi N, Daida H, Ishiguro N, Chachin M, Sugioka T, et al.

Assessing the cardiovascular risk between celecoxib and nonselective nonsteroidal antiinflammatory drugs in patients with rheumatoid arthritis and osteoarthritis - A 3-year nationwide comparative observational study in Japan (ACCEPT) -. Circ J. 2014;78(1):194–205.

289. Chelly JE, Singla SK, Melson TI, Lacouture PG, Paadre S, Carr DB. Safety of a Novel Parenteral Formulation of Diclofenac after Major Orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial. Pain Med (United States). 2013;14(5):749–61.

290. Kellner HL, Li C, Essex MN. Efficacy and safety of celecoxib versus diclofenac and omeprazole in elderly arthritis patients: A subgroup analysis of the CONDOR trial. Curr Med Res Opin. 2012;28(9):1537–45.

291. Roth SH, Fuller P. Pooled safety analysis of diclofenac sodium topical solution 1.5% (w/w) in the treatment of osteoarthritis in patients aged 75 years or older. Clin Interv Aging. 2012;7:127–37.

292. Baraf HSB, Gold MS, Petruschke RA, Wieman MS. Tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. Am J Geriatr Pharmacother. 2011;10(1):47–60.

293. Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. Aliment Pharmacol Ther. 2010;32(10):1240–8.

294. Turajane T, Wongbunnak R, Patcharatrakul T, Ratansumawong K, Poigampetch Y, Songpatanasilp T. Gastrointestinal and cardiovascular risk of non-selective NSAIDs and COX-2 inhibitors in elderly patients with knee osteoarthritis. J Med Assoc Thai 2009; 2009;92(6):S19-26.

295. Laine L, Curtis SP, Langman M, Jensen DM, Cryer B, Kaur A, et al. Lower Gastrointestinal Events in a Double-Blind Trial of the Cyclo-Oxygenase-2 Selective Inhibitor Etoricoxib and the Traditional Nonsteroidal Anti-Inflammatory Drug Diclofenac. Gastroenterology. 2008;135(5):1517–25.

296. Rahme E, Bardou M, Dasgupta K, Toubouti Y, Ghosn J, Barkun AN. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: A

retrospective cohort study. Rheumatology. 2007;46(2):265–72.

297. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet. 2006;368(9549):1771–81.

298. Han MH, Nam JH, Noh E, Lee EK. Gastrointestinal risk of non-steroidal anti-inflammatory drugs and gastroprotective agents used in the treatment of osteoarthritis in elderly patients: A nationwide retrospective cohort study. Int J Clin Pharmacol Ther. 2019;57(11):531–41.

299. Antonijevic N, Zivkovic I, Jovanovic L, Dragan M, Kocica M, Mrdovic I, et al. Dabigatran - Metabolism, Pharmacologic Properties and Drug Interactions. Curr Drug Met. 2017;18(7):622–35.

300. Mallen SR, Essex MN, Zhang R. Gastrointestinal tolerability of NSAIDs in elderly patients: A pooled analysis of 21 randomized clinical trials with celecoxib and nonselective NSAIDs. Curr Med Res Opin. 2011;27(7):1359–66.

301. Nikolaus T, Zeyfang A. Pharmacological Treatments for Persistent Non-Malignant Pain in Older Persons. Drugs and Aging. 2004;21(1):19–41.

302. Tripathi BK, Srivastava AK. Diabetes mellitus : Complications and therapeutics. Med Sci Monit. 2006;12(7):130–47.

303. Johnson AG, Nguyen TV DR. Do Nonsteroidal Anti-inflammatory Drugs Affect Blood Pressure? A Meta-Analysis. Ann Int Med. 1994;121:289–300.

304. Olsen AMS, Gislason GH, McGettigan P, Fosbøl E, Sørensen R, Hansen ML, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA - J Am Med Assoc. 2015;313(8):805–14.

305. Torres M, Barrionuevo M, Kowalski M, Blanca M. Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs. Immunol Allergy Clin North Am. 2014;34(3):507–24.

306. Inmaculada D, Salas M, Perkins J, Barrionuevo E, Gaeta F, Cornejo-Garcia J, et al. Hypersensitivity Reactions to Non-Steroidal Anti-Inflammatory Drugs. Curr

Pharm Des. 2016;22(45):6784–802.

307. Reginster JY. Cardiac concerns associated with strontium ranelate. Expert Opin Drug Saf. 2014;13(9):1209–13.

308. Herdeiro MT, Figueiras A, Polonia J, Jesus Gestal-Otero J. Physicians Attitudes and Adverse Drug Reaction Reporting. Drug Saf. 2006;28(9):825–33.

309. National Institute of Statistics. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0001272&xlang=pt&contexto=bd&selTab=tab2 (Accessed 25 june 2021).

310. Stojanovic M, Vukovic M, Jovanovic M, Dimitrijevic S, Radenkovic M. Potentially Inappropriate Medications in Nursing Home Residents : A Comparison of Two Approaches. Eval Heal Prof. 2020;22:1–6.

311. Stojanović M, Vuković M, Jovanović M, Dimitrijević S, Radenković M. GheOP3S tool and START/STOPP criteria version 2 for screening of potentially inappropriate medications and omissions in nursing home residents. J Eval Clin Pract. 2020;26(1):158–64.

312. Moßhammer D, Haumann H, Mörike K, Joos S. Polypharmacy—an Upward Trend with Unpredictable Effects. Dtsch Arztebl Int. 2016;113:627–33.

313. Castilho I, Rocha E, Magalhães S, Vaz Z, Costa A. Cartas ao Editor, Acta Med Port 2020 Sep;33(9):622-632 Polifarmácia e Utilização de Medicação Potencialmente Inapropriada no Idoso com Idade Igual ou Superior a 75 Anos: O Caso de uma Unidade de Saúde Familiar. Acta Med Port 2020. 2020;33(9):622–32.

314. Naveiro-Rilo J, Diez-Juárez D, Flores-Zurutuza M, Molina-Mazo R, Alberte-Pérez C. Intervención en ancianos con multimorbilidad y polimedicados : resultados en la prescripción y en la calidad de vida. Rev Calid Asist. 2014;29(5):256–62.

315. Brunetti E, Aurucci ML, Boietti E, Gibello M, Sappa M, Falcone Y, et al. Clinical Implications of Potentially Inappropriate Prescribing According to STOPP/ START Version 2 Criteria in Older Polymorbid Patients Discharged From Geriatric and Internal Medicine Wards : A Prospective Observational Multicenter Study. JAMDA. 2019;20(11):1476.e1-1476.e10.

316. Onder G, Liperoti R, Fialova D, Topinkova E, Tosato M D, P et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci. 2012;67(6):698–704.

317. De Oliveira Martins S, Soares MA, Foppe Van Mil JW, Cabrita J. Inappropriate drug use by Portuguese elderly outpatients - Effect of the Beers criteria update. Pharm World Sci. 2006;28(5):296–301.

318. da Costa FA, Periquito C, Carneiro MC, Oliveira P, Fernandes AI, Cavaco-Silva P. Potentially inappropriate medications in a sample of Portuguese nursing home residents: Does the choice of screening tools matter? Int J Clin Pharm. 2016;38:1103–11.

319. Huang AR, Mallet L, Rochefort CM, Eguale T BD, R T. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs Aging. 2012;29(5):359–76.

320. Toepfer S, Bolbrinker J, Konig M, Steinhagen-Thiessen E, Kreutz R, Demuth I. Potentially inappropriate medication in older participants of the Berlin Aging Study II (BASE- II) – Sex differences and associations with morbidity and medication use. PLoS One. 2019;14(12):1–12.

321. Heider D, Matschinger H, Meid AD, Quinzler R, Adler B, Gu C, et al. The impact of potentially inappropriate medication on the development of health care costs and its moderation by the number of prescribed substances. Results of a retrospective matched cohort study. PLoS One. 2018;1–12.

322. Hyttinen V, Jyrkka J, Valtonen H. A Systematic Review of the Impact of Potentially Inappropriate Medication on Health Care Utilization and Costs Among Older Adults. Med Care. 2016;54(10):950–64.

323. Unutmaz GD, Soysal P, Tuven B, Isik AT. Costs of medication in older patients : before and after comprehensive geriatric assessment. Clin Interv Aging. 2018;13:607–13.

324. Marroquín EC, Iglesia NM, Cobos LP. Adecuación dela Prescripción Farmaceutica en Personas de 65 Años o más en Centros de salud Docentes de Cáceres. Rev Esp Salud Pública. 2012;86(4):419–34.

325. Akande-Sholabi W, Adebusoye L, Olowookere O. Potentially inappropriate

medication use among older patients attending a geriatric centre in south-west Nigeria. Pharm Pract (Granada). 2018;16(3):1–7.

326. O'Connor MN, O'Sullivan D, Gallagher PF, Eustace J, Byrne S, O'Mahony D. Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial. JAGS. 2016;64:1558–66.

327. Scott I, Jayathissa S. Quality of drug prescribing in older patients : is there a problem and can we improve it? Intern Med J. 2010;40(1):7–18.

328. Muhlack DC, Hoppe LK, Weberpals J, Brenner H, Schöttker B. The Association of Potentially Inappropriate Medication at Older Age With Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies. J Am Med Dir Assoc. 2017;18(3):211–20.

329. Klarin I, Wimo A, Fastbom J. The Association of Inappropriate Drug Use with Hospitalisation and Mortality. Drugs Aging. 2005;22(1):69–82.

330. Green JL, Hawley JN, Rask KJ. Is the Number of Prescribing Physicians an Independent Risk Factor for Adverse Drug Events in an Elderly Outpatient Population? 2007;5(1):31–9.

331. Gadzhanova S, Ilomäki J, Roughead EE. COX-2 inhibitor and non-selective NSAID use in those at increased risk of NSAID-related adverse events: A retrospective database study. Drugs and Aging. 2013;30(1):23–30.

332. Bahadur S, Keshri L, Pathak K. Adverse Drug Reactions and Safety Considerations of NSAIDs: Clinical Analysis. Curr Drug Saf. 2012;6(5):310–7.

333. Nelson JM, Dufraux K, Cook PF. The relationship between glycemic control and falls in older adults. J Am Geriatr Soc. 2007;55(12):2041–4.

334. Feil DG, Zhu CW, Sultzer DL. The relationship between cognitive impairment and diabetes self-management in a population-based community sample of older adults with Type 2 diabetes. J Behav Med. 2012;35(2):190–9.

335. Abdelhafiz AH, Rodrí L, Morley JE, Sinclair AJ. Hypoglycemia in Older People - A Less Well Recognized Risk Factor for Frailty. Aging Dis. 2015;6(2):156–67.

336. Barkin RL, Beckerman M, Blum SL, Clark FM, Koh EK, Wu DS. Should Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) be prescribed to the older adult? Drugs and Aging. 2010;27(10):775–89.

337. Monteiro C, Silvestre S, Duarte AP, Alves G, Monteiro C, Silvestre S, et al. Assessment of suspected adverse drug reactions in elderly patients with diabetes mellitus based on a Portuguese spontaneous reporting database : analysis of reporting from 2008 to 2018. Expert Opin Drug Saf. 2021;20(7):845–53.

338. Monteiro C, Silvestre S, Duarte AP, Alves G. Safety of Non-Steroidal Anti-Inflammatory Drugs in the Elderly : An Analysis of Published Literature and Reports Sent to the Portuguese Pharmacovigilance System. Int J Environ. 2022;19(3541):1–18.

Appendices

Appendix 1

Table S.1.1: Suspected Adverse Drug Reactions according to Preferred Terms classification, classified as 'not-labelled' according to the Summary of Product Characteristics

Chemical substances	Preferred terms	Number of occurrences
Acenocoumarol	Melaena	1
Acetylsalicylic acid	Haemoglobin decreased Metabolic acidosis	1 1
Acyclovir	Abnormal faeces Faeces discoloured	1 1
Allopurinol	Odynophagia Hypotension Sepsis Odynophagia Delirium	1 1 1 1 1
Amantadine	Livedo reticularis Ischaemia	1 1
Aminophylline	Chest pain Hypertensive crisis	1 1
Amiodarone	Phlebitis	4
Amitriptyline	Dysphagia Oromandibular dystonia	2 2
Amlodipine+atorvastatin+metformin+clopidogrel +pantoprazole[b]	Aortic aneurysm	1
Amlodipine+metformin+olmesartan medoxomil[b]	Venous aneurysm Aneurysm	1 1
Amoxicillin	Pleural effusion Pyrexia Blood lactic acid Acidosis	1 1 1 1

Amphotericin B	Cyanosis	1
Anastrozole	Hot flush Lacrimation increased Eye pruritus Ocular hyperaemia Feeling hot Dysgeusia Hyperhidrosis	1 1 1 1 1 1 1
Azilsartan medoxomil and diuretics [a]	Joint swelling Musculoskeletal stiffness	1 1
Apixaban	Haematuria	1
Atorvastatin	Diarrhoea haemorrhagic	1
Azithromycin	Weight decreased Amnestic disorder	1 1
Betahistine	Dizziness Diarrhoea Disorientation Memory impairment Body temperature fluctuation	2 1 1 1 1
Bicalutamide	Urinary incontinence Hot flush Musculoskeletal pain Pain in extremity Vertigo	1 1 1 1 1
Bisoprolol	Rhinorrhoea	2
Bosentan	Abdominal pain upper	1
Carbamazepine	Drug reaction with eosinophilia and systemic symptoms	1
Celecoxib	Ageusia Weight decreased	1 1
Ciprofloxacin	Gingival bleeding	1
Cobamamide	Head discomfort Muscular weakness	1 1

	Malaise	1
	Nausea	1
	Palpitations	1
	Fatigue	1
	Vertigo	1
Dabigatran etexilate	Hypotension	1
	Haematuria	1
Dapagliflozin	Blood glucose increased	2
	Feeling hot	1
	Uterine prolapse	1
	Hyperkalaemia	1
	Renal injury	1
	Fatigue	1
	Somnolence	1
	Arthralgia	1
	Genital tract inflammation	1
	Dehydration	1
	Nausea	1
	Vomiting	1
Deferasirox	Melaena	1
Denosumab	Aggression	1
	Decreased appetite	1
	Asthenia	1
	Dysphagia	1
	Insomnia	1
	Fatigue	1
	Malaise	1
Dexamethasone and anti-infectives[a]	Retinal detachment	1
Diazepam	Somnolence	1
	Pyrexia	1
	Dehydration	1
Diclofenac	Semen discolouration	1
Digoxin	Renal failure	1
	Diet refusal	1
Dulaglutide	Myalgia	1
	Headache	1
Empagliflozin	Pancreatitis acute	1

Empagliflozin+ rosuvastatin and ezetimib[a]	Diarrhoea haemorrhagic	1
Erdosteine	Dizziness Disorientation	1 1
Ertapenem	Cardio-respiratory arrest Hypoxia	1 1
Escitalopram	Colitis ulcerative Melaena Pus in stool	1 1 1
Exenatide	Increased appetite Arthralgia Renal pain Myalgia Asthenia	1 1 1 1 1
Fenofibrate	Weight increased	1
Fentanyl	Blood pressure increased	1
Ferrous sulfate	Paraesthesia Pain in extremity	1 1
Fluconazole	Polyuria Urine output decreased	1 1
Flunarizine	Anal incontinence Piloerection Pain	1 1 1
Gliclazide	Melanosis Haematoma	1 1
Glyceryl trinitrate	Dyspnoea	1
Hidrosmin	Hepatitis toxic	1
Imatinib	Tooth loss Dementia Neurodegenerative disorder	1 1 1
Indacaterol and glycopyrronium bromide[a]	Hypertension Increased appetite Gynaecomastia Blood prolactin increased	1 1 1 1

Indapamide	Glossitis Dyspepsia Malaise	1 2 2
Influenza, inactivated, split virus or surface antigen	Diabetes mellitus Hyperglycaemia	1 1
Insulin (human)	Blood glucose increased	1
Insulin (human) +insulin glargine[b]	Hyperglycaemia Malaise Cerebrovascular accident	1 1 1
Insulin (human)+insulin glargine [b]	Blood glucose increased	1
Insulin aspart	Hyperglycaemia	1
Insulin glargine	Disease progression Aortic valve incompetence Acute pulmonary oedema	1 1 1
Insulin lispro	Blood glucose increased	1
Insulin lispro+sitagliptin[b]	Respiratory failure Pneumonia aspiration Anaemia	1 1 1
Irbesartan	Decreased appetite;	2
Iron, parenteral preparations	Vision blurred Seizure Anxiety Hypoaesthesia	1 2 1 1
Lamivudine	Nervousness Thinking abnormal	1 1
Lamivudine and abacavir[a]	Haematuria Joint swelling Palpable purpura Vasculitis	1 1 1 1
Lercanidipine	Ear discomfort Agitation	1 1
Levodropropizine	Choluria Faeces pale	1 1

Levofloxacin	Urinary incontinence	1
Levothyroxine sodium	Venous thrombosis Retroperitoneal haematoma	1 1
Linagliptin	Insomnia Neutrophilia Blood creatinine increased Blood urea increased C-reactive protein increased Renal function test abnormal Ear pain Nasal congestion Nausea Eye pain Ear pruritus Eye pruritus	1 1 1 1 1 1 1 1 1 1 1 1
Magnesium compounds	Feeling jittery Vision blurred	1 1
Meropenem	Hepatitis toxic	2
Metamizole sodium	Abdominal pain Gastrointestinal sounds abnormal Constipation Anxiety Hallucination Incoherent Vomiting	1 1 1 1 1 1 1
Metformin	Cardiac failure Urosepsis Inflammatory Myofibroblastic tumour Craniocerebral injury Paraesthesia Hyperlactacidaemia Hyperhidrosis Haematochezia Oedema peripheral Septic shock Murphy's sign positive Pyelonephritis	1 5 1 1 1 1 1 1 1 1 1 1

	Feeling cold	1
	Cold sweat	1
	Fatigue	1
	Hemiparesis	2
	Pyelonephritis acute	1
	Dizziness	1
	Tremor	1
	Hyperglycaemia	1
	Hypertension	1
	Swollen tongue	1
	Tongue discolouration	1
	Plicated tongue	1
	Oral dysaesthesia	1
	Tongue dry	1
	Tongue ulceration	1
	Leukocytosis	1
	Malaise	1
Metformin and alogliptin[a]	Visual impairment	1
	Vision blurred	1
Metformin and sitagliptin[a]	Blood urea increased	2
	Hyperglycaemia	1
	White blood cell count increased	1
	Blood glucose increased	1
	Haemoglobin decreased	1
	Blood creatinine increased	1
	Dizziness	1
	Balance disorder	1
Metformin and vildagliptin[a]	Blood glucose increased	2
Metformin+furosemide+metformin and sitagliptin[ba]	Cardiac arrest	1
Metformin+amlodipine+olmesartan medoxomil[b]	Aneurysm	1
Metformin+lisinopril[b]	Ischaemic stroke	1
Metformin+perindopril[b]	Overlap syndrome	1
	Autoimmune disorder	1
Metformin+ramipril+tamsulosin[b]	Sweat gland tumour	1
Metformin+vildagliptin+gliclazide[b]	White blood cell count increased	1

Mirabegron	Onychomadesis Malaise	1 1
Olmesartan medoxomil and diuretics[a]	Blood pressure increased	2
Pantoprazole	Tachycardia	2
Pantoprazole+dabigatran etexilate[b]	Inflammatory marker increased	1
Phenytoin	Hypervolaemia Hyponatraemia	1 1
Piperacillin and enzyme inhibitor[a]	Myalgia Tremor	1 1
Piribedil	Headache Tinnitus	1 1
Polystyrene sulfonate	Myalgia	2
Pravastatin and fenofibrate[a]	Anxiety	2
Propylthiouracil	Cough	2
Quetiapine	Inappropriate antidiuretic hormone secretion Hypokalaemia Fall Paraesthesia oral	1 1 1 1
Rilmenidine	Gynaecomastia	2
Rivaroxaban	Dry mouth	2
Simvastatin	Gingival swelling	1
Sitagliptin	Blindness Confusional state Faeces discoloured Chromaturia Insomnia Night sweats;	1 1 1 1 1 1
Sitagliptin +corticosteroids (unspecified)[b]	Blindness Sudden visual loss Temporal arteritis	1 1 1

	Optic ischaemic neuropathy	1
Sofosbuvir and ledipasvir[a]	Aphthous ulcer Muscle spasms Peripheral swelling	2 1 1
Tamsulosin	Peripheral swelling;	1
Tapentadol	Dysgeusia	2
Terbinafine	Dysarthria Dry mouth	2 2
Ticagrelor	Acute myocardial infarction	1
Ticagrelor+warfarin+acetylsalicylic acid[b]	Hypovolaemic shock	1
Tramadol, combinations	Blood pressure increased	1
Trazodone	Vision blurred Eyelid ptosis	1 1
Venlafaxine	Hyponatraemia	1
Vildagliptin	Polyuria Asthenia Blood creatinine increased Headache Hyperkalaemia Malaise Blood urea increased	1 1 1 1 1 1 1
Vinorelbine	Swelling Pain	2 2
Warfarin	Abdominal pain lower Hallucinations, mixed	1 1

[a] Fixed combinations of blood glucose lowering drugs (patient taking only a medication)

[b] Combinations of two or more different medications (patient taking different medication each one containing a chemical substance)

Appendix 2

Patient Preference and Adherence

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ORIGINAL RESEARCH

Medication Evaluation in Portuguese Elderly Patients According to Beers, STOPP/START Criteria and EU(7)-PIM List – An Exploratory Study

This article was published in the following Dove Press journal:
Patient Preference and Adherence

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Purpose: The increase in drug prescription for the elderly raises the risk of the occurrence of potentially inappropriate medications (PIMs), thus increasing the incidence of drug-related problems. Likewise, potential prescribing omissions (PPOs) are also highly prevalent in the elderly. This study aimed at assessing the prevalence of PIMs in the elderly by using the EU (7)-PIM list, STOPP criteria version 2 and the Beers criteria version 2015, as well as the prevalence of PPOs by applying the START criteria version 2 in elderly nursing home residents and outpatients of the Eastern Central Region of Portugal.

Patients and Methods: A descriptive cross-sectional study was carried out in a sample of 90 Portuguese elderly people. Age, gender, diagnoses and medication history were collected from the patients' clinical records. The prevalence of PIMs and PPOs was measured according to each of the criteria applied.

Results: The patients' ages ranged from 65 to 103 years, with an average age of 84.15 years. In addition, the average number of medications prescribed was 7.6. The STOPP criteria identified 250 PIMs affecting 77 patients (85.5%), the EU(7)-PIM list detected 94 PIMs in 58 patients (64.4%) and the Beers criteria identified 69 PIMs in 51 patients (56.6%). Therefore, the STOPP criteria version 2 identified substantially more PIMs than the other two tools. Furthermore, by applying the START criteria 68 PPOs were detected in 52 patients (57.7%).

Conclusion: A high prevalence of PIMs and PPOs was observed, suggesting the need to implement actions aimed at reducing the phenomenon and thus help to improve the quality of care provided in nursing homes. The variations in prevalence with the different tools suggest the need to carefully choose the tool for medication review in the elderly.

Keywords: potentially inappropriate medications, potential prescribing omissions, EU(7)-PIM list, STOPP/START criteria version 2, Beers criteria version 2015, elderly

Introduction

Increasing drug prescription raises the risk of the occurrence of potentially inappropriate medications (PIMs) prescribing.[1] In this context, several studies have suggested a high prevalence of medication prescription in the elderly, increasing the presence of drug-related problems (increased frequency of adverse events, augmented iatrogenic morbidity and mortality, and increased hospitalization rate).[2–5] These problems are usually associated with inadequate dosing regimens in the elderly, with drug interactions, and even with medication duplication.[2–5] Furthermore, there are increasing problems of

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DovePress
http://doi.org/10.2147/PPA.S247013

adherence to therapy[6] and an increase in health expenditures associated with polypharmacy.[7–11] Inappropriate prescription is therefore considered a major health concern.[3,12] In addition to the number of medications prescribed, female gender and dependency for daily life activities have also been associated with a higher prevalence of PIMs.[13]

Polypharmacy, defined as the use of five or more drugs,[14] does not necessarily imply the presence of inappropriate prescriptions, but it has been consistently associated with a higher risk of PIMs. It was evidenced that reducing the number of drugs used, through medication review programs, may reduce the risk of PIMs.[9] In this context, a recent systematic review and meta-analysis showed that the use of PIMs increases mortality (risk ratio 1.59, 95% confidence interval 1.45–1.75).[15]

In the elderly, in addition to PIMs, potential prescribing omissions (PPOs), ie, medications that are not prescribed but that are clinically indicated, are also highly prevalent.[3]

Given the pharmacoeconomic implications of polypharmacy, the British Geriatrics Society recommends medication review interventions based on the principles of geriatric assessment for all elderly people identified with indicators of greater frailty (eg, falls, delirium, and immobility) by applying an evidence-based checklist such as the STOPP (Screening Tool of Older People's Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria.[16] The STOPP criteria were developed to identify PIMs and the START criteria were designed to identify PPOs. These tools were originally developed in Ireland and published for the first time in 2008. They were developed by using the Delphi method and were organised according to the main physiological systems affected by specific drugs or drug classes.[17] These criteria were recently revised by experts from 13 European countries in an attempt to extend their application. In fact, in light of the current scientific evidence, they were updated by removing some criteria and adding others and, presently, 87 STOPP criteria and 35 START criteria are established.[18] These criteria have the advantage of being easy to apply and it has already been demonstrated, in different European centres, that they are reliable and reproducible.[2,3] Importantly, by the application of these criteria, there has been a reduction in the number of PIMs associated adverse events, and costs in health care, as well as a decrease in the rate of iatrogenic-based hospitalization.[9–11,19–21] Therefore, these tools may be effective in improving prescribing quality, and clinical, humanistic, and economic outcomes as well.[22] There are also studies evidencing their reliability even when applied by pharmacists or other healthcare professionals, helping to improve the quality of care in geriatric patients.[23,24]

The Beers criteria of the American Geriatric Society, originally published in 1991, were also developed by using the Delphi method, and they have had multiple updates. These criteria were created to support the clinical prescription in individuals 65 years of age or older. In addition to the list of PIMs, the Beers criteria include medications that should be avoided or their doses adjusted based on renal function and drug interactions that could lead to damage in the elderly.[25–27]

Since the introduction of the first version of Beers criteria by Dr Mark Beers in 1991, several other screening tools have been developed and published in the USA, Canada and European countries. Recently, an expert-consensus PIMs list covering the drugs marketed in seven European countries (Finland and Sweden in Scandinavia, France and Spain in southern Europe, Germany and the Netherlands in central Europe, and Estonia in Eastern Europe),[28] called EU(7)-PIM list (ie, European list of Potentially Inappropriate Medications) was established. This list consists of 282 chemical substances or drug classes from 34 therapeutic groups and includes recommendations for dose adjustments and therapeutic alternatives. The EU(7)-PIM list is organised in two categories, independent of the diagnosis or considering the diagnosis, and it can be applied as a screening tool to identify PIMs in databases where little clinical information is available.[28]

In Portugal, as in other Western countries, there has been an increase in the average lifespan and, consequently, in the number of elderly people. Given that several explicit criteria for PIMs and/or PPOs detection have been developed, which have been found to be effective and reliable tools to support medication review interventions in the elderly, it is fully justified to apply and compare them in Portuguese elderly patients. Indeed, contrary to what happens in other countries, few studies have been published in Portugal on this matter, and these only applied the Beers criteria[29] and STOPP/START criteria.[30,31] Actually, to the best of our knowledge, the EU(7)-PIMs list has never been applied before in Portugal and according to literature, this tool is deemed to be sensitive even when the clinical information available is minimal. So, it is important to evaluate if the EU(7)-PIMs list brings clinical benefits relatively to other tools already used in Portugal. Hence, it was considered opportune to apply and compare the results generated by these three tools in the medication review of geriatric patients institutionalized or attending a day-care centre. The primary aim of the present study

was to assess and compare the prevalence of PIMs and PPOs in a sample of elderly nursing home residents or outpatients of the Eastern Central Region of Portugal using three different tools (ie, Beers criteria, STOPP/START criteria and the EU(7)-PIMs list), thus inferring if the choice of the medication review screening tool is important to detect PIMs. In addition, this study aimed to compare the obtained data with the other studies carried out in other regions of Portugal and analyse the use of drugs with potential consequences on the frail elderly.

Patients and Methods

A descriptive cross-sectional study involving the analysis of clinical records of elderly nursing home residents or outpatients attending a day-care centre in the Eastern Central Region of Portugal was performed over a period of one year.

The study was based on a convenience sample, which included elderly nursing home residents and residents with total independence (outpatients, ie, people who use the nursing home as an adult day-care centre) with age ≥65 years.

The data collected from the patient's medical records included socio-demographic data, current diagnoses, past medical history, laboratory results, vital signs measured in nursing home (eg, blood pressure) and prescribed therapy (drug substance, index date and daily dosage). Whenever the information was missing or unclear, the responsible professional caregiver (physician or nurse) was contacted.

The medicines and the diagnosis were classified according to the Anatomical Therapeutic Chemical Classification (ATC/DDD Index 2017) and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) version 2016, respectively.

All medication included in the study was analysed by applying the Beers (version 2015), the STOPP/START criteria version 2 as well as the EU(7)-PIM list. To perform a comparison with all criteria, only patients with an established diagnosis were included. The criteria were applied by two independent researchers, a practicing clinical pharmacist and a clinician. Discrepancies in the clinical judgement were resolved by discussion involving the other researchers.

Data analysis was performed using descriptive statistics as mean and range, absolute frequency and percentages.

This study received approval from the Ethics Committee of the University of Beira Interior (n.º CE-UBI-Pj-2017-004; june 26, 2017) and was conducted in agreement with the principles of the Declaration of Helsinki; all participants provided written informed consent.

Results

Data were collected from 90 patients, of which 71 (78.9%) were female, 48 were nursing home residents and 42 used the nursing home as an adult day-care centre (Table 1). The average age (overall range) was 84.15 (65–103) years. The average number of prescribed drugs per patient was 7.6, 30 of them had taken between 5 and 9 medicines and 33 had taken 9 or more medicines. Circulatory system diseases were the most prevalent, affecting 72 (80.0%) of patients, followed by endocrine, nutritional and metabolic diseases (n = 46, 51.1%), and mental and behavioural disorders (n = 43, 47.8%). Hypertension, dyslipidaemias and dementia were the most prevalent diseases in those three groups of health problems, respectively. Detailed information on the study population is provided in Table 1.

The application of the Beers criteria version 2015 identified 69 PIMs in 51 (56.6%) patients, considering the panel's recommendations and specificity.[25] Most of patients presented one PIM and in 14 patients two or three PIMs were detected (Table 2). In the STOPP criteria, the diagnosis information is important to evaluate the inappropriateness of medications.[18] By applying the STOPP criteria 250 PIMs were identified in 77 (85.5%) patients. The number of them having one or more PIMs was 17 and 60, respectively, and the majority of patients presented 4 PIMs (Table 2). The application of EU(7)-PIM list considering diagnosis identified 94 PIMs and, in the 90 patients, 58 (64.4%) had PIMs associated and 35 had one PIM prescribed (Table 2).

The drugs most commonly associated with PIMs when applying the Beers criteria were short- and intermediate-acting benzodiazepines (20 and 28 patients had been prescribed with alprazolam and lorazepam, respectively). Some patients had taken two short- and intermediate-acting benzodiazepines and one long-acting benzodiazepine. We found 7 individuals with a diagnosis of dementia that had taken one or two benzodiazepines, one person had taken zolpidem, three people had taken two benzodiazepines and two had taken an antipsychotic and an anticholinergic agent. Analyzing the "falls" history one patient had been prescribed with alprazolam, zolpidem and amitriptyline, another patient had tapentadol and two had benzodiazepines (lorazepam, alprazolam). Considering the PIMs to be used with caution in older adults, 54 patients had mirtazapine and 34 had been prescribed

Table 1 Characteristics of the Study Sample (N = 90)

Characteristics		Study Sample (N = 90)
Age, average (range)		84.15 (65–103)
Sex, *n*	Male Female	19 (21.1%) 71 (78.9%)
Nursing homes residents		48 (53.3%)
Residents with total independence (outpatients, ie, people who use the nursing home as an adult day-care centre)		42 (46.7%)
Number of medicines	0–4 5–9 ≥ 9	26 (30.0%) 30 (33.3%) 33 (36.7%)
Number of prescribed drugs (average per patient)	7.6	
Health problems (ICD-10)*	Neoplasms Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism Endocrine, nutritional and metabolic diseases Mental and behavioural disorders Diseases of the nervous system Diseases of the eye and adnexa Diseases of the ear and mastoid process Diseases of the circulatory system Diseases of the respiratory system Diseases of the digestive system Diseases of the skin and subcutaneous tissue Diseases of the musculoskeletal system and connective tissue Diseases of the genitourinary system	5 (5.5%) 10 (11.1%) 46 (51.1%) 43 (47.8%) 10 (11.1%) 4 (4.4%) 11 (12.2%) 72 (80.0%) 17 (18.9%) 15 (16.7%) 1 (1.1%) 32 (35.5%) 17 (18.9%)

Note: *International Statistical Classification of Diseases and Related Health Problems 10th Revision.

diuretics (Table 3). In short, medication acting on the central nervous system (CNS) was responsible for the majority of the PIMs.

The PIMs most frequently identified by applying the STOPP criteria were drugs prescribed beyond the recommended duration, specifically benzodiazepines taken for 4

Table 2 Summary of Patients with Potentially Inappropriate Medications (PIMs) Identified in the Study Sample (N = 90) by Beers' (Version 2015), STOPP Criteria (Version 2) and EU(7)-PIM List

PIMs	Beers 2015, n (%)	STOPP Criteria, n (%)	EU(7)-PIM List, n (%)
1 PIM	37 (41.1%)	17 (18.9%)	35 (38.9%)
2 PIMs	10 (11.1%)	6 (6.6%)	13 (14.4%)
3 PIMs	4 (4.4%)	18 (20.0%)	7 (7.8%)
4 PIMs	0 (0.0%)	24 (26.7%)	3 (3.3%)
≥5 PIMs	0 (0.0%)	12 (13.3%)	0 (0.0%)
Total number of patients with PIMs	51 (56.6%)	77 (85.5%)	58 (64.4%)
Total number of PIMs	69	250	94

Table 3 Results Observed by the Application of 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medications (PIMs) to Be Used with Caution in Older Adults

PIMs to Be Used with Caution	Number of Patients
Aspirin for primary prevention of cardiac events in adults aged ≥80	17
Antipsychotics	26
Diuretics	34
Carbamazepine	2
Mirtazapine	54
Serotonin–norepinephrine reuptake inhibitors	2
Selective serotonin reuptake inhibitors	15
Tricyclic antidepressants	5
Vasodilators	1

Table 4 Number of Patients with Potentially Inappropriate Medications (PIMs) Identified by the STOPP Criteria (Top Five)

Criteria	n
Drug prescribed beyond the recommended duration, where treatment duration is well defined	58
Duplicate drug class prescription	12
Benzodiazepines for ≥4 weeks	54
Benzodiazepines	54
Neuroleptic drugs	28

weeks or longer, the most prescribed being lorazepam and alprazolam (Table 4). The elderly have an increased risk of falls and benzodiazepines and neuroleptics were the agents most found as PIMs in these people. Nursing home residents (64.6%) had taken benzodiazepines and 37.5% neuroleptics. In outpatients, we found 54.8% with benzodiazepines and 23.8% with neuroleptics. Olanzapine was the neuroleptic drug most found in the nursing home residents, and in the outpatients was quetiapine. Duplicated drug class prescription was also observed, particularly two or more benzodiazepines and two or more neuroleptics.

The most frequently identified PIMs using the EU(7)-PIM list involved anxiolytics (lorazepam > 1 mg/day and alprazolam), hypnotics and sedatives (zolpidem) in prolonged use.

The application of the START criteria identified 68 PPOs when considering the diagnosis. In addition, 52 patients had PPOs and, among these, 39 had one PPO (Table 5). The majority of PPOs involved the annual administration of seasonal trivalent influenza vaccine, detecting 36 patients who had not taken this vaccine. The bone anti-resorptive or anabolic therapy in patients with documented osteoporosis and/or previous history of fragility fracture(s) and antiplatelet therapy with a documented history of coronary, cerebral or peripheral vascular disease were the other PPOs most found (8 patients).

Table 5 Summary of Patients with Potential Prescribing Omissions (PPOs) Identified in the Study Sample (N = 90) by START Criteria (Version 2) Considering the Diagnosis

PPOs	START, n (%)
1 PPO	39 (43.3%)
2 PPOs	11 (12.2%)
3 PPOs	1 (1.1%)
4 PPOs	1 (1.1%)
≥5 PPOs	0 (0.0%)
Total number of patients with PPOs	52 (57.7%)
Total number of PPOs	68

Discussion

In Portugal, as in many other countries, patient care is a priority and demands policy measures to foster clinical practice improvement and better quality of life for the patient.[32] The majority of the elderly patients evaluated were taking at least one or more inappropriate drugs.[5,29-31,33,34] In a polymedicated elderly person, it is important to use tools that detect the majority of PIMs to avoid any potential problems associated with inappropriate medication and thus improve their quality of life. According to literature, adverse events associated with the use of drugs occur in 15% or more of the elderly population and could be prevented.[35] A recent study concluded that PIMs and polypharmacy are frequently observed in hospital-discharged patients increasing the risk of unplanned hospital readmission.[36] The drugs most frequently associated with inappropriate prescribing are antiplatelet agents with over-prescribing and omission, and benzodiazepines in prolonged use.[37,38] In addition, the long-term use of non-steroidal anti-inflammatory drugs has also been identified by applying the STOPP criteria.[6] In Portugal, a study about institutionalized people found a total of 484 drug-related problems (DRP) in 31 elderly patients (median: 15 DRP/patient).[31] Another study showed that the prevalence of PIMs, regardless of the tool used, was high.[30] Our study was the only to make a detailed comparison of the detected PIMs using three different screening tools and provides useful insights regarding the prevalence of inappropriate prescription in an elderly population belonging to the Eastern Central Region of Portugal.

In the present study, we found patients polymedicated with multiple comorbidities, very similar to others studies.[19,31,36] The fact that we had more women than men in our sample leads us to hypothesize that women tend to live longer and be more prone to have physical or psychological complaints.

Applying the STOPP version 2 criteria we detected significantly more PIMs in comparison with the EU(7)-PIM list and Beers criteria version 2015. The higher number of PIMs identified by the STOPP version 2 criteria may be due to the high sensitivity of these criteria for the European reality.[39] In addition, there were significant differences in the number of PIMs detected depending on the tool used. In fact, the STOPP criteria are the screening tool that detected a higher number of PIMs.[30] These results seem to be in accordance with a study carried out in Croatia, in which the application of the STOPP version 2 criteria identified significantly more PIMs than the EU(7)-PIM list.[39] On the other hand, in a study in Lithuania, the EU(7)-PIM list detected more PIMs than the Beers criteria version 2015, such as a study conducted at the Gerontology Center Belgrade.[40,41]

Regardless of the existing differences in the number of PIMs detected with the above-mentioned protocols, with all of them it was observed that benzodiazepines prescribing was the most prevalent PIM and that the drugs acting on the CNS were responsible for the majority of the PIMs found. In addition, a notable proportion of PIMs was also associated with drugs targeting the CNS, which adversely affects the stability or mobility of patients. These results are in agreement with those obtained in other similar studies carried out in Portugal and other European countries.[5,29-31,33,38,41]

In our study, in contrast to the others performed in Portugal, alprazolam and lorazepam were the two drugs most commonly prescribed as PIMs. In the study performed in pharmacies in Lisbon, diazepam and ticlopidine were the drugs associated with inappropriateness.[29] The consumption of benzodiazepines and neuroleptics was higher in the nursing home residents, in fact, previous research has reported an increased risk of mental health issues among the elderly living in residential care facilities,[42] which could explain our results.

In contrast, in similar studies carried out in Portugal, no patient was using ticlopidine, and only one patient, with complicated peptic ulcer disease or erosive peptic oesophagitis, was using a PPI.[18,31] However, the decrease in the use of PPI is due, most likely, to the new recommendations on the safety of its use.[43]

Another worrying aspect of detected PIMs was the duplicated drug classes at the top of the list, which was mainly represented by benzodiazepines and antipsychotics, similarly to those observed in a study carried out in Lisbon and Alentejo, in Portugal.[30] In this context, it is important to mention that the average consumption of these two drug classes in Portugal is higher than in most European countries,[32] having potential consequences on the frail elderly.[33,38,44]

The Beers criteria version of 2015 include the table "for Non-Anti-Infective Medications That Should Be Avoided or Have Their Dosage reduced with Varying Levels of Kidney Function in Older Adults,"[25] but we did not assess patients in this context. However, we detected cases of patients taking drugs from this table, but there was no registration of creatinine clearance values in their clinical records and therefore it was not possible to assess whether the use of these drugs was or not potentially inappropriate.

The most commonly detected PPOs were associated with the area of cardiovascular prevention, specifically the absence of antiplatelet therapy, and in flu prevention the missing annually seasonal trivalent influenza vaccine.[45] In this context, the flu vaccine is strongly recommended and is free of charge on the National Health Service in Portugal for people aged 65 or older.[46] However, in some nursing homes, the administration of the influenza vaccine is only carried out on patients who have a medical prescription or in patients whose responsible relatives have given permission. A study performed in elderly patients that visited their primary care physician showed that the absence of antiplatelet therapy was, also, a highly ranked PPO based on START criteria.[38]

Another important group with omissions was the musculoskeletal system medication, but in our study, it was not attributed to the absence of vitamin D, rather to the absence of a bone anti-resorptive or anabolic therapy, in contrast to the study performed in nursing homes located in the region of Lisbon and Alentejo.[30] In the analysis of medical data, we did not detect any contraindication to the use of this class of drugs.

In addition to the high prevalence of polymedication in the study population, a notable proportion of PIMs was detected. Depending on the screening tools applied, the prevalence of PIMs varied significantly. In this context, the STOPP criteria identified more PIMs in this sample than the other two tools, and it should, therefore, be preferred.[30,39] Furthermore, these results suggest that there is the need for urgent interventions to improve instructions for safe drug use in elderly patients, to decrease the number of drugs whenever possible, and to increase the appropriateness of the medication regimen. Prescribing, in the future, will likely become an act supported by drug screening tools to alert doctors about potential PIMs.

Nonetheless, there were some limitations intrinsic to this study. The main one was the small sample size, which is a regional sample, which is not representative of the national population as a whole. In addition, incomplete documentation of patients' current diagnoses and biochemical information in analysing the clinical records may have led to a lower rate of PIMs reported in some cases, or a higher rate of reporting in others (ie, where a medicine was clinically indicated but the patient's clinical data did not support the indication). All the protocols to identify PIMs also have inherent limitations to their use. For example, there may be a difference between recommendations derived from evidence and what is in the individual patient's best interest.[47] On the other hand, the differences between the protocols and the medicines used in the countries where these tools were originally developed can also be important.

Conclusion

It is urgent to perform actions to reduce PIMs and PPOs and therefore to improve care quality. STOPP version 2 criteria identified substantially more PIMs than the EU(7)-PIM list and Beers criteria. The variations in prevalence detected with the different tools indicate that a careful choice of the tool for medication review in the elderly is important. High consumption of benzodiazepines and antipsychotics was found, having potential consequences on the frail elderly, suggesting the need for the implementation of medication review programs and interventions to improve instructions for a safer drug use in the elderly. Reducing the number of medications whenever possible, and increasing the appropriateness of the medication regimen is needed. Although screening tools will never replace the clinical assessment and judgement, they can be used as a systematic approach for improving prescribing practices in older populations. Incorporating the use of these tools by other health professionals, like nurses and pharmacists, into everyday practice could play an important role in improving the quality of pharmacotherapy and review medication of elderly nursing home residents.

Acknowledgments

The authors would like to thank the elderly patients who participated in this study and the physicians and nurses who had a fundamental contribution to obtain the clinical information required for this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Laroche M, Charmes J, Nouaille Y, Picard N, Merle L. Is inappropriate medication use a major cause of adverse drug reactions in the elderly? *Br J Clin Pharmacol*. 2006;63(2):177–186. doi:10.1111/j.1365-2125.2006.02831.x
2. O´Connor MN, Gallagher P, O´Mahony D. Inappropriate prescribing. Criteria, detection and prevention. *Drugs Aging*. 2012;29(6):437–452. doi:10.2165/11632610-000000000-00000
3. Gallagher P, Baeyens J, Topinkova E, et al. Inter-rater reliability of STOPP (Screening Tool of Older Persons ' Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria amongst physicians in six European countries. *Age Ageing*. 2009:603–606. doi:10.1093/ageing/afp097.
4. Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality. *Drugs Aging*. 2005;22 (1):69–82. doi:10.2165/00002512-200522010-00005
5. Onder G, Liperoti R, Fialova D, et al. Polypharmacy in nursing home in Europe: results from the SHELTER study. *J Gerontol a Biol Sci Med Sci*. 2012;67(6):698–704. doi:10.1093/gerona/glr233
6. Marroquín EC, Iglesia NM, Cobos LP. Adecuación dela Prescripción Farmaceutica en Personas de 65 Años o más en Centros de salud Docentes de Cáceres. *Rev Esp Salud Pública*. 2012;86(4):419–434. doi:10.4321/S1135-57272012000400009
7. Bradley MC, Fahey T, Cahir C, et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. *Eur J Clin Pharmacol*. 2012;68(10):1425–1433. doi:10.1007/s00228-012-1249-y
8. Delgado Silveira E, Garcia M, Montero-Errasquin B, Cruz-Jentoft AJ, Gallagher PF, Sachez Castelhano C. Inappropriate prescription in older patients: the STOPP/START criteria. *Rev Esp Geriatr Gerontol*. 2009;44(5):273–279. doi:10.1016/j.regg.2009.03.017
9. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. *BJCP*. 2010;69(5):543–552. doi:10.1111/j.1365-2125.2010.03628.x
10. Hyttinen V, Jyrkka J, Valtonen H. A systematic review of the impact of potentially inappropriate medication on health care utilization and costs among older adults. *Med Care*. 2016;54(10):950–964. doi:10.1097/MLR.0000000000000587
11. Heider D, Matschinger H, Meid AD, et al. The impact of potentially inappropriate medication on the development of health care costs and its moderation by the number of prescribed substances. Results of a retrospective matched cohort study. *PLoS One*. 2018:1–12. doi:10.1371/journal.pone.0198004.
12. Spinewine A, Schmader KE, Barber N, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet*. 2007;370(9582):173–184. doi:10.1016/S0140-6736(07)61091-5
13. Kara Ö, Arık G, Kızılarslanoglu MC, et al. Potentially inappropriate prescribing according to the STOPP/START criteria for older adults. *Aging Clin Exp Res*. 2016;28(4):761–768. doi:10.1007/s40520-015-0475-4
14. Kuijpers MAJ, Van Marum RJ, Egberts ACG, Jansen PAF, Oldy T. Relationship between polypharmacy and underprescribing. *BJCP*. 2007;65(1):130–133. doi:10.1046/j.0306-5251.2007.02961.x
15. Muhlack DC, Hoppe LK, Weberpals J, Brenner H, Schöttker B. The association of potentially inappropriate medication at older age with cardiovascular events and overall mortality: a systematic review and meta-analysis of cohort studies. *J Am Med Dir Assoc*. 2017;18 (3):211–220. doi:10.1016/j.jamda.2016.11.025
16. Road W, House TB, Trust F, Yorkshire W. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. *Age Ageing*. 2014;43(6):744–747. doi:10.1093/ageing/afu138
17. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther*. 2008;46(2):72–83. doi:10.5414/cpp46072
18. O´Mahony D, O´Sullivan D, Byrne S, O´Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2014;1–6. doi:10.1093/ageing/afu145
19. Naveiro-Rilo JC, Diez-Juárez D, Flores-Zurutuza ML, Molina-Mazo R, Alberte-Pérez C. Intervencion en ancianos con multimorbilidad y polimedicados: resultados en la prescripcio n y en la calidad de vida. *Rev Calid Asist*. 2014;29(5):256–262. doi:10.1016/j.cali.2014.06.002
20. Dalleur O, Boland B, Losseau C, et al. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. *Drugs Aging*. 2014;31 (4):291–298. doi:10.1007/s40266-014-0157-5
21. Unutmaz GD, Soysal P, Tuven B, Isik AT. Costs of medication in older patients: before and after comprehensive geriatric assessment. *Clin Interv Aging*. 2018;13:607–613. doi:10.2147/CIA.S159966

22. Hill-Taylor B, Walsh KA, Stewart S, Hayden J, Byrne S, Sketris IS. Effectiveness of the STOPP/START (Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right Treatment) criteria: systematic review and meta-analysis of randomized controlled studies. *J Clin Pharm Ther*. 2016;41(2):158–169. doi:10.1111/jcpt.12372
23. Gillespie U, Alassaad A, Hammarlund-Udenaes M, et al. Effects of pharmacists ' interventions on appropriateness of prescribing and evaluation of the instruments ' (MAI, STOPP and STARTs ') ability to predict hospitalization — analyses from a randomized controlled trial. *PLoS One*. 2013;8:5. doi:10.1371/journal.pone.0062401
24. Sullivan DO, Mahony DO, Connor MNO, et al. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. *Drugs Aging*. 2014;31:471–481. doi:10.1007/s40266-014-0172-6
25. Samuel MJ. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63(11):2227–2246. doi:10.1111/jgs.13702
26. Salbu RL, Feuer J. A closer look at the 2015 Beers Criteria. *J Pharm Pract*. 2017;30(4):419–424. doi:10.1177/0897190016663072
27. Steinman MA, Beizer JL, Dubeau CE, Laird RD, Lundebjerg NE, Mulhausen P. How to use the American Geriatrics Society 2015 Beers Criteria - a guide for patients, clinicians, health systems, and payors. *J Am Geriatr Soc*. 2015;63(11):e1–7. doi:10.1111/jgs.13701
28. Renom-Guiteras A, Meyer G, Thürmann PA. The EU(7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. *Eur J Clin Pharmacol*. 2015;71(7):861–875. doi:10.1007/s00228-015-1860-9
29. de Oliveira Martins S, Soares MA, Foppe Van Mil JW, Cabrita J. Inappropriate drug use by Portuguese elderly outpatients - Effect of the Beers criteria update. *Pharm World Sci*. 2006;28(5):296–301. doi:10.1007/s11096-006-9046-2
30. da Costa FA, Periquito C, Carneiro MC, Oliveira P, Fernandes AI, Cavaco-Silva P. Potentially inappropriate medications in a sample of Portuguese nursing home residents: does the choice of screening tools matter? *Int J Clin Pharm*. 2016;38(5):1103–1111. doi:10.1007/s11096-016-0337-y
31. Silva C, Ramalho C, Luz I, Monteiro J, Fresco P. Drug-related problems in institutionalized, polymedicated elderly patients: opportunities for pharmacist intervention. *Int J Clin Pharmacol*. 2015;37:327–334. doi:10.1007/s11096-014-0063-2
32. Ravera S, Hummel SA, Stolk P, Heerdink RE, de Gier J. The use of driving impairing medicines: a European survey. *Eur J Clin Pharmacol*. 2009;65:1139–1147. doi:10.1007/s00228-009-0695-7
33. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge D, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs Aging*. 2012;29(5):359–376. doi:10.2165/11599460-000000000-00000
34. Toepfer S, Bolbrinker J, Konig M, Steinhagen-Thiessen E, Kreutz R, Demuth I. Potentially inappropriate medication in older participants of the Berlin Aging Study II (BASE- II) – sex differences and associations with morbidity and medication use. *PLoS One*. 2019;14(12):1–12. doi:10.1371/journal.pone.0226511
35. Pretorius RW, Gataric G, Swedlund SK, Miller JR. Reducing the risk of adverse drug events in older adults. *Am Fam Physician*. 2013;87(5):331–336.
36. Brunetti E, Aurucci ML, Boietti E, et al. Clinical implications of potentially inappropriate prescribing according to STOPP/START version 2 criteria in older polymorbid patients discharged from geriatric and internal medicine wards: a prospective observational multicenter study. *J Am Med Dir Assoc*. 2019;20(11):1476.e1-1476.e10. doi:10.1016/j.jamda.2019.03.023
37. Paci J, Alfaro M, Alonso F, San- Martín M. Prescripción inadecuada en pacientes polimedicados mayores de 64 años en atención primaria. *Aten Primaria*. 2015;47(1):38–47. doi:10.1016/j.aprim.2014.03.013
38. Stojanović M, Vuković M, Dimitrijević S. GheOP 3 S tool and START/STOPP criteria version 2 for screening of potentially inappropriate medications and omissions in nursing home residents. *J Eval Clin Pract*. 2020;26:158–164. doi:10.1111/jep.13107
39. Mucalo I, Hadžiabdić MO, Brajković A, et al. Potentially inappropriate medicines in elderly hospitalised patients according to the EU(7)-PIM list, STOPP version 2 criteria and comprehensive protocol. *Eur J Clin Pharmacol*. 2017;73(8):991–999. doi:10.1007/s00228-017-2246-y
40. Grina D, Briedis V. The use of potentially inappropriate medications among the Lithuanian elderly according to Beers and EU(7)-PIM list – a nationwide cross-sectional study on reimbursement claims data. *J Clin Pharm Ther*. 2017;42(2):195–200. doi:10.1111/jcpt.12494
41. Stojanovic M, Vukovic M, Jovanovic M, Dimitrijevic S, Radenkovic M. Potentially inappropriate medications in nursing home residents: a comparison of two approaches. *Eval Heal Prof*. 2020;22:1–6. doi:10.1177/0163278719900653
42. Gleeson H, Hafford-letchfield T, Quaife M, et al. Preventing and responding to depression, self- harm, and suicide in older people living in long term care settings: a systematic review. *Aging Ment Health*. 2019;23(11):1467–1477. doi:10.1080/13607863.2018.1501666
43. Infarmed. Comunicado de imprensa 1/1 inibidores da bomba de protões (IBP) campanha visa alertar para os riscos dos medicamentos para a acidez do estômago[press release 1/1 proton pump inhibitors (IBP) visa warning campaign for risks of drugs for stomach acidity]. Available from: http://www.infarmed.pt/documents/15786/1879176/Comunicado+-+Campanha+IBP/bb11fdf6-cb41-408a-a186-99bca397fc46. Acessed August 21, 2018. Portuguese.
44. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. *Drugs Aging*. 2012;29(10):829–837. doi:10.1007/s40266-012-0016-1
45. Barry PJ, Gallagher P, Ryan C, O'Mahony D. START (screening tool to alert doctors to the right treatment)— an evidence-based screening tool to detect prescribing omissions in elderly. *Age Ageing*. 2007;36:632–638. doi:10.1093/ageing/afm118
46. DGS. Guidance nº 018/2017, 26 September 2017, Available from: https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/gripe/normas-e-orientacoes.aspx. Acessed August 21, 2018.
47. Golomb BA, Chan VT, Evans MA, Koperski S, White HL, Criqui MH. The older the better: are elderly study participants more non-representative? A cross-sectional analysis of clinical trial and observational study samples. *BMJ Open*. 2012;2:6. doi:10.1136/bmjopen-2012-000833