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Potentially Inappropriate Prescribing in Elderly: Application of STOPP/START Criteria in Portuguese Patients

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CHAVE MÓVEL

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Que o mar unisse, já não separasse.
Sagrou-te, e foste desvendando a espuma,
E a orla branca foi de ilha em continente,
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E viu-se a terra inteira, de repente,
Surgir, redonda, do azul profundo.
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Resumo alargado

Resumo alargado

O envelhecimento crescente da população é multifatorial, mas resulta sobretudo de baixas taxas de natalidade e do aumento da esperança média de vida. Embora o aumento da esperança média de vida reflita o sucesso de medidas de saúde pública, o envelhecimento da população traduz-se numa maior morbilidade e incidência de doenças crónicas, o que suscita preocupações quanto à sustentabilidade da gestão dos doentes e dos sistemas de saúde.

De facto, as doenças crónicas, mais prevalentes nas pessoas idosas (com 65 ou mais anos), culminam em multimorbilidade e, consequentemente, na utilização simultânea de vários fármacos. É de notar que a polifarmácia, globalmente aceite como a utilização de cinco ou mais fármacos, está associada a uma maior probabilidade de ocorrência de reações adversas a medicamentos, problemas relacionados com medicamentos e prescrição potencialmente inapropriada. Por sua vez, as reações adversas a medicamentos são responsáveis por internamentos hospitalares, custos de saúde, morbilidade e mortalidade, apesar de mais de metade poderem ser evitáveis.

A gestão destes doentes com um perfil farmacoterapêutico cada vez mais complexo exige uma abordagem cuidadosa, nomeadamente aquando da transição de cuidados, e a definição e monitorização de um plano individual de intervenção para cada doente.

No âmbito dos cuidados continuados, em Portugal, onde a esperança média de vida é ligeiramente superior à média europeia, foi criada a Rede Nacional de Cuidados Continuados Integrados (RNCCI) em 2006, por iniciativa do Ministério do Trabalho e da Solidariedade Social e do Ministério da Saúde. A RNCCI é formada por um conjunto de instituições públicas e privadas que prestam cuidados continuados de saúde e apoio social a doentes provenientes do hospital ou da comunidade, que se encontram em situação de dependência e necessitam de ajuda para lidar com limitações mentais, sociais e/ou físicas. Apesar deste apoio ser independente da idade, a verdade é que uma percentagem muito significativa dos seus doentes é naturalmente idosa.

A RNCCI abrange mais de 10.000 camas de internamento distribuídas, a nível nacional, por diversas Unidades de Cuidados Continuados Integrados (UCCI). No entanto, existe ainda uma lacuna significativa na investigação que explore a medicação destes doentes, especialmente no que concerne à polifarmácia e à prescrição potencialmente inapropriada, também associada à ocorrência de reações adversas a medicamentos, risco de hospitalização, readmissão hospitalar, custos elevados, menor qualidade de vida e até maior mortalidade.

A prescrição potencialmente inapropriada é uma preocupação crescente que respeita a: medicamentos potencialmente inapropriados (PIM), sobreprescrição (utilização de medicamentos sem uma indicação clínica clara) ou prescrição incorreta (utilização de um medicamento indicado quando o risco ultrapassa o benefício ou quando existe uma alternativa

mais segura ou mais eficaz); e prescrições potencialmente omissas (PPO), ou subprescrição (não prescrição de um medicamento benéfico para o qual existe uma indicação clínica clara).

No contexto da prática clínica, foram desenvolvidas diversas ferramentas para identificar prescrições potencialmente inapropriadas. A lista de Beers, uma das primeiras a ser desenvolvida, tem vindo a ser amplamente utilizada. No entanto, como muitos dos medicamentos incluídos nesta lista não estão comercializados na maioria dos países europeus, a sua aplicabilidade é limitada. Por sua vez, os critérios STOPP/START *(Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment)* permitem identificar PIM e PPO, que também têm consequências nefastas para os doentes, e as versões atualizadas demonstraram cobrir PIMs com maior significado clínico. Apesar da relevância destes critérios, a sua aplicação em Portugal é escassa e praticamente inexistente em contextos específicos, como as UCCI. Assim, o presente estudo propôs-se a colmatar várias lacunas existentes na investigação portuguesa, nomeadamente no que concerne aos doentes das UCCI, analisando a prescrição de 180 doentes oriundos de 8 UCCI distintas.

Em primeiro lugar, analisou-se a relação entre as características demográficas e clínicas com o padrão de utilização de medicamentos e a polifarmácia. A média de fármacos prescritos por doente foi de oito e cerca de 90% dos doentes estava polimedicado. A regressão logística multivariada revelou que a polifarmácia estava significativamente associada à UCCI, quando comparadas duas instituições, e também com o Índice de Comorbidade de Charlson (CCI). O CCI é um índice que resulta da soma entre a ponderação da idade (1 ponto por cada década acima dos 50 anos, com um máximo de 4 pontos) e uma ponderação atribuída a várias doenças (de 1 a 6). O CCI prevê a sobrevida a 10 anos de doentes com múltiplas comorbilidades, sendo que pontuações mais altas indicam situações de saúde mais graves e, consequentemente, um pior prognóstico.

Em seguida, foi determinada a prevalência de PIM e PPO nos doentes idosos, através da aplicação dos critérios STOPP/START, e foram investigados potenciais preditores. PIM teve uma prevalência de 85,1% e envolveu principalmente fármacos que atuam no sistema nervoso central e psicotrópicos. PPO teve uma prevalência de 81,4% e esteve associada sobretudo a fármacos que atuam no sistema musculoesquelético e no sistema cardiovascular. A regressão logística revelou que os preditores de PIM foram o género feminino, a proveniência do hospital e o número de medicamentos. Por sua vez, PPO esteve significativamente associado ao CCI e à história recente de fraturas.

Por fim, foram exploradas as diferenças entre os doentes idosos com idades entre os 75 e os 84 anos e osidosos mais velhos (i.e, com 85 ou mais anos) no que respeita à prevalência e aos fatores associados a PIM e PPO. Os doentes mais idosos eram mais dependentes nas atividades de vida diária e apresentaram um CCI superior, apesar de serem os doentes idosos com idades entre os 75 e os 84 anos a revelar um maior número de fármacos diários e de doses orais. Para além disso, os doentes entre os 75 e os 84 anos tiveram uma maior proveniência do hospital e eram mais obesos. A PIM foi inferior nos doentes mais velhos, no entanto, a prevalência de PIM e PPO não foi significativamente diferente entre os dois grupos etários. As PIM e PPO mais prevalentes

foram as mesmas, mas os doentes mais velhos com história de quedas tinham mais provavelmente uma PPO associada à omissão da prescrição de vitamina D. A regressão logística revelou que o número de medicamentos foi um preditor comum de PIM. No caso dos PPO, o género masculino e o risco de queda foram preditores no grupo dos 75 aos 84 anos, enquanto o número de comorbilidades foi preditor no grupo com 85 ou mais anos.

As conclusões deste estudo visam contribuir para a melhoria da qualidade dos cuidados de saúde prestados a idosos, alertando para a necessidade de otimização da terapêutica medicamentosa, tendo em consideração uma abordagem holística, mas individualizada. A interação dinâmica entre o envelhecimento, a multimorbilidade, a polifarmácia e a prescrição inapropriada podem resultar em consequências nocivas marcantes, tanto do ponto de vista económico como, mais importante ainda, do ponto de vista da vida do doente. A adoção de boas práticas de prescrição aliada à identificação precoce de PIM e PPO poderá permitir reduzir os riscos e melhorar os resultados em saúde dos doentes. Para além disso, a identificação de preditores de prescrição inapropriada poderá fornecer dados importantes para a implementação de futuras políticas de saúde e práticas clínicas adequadas à crescente população idosa em Portugal.

Palavras-chave

Idosos; medicamentos; polifarmácia; morbilidade; Portugal; critérios STOPP; critérios START; medicamentos potencialmente inapropriados; prescrições potencialmente omissas.

Abstract

Abstract

The ageing of the population is a multifactorial phenomenon, primarily resulting from low birth rates and an increase in average life expectancy. While the increase in life expectancy reflects the success of public health measures, population ageing leads to greater morbidity and an increased incidence of chronic diseases. This raises concerns about the sustainability of patient management and health systems.

Chronic diseases are more prevalent in older people (those aged 65 or over) and result in multimorbidity, which leads to the simultaneous use of several drugs. Polypharmacy — defined as the use of five or more drugs — is associated with an increased risk of adverse drug reactions, drug-related problems, and potentially inappropriate prescribing. Adverse drug reactions are responsible for hospital admissions, health costs, morbidity and mortality, even though more than half of them are preventable.

The management of these patients with an increasingly complex pharmacotherapeutic profile requires a careful approach, particularly when transitioning care, requires the definition and monitoring of an individual intervention plan for each patient.

In Portugal, where the average life expectancy is slightly higher than the European average, the National Network for Integrated Continuing Care (RNCCI) was created in 2006 by the Ministries of Labour and Social Solidarity, and Health. The RNCCI comprises a group of public and private institutions that provide long-term healthcare and social support to the patients leaving hospital or joining from the community who are dependent and require assistance with mental, social and/or physical limitations. Although this support is independent of age, a significant proportion of patients are elderly.

The RNCCI has more than 10,000 inpatient beds, which are distributed across several Units for Integrated Continuous Care (UCCI) nationwide. However, research into the medication of these patients is still lacking, particularly on polypharmacy and potentially inappropriate prescribing. This is also associated with the occurrence of adverse drug reactions, the risk of hospitalisation and readmission, high costs, a lower quality of life and even higher mortality.

Potentially inappropriate prescribing is a growing concern in terms of potentially inappropriate medication (PIM), overprescribing (prescribing medication without a clear clinical indication) and incorrect prescribing (prescribing an indicated medication when the risk outweighs the benefit, or when a safer or more effective alternative is available); it also refers to potential prescribing omissions (PPO), or underprescribing (failing to prescribe a beneficial medication for which there is a clear clinical indication).

Various tools have been developed in the context of clinical practice to identify potentially inappropriate prescriptions. One of the first to be developed was the Beers list, which has been

widely used. However, as many of the medicines included in this list are not marketed in most European countries, its applicability is limited. The STOPP/START criteria (Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment) can identify PIM and PPO, both of which can have harmful consequences for patients. The updates of the criteria have been shown to cover PIM with greater clinical significance. Despite the relevance of these criteria, they are rarely applied in Portugal and are practically non-existent in specific contexts, such as UCCI. Therefore, this study aimed to address several gaps in Portuguese research, particularly regarding UCCI patients, by analysing the prescriptions of 180 patients from eight different UCCI.

Firstly, the relationship between demographic and clinical characteristics and medication use patterns, including polypharmacy was analysed. On average, eight drugs were prescribed per patient, and around 90% of patients were polymedicated. Multivariate logistic regression revealed that polypharmacy was significantly associated with UCCI when two institutions were compared, as well as with the Charlson Comorbidity Index (CCI). The CCI is an index resulting from the sum of age weighting (one point for each decade over the age of 50, up to a maximum of four points) and a weighting assigned to various diseases (from one to six). It predicts the 10-year survival rate of patients with multiple comorbidities: higher scores indicate more serious health conditions and, consequently, a worse prognosis.

Then, the prevalence of PIM and PPO in elderly patients was determined by applying the STOPP/START criteria, after which potential predictors were investigated. PIM was found to have a prevalence of 85.1%, mainly involving drugs that act on the central nervous system and psychotropic drugs. PPO had a prevalence of 81.4%, mainly involving drugs that act on the musculoskeletal and cardiovascular systems. Logistic regression analysis showed that the predictors of PIM were female gender, hospital admission and the number of medications taken. In turn, PPO was significantly associated with CCI and a recent history of fractures.

Finally, we explored differences in the prevalence and associated factors of PIM and PPO between the patients aged 75–84 years and the oldest-old patients (i.e., aged 85 or over). The oldest-old patients were more dependent on activities of daily living and had a higher CCI. However, patients aged 75–84 patients took more daily drugs and had higher oral doses; additionally, patients in this age group were more likely to have been hospitalized and to be obese. Although PIM was lower in older patients (≥85 years), the prevalence of PIM and PPO did not differ significantly between the two age groups. The most prevalent cases of PIM and PPO were the same, but older patients with a history of falls were more likely to have a PPO associated with an omitted vitamin D prescription. Logistic regression analysis showed that the number of medications was a common predictor of PIM. For PPO, male gender and risk of falls were predictors in the 75–84 age group, while number of comorbidities was a predictor in the group aged 85 or over.

This study aims to improve the quality of healthcare provided to the elderly by highlighting the need to optimise drug therapy with a holistic but individualised approach. The dynamic interaction between ageing, multimorbidity, polypharmacy and inappropriate prescribing can result in significant harm, both economically and, more importantly, in terms of patients' lives.

Adopting good prescribing practices alongside the early identification of PIM and PPO could reduce risks and improve patients' health outcomes. Furthermore, identifying predictors of inappropriate prescribing could provide valuable information for the development of future health policies and clinical practices tailored to Portugal's growing elderly population.

Keywords

Older people; medications; polypharmacy; morbidity; Portugal; STOPP criteria; START criteria; potentiallly inappropriate medication; potential prescribing omission.

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Publications related to this thesis

Candeias, C., Gama, J., Rodrigues, M., Falcão, A., Alves, G. Potentially Inappropriate Medications and Potential Prescribing Omissions in Elderly Patients Receiving Post-Acute and Long-Term Care: Application of Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment Criteria. *Front Pharmacol* **2021**, *12*, doi:10.3389/fphar.2021.747523.

Candeias, C., Gama, J., Rodrigues, M., Falcão, A., Alves, G. Patients' Characterization, Pattern of Medication Use, and Factors Associated with Polypharmacy: A Cross-Sectional Study Focused on Eight Units of the Portuguese National Network for Long-Term Integrated Care. *Healthcare* **2023**, *12(1),* 57, doi:10.3390/healthcare12010057.

Candeias, C., Gama, J., Rodrigues, M., Meirinho, S., Falcão, A., Castelo-Branco, M., Alves, G. Potentially Inappropriate Prescribing to Older Patients Admitted to Units for Integrated Continuous Care: Application of STOPP/START Criteria. *J Clin Med* **2025**, *14(9),* 2861, doi:10.3390/jcm14092861.

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List of abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACOVE	Assessing Care of Vulnerable Elders
ADE	Adverse drug event
ADL	Activities of daily living
ADR	Adverse drug reaction
ARB	Angiotensin-II receptor blocker
ATC	Anatomical Therapeutic Chemical
BBB	Blood-brain barrier
CCI	Charlson Comorbidity Index
CI	Confidence interval
CNS	Central nervous system
DALYs	Disability-adjusted life years
DBI	Drug Burden Index
DNA	Deoxyribonucleic acid
DRPs	Drug-related problems
ECCI	Integrated Continued Care Teams
GFR	Glomerular filtration rate
HEDIS	Health Effectiveness Data and Information Set
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
INFARMED	National Authority of Medicines and Health Products, I.P.
MAI	Medication appropriateness index
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratios
PIM	Potentially inappropriate medication
P-gp	P-glycoprotein
PPO	Potential prescribing omission
RNCCI	Portuguese National Network for Long-term Integrated Care
SD	Standard deviation
SNS	National Health Service
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older People's Prescriptions
UC	Convalescence Units
UCCI	Units for Integrated Continuous Care
ULDM	Long-Term and Maintenance Units
UMDR	Medium-Term and Rehabilitation Units

USA	United States of America
WHO	World Health Organization
YLLs	Years of life lost

Chapter I

General introduction

Chapter I – General introduction

I.1. Aging of the population

Aging worldwide is arguably the most pressing economic, health, and social challenge we face today [1]. People around the world are living longer and most individuals can anticipate reaching their sixties and beyond [2]. The increase of life expectancy and the decline of fertility rates have led to the aging of the global population, causing significant changes in its age structure [3]. Moreover, the aging population has led to an increase in chronic conditions like diabetes mellitus, hypertension, osteoarthritis, osteoporosis and cancer, along with various cognitive challenges, such as dementia and depression, and also some social factors, all of which present significant public health concerns [4].

According to recent prospects, the global population is projected to keep increasing over the next 50 to 60 years, peaking at approximately 10.3 billion in the mid-2080s, compared to 8.2 billion in 2024. By the late 2070s, the global population of individuals aged 65 and older is expected to reach 2.2 billion, exceeding the number of children under 18 [5].

This is a global phenomenon. However, although population aging – the shift towards an older demographic – initially began in high-income countries (for instance, 30% of Japan's population is already over 60), it is now a challenge for low- and middle-income countries, wherethe most significant changes are being seen [2].

Historically, the United Nations and most researchers have relied on measures and indicators of population aging that are primarily or entirely based on chronological age, defining older individuals as those aged 60 or 65 and above [6].

In turn, "elderly" is defined as individuals aged 65 and older, with those between 65 and 74 categorized as "early elderly" and those over 75 as "late elderly" [7]. Other authors considered three groups: youngest-old, ages 65 to 74 years; middle-old, 75 to 84 years; and oldest-old, ≥85 years [8].

I.1.1. Aging in the world

In the past century, the world has experienced unmatched reductions in mortality rates, resulting in a rapid rise in the global population. This century will witness declining fertility rates alongside aging populations [9]. This trend appears to continue in recent prospects (Figure I.1) [5].

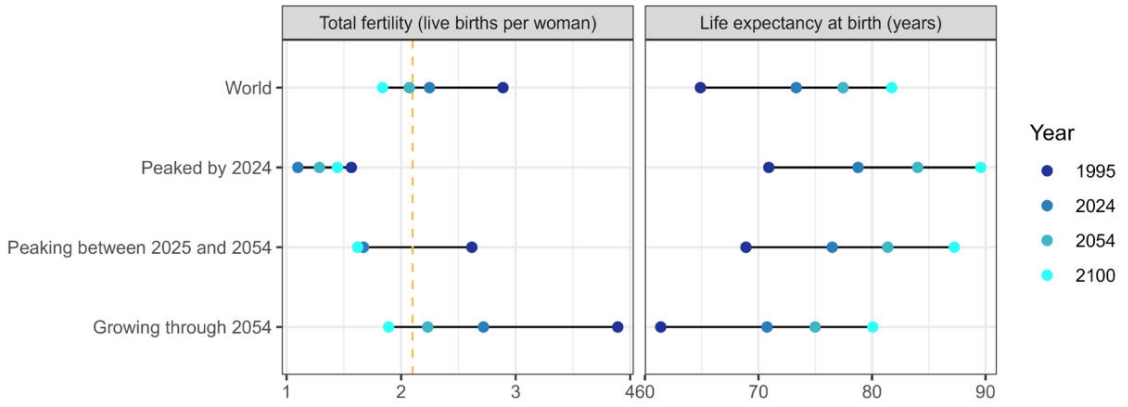

Figure I.1. Total fertility and life expectancy at birth, globally, by timing of the peak in population size, estimates for 1995 and projections (medium scenario), 2024, 2054 and 2100 [5].

By 2030, one in six people globally will be 60 years or older. During this period, the number of people aged 60 and above will rise from 1 billion in 2020 to 1.4 billion. By 2050, the global population of individuals aged 60 and older is projected to double, reaching 2.1 billion. Additionally, the number of people aged 80 or older is expected to triple between 2020 and 2050, reaching 426 million [2]. In fact, population growth occurs largely at the expense of an increase in the older population (Figure I.2).

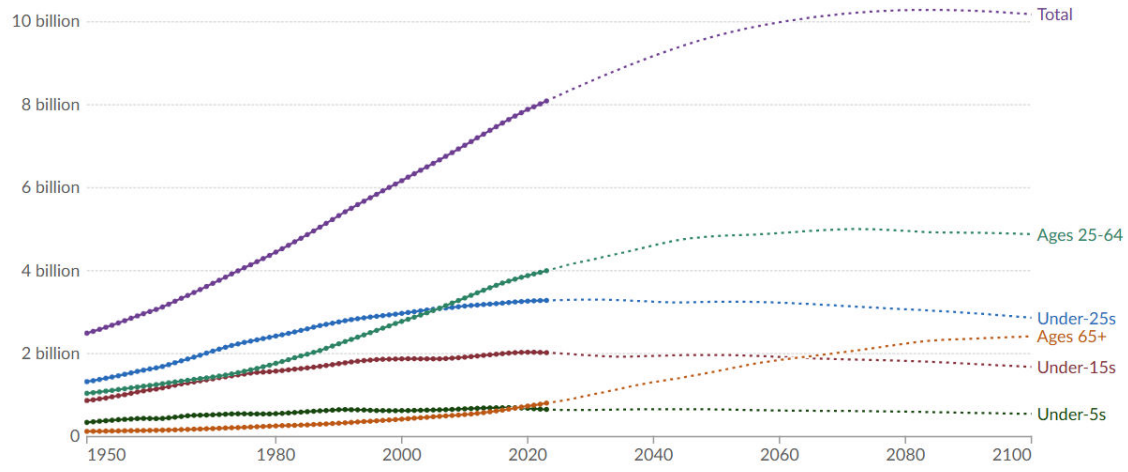

Figure I.2. Future projections of population by age group 1950 to 2100 from United Nations, World Population Prospects (2024) [10].

This demographic shift has raised significant concerns globally, especially in developing countries (Figure I.3), where the increasing proportion of older adults has become a critical issue [11].

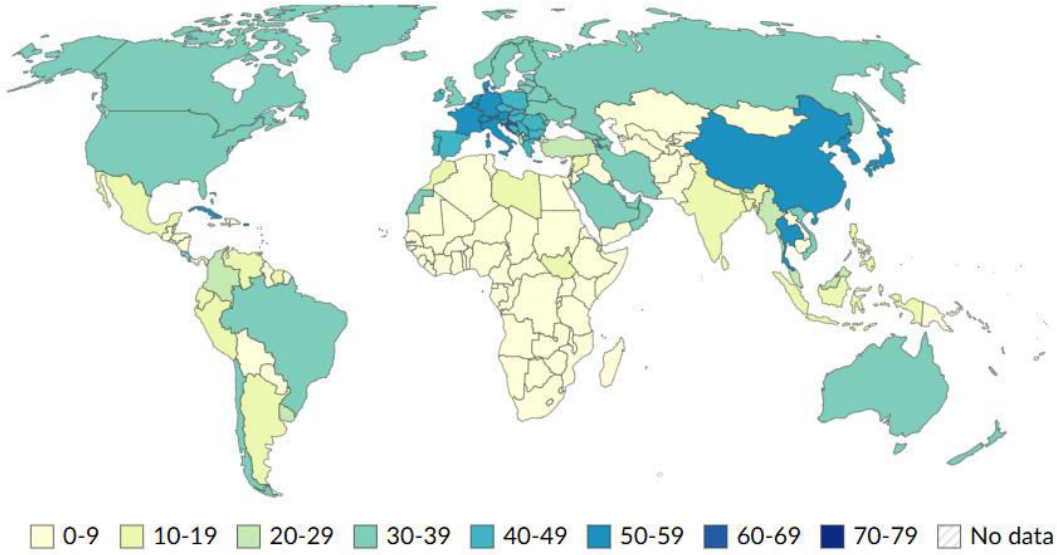

Figure I.3. Map presenting the age group with the largest population in 2023 from United Nations, World Population Prospects (2024) [12].

Despite the less developed countries being in the early or middle stages of aging, with a small but growing older population, it is expected a gradual increase in the number and proportion of elderly, for which the majority will need a lot of support [13].

I.1.2. Aging in Portugal

Demographic aging in Portugal continues to increase (Figure I.4). Recent data reveal that Portuguese aged 65 or over are more than 2.5 million people and has surpassed 3 thousand people aged 100 [14].

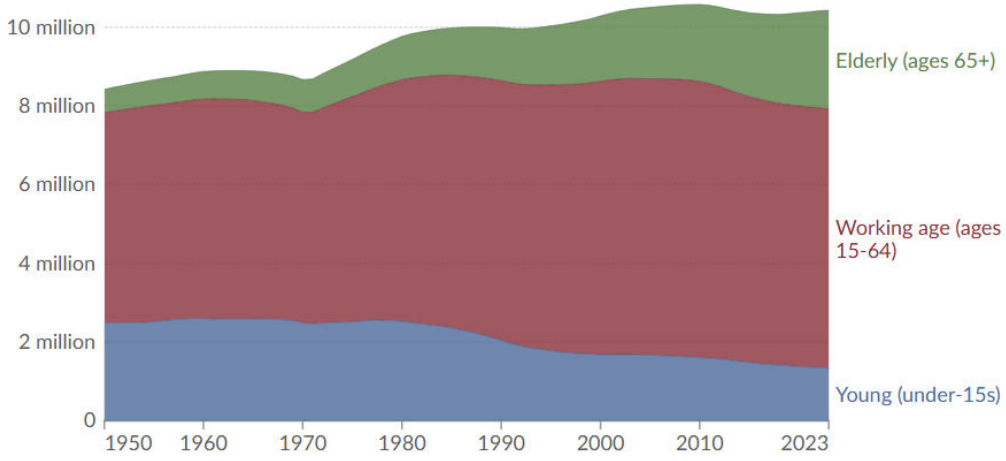

Figure I.4. Population of young, working-age and elderly, Portugal, from United Nations, World Population Prospects (2024) [15].

Considering the decade from 2012 to 2022, Portugal recorded the biggest increase in the average age in Europe, of 4.7 years, going from 42.1 to 46.8 years [16]. Furthermore, Portugal has the second highest old age dependency ratio, at 38.2% (Table I.1), and prospections show that this growth will continue in the future (Figure I.5) [17]. Portugal is behind Finland (38.3%) and followed by Italy (38.0%), while the lowest ratios were recorded in Ireland (23.7%), Luxembourg (21.8%), and Cyprus (20.6%) (Table I.1) [18].

Table I.1. Old-age dependency ratio, 1950 to 2023, adapted from United Nations, World Population Prospects (2024) [18].

Country/area	1950	2023	Absolute Change	Relative Change
Finland	10.4%	38.3%	+27.9 pp	+267%
Portugal	11.1%	38.2%	+27.2 pp	+245%
Italy	12.4%	38.0%	+25.6 pp	+207%
Greece	10.5%	37.3%	+26.8 pp	+255%
Croatia	10.1%	36.2%	+26.1 pp	+258%
Germany	13.4%	36.0%	+22.6 pp	+168%
France	17.3%	35.3%	+18.0 pp	+104%
Bulgaria	9.5%	34.3%	+24.8 pp	+262%
Latvia	15.6%	33.9%	+18.3 pp	+117%
Slovenia	11.6%	33.4%	+21.8 pp	+187%
Estonia	16.5%	33.1%	+16.6 pp	+101%
Sweden	15.3%	33.0%	+17.7 pp	+115%
Denmark	14.0%	32.4%	+18.4 pp	+132%
Czechia	12.3%	32.2%	+19.9 pp	+162%
Hungary	11.6%	32.2%	+20.6 pp	+177%
Belgium	16.2%	31.7%	+15.4 pp	+95%
Spain	10.9%	31.2%	+20.3 pp	+185%
Netherlands	12.3%	31.1%	+18.9 pp	+153%
Austria	15.6%	30.7%	+15.1 pp	+97%
Romania	11.2%	30.7%	+19.5 pp	+174%
Lithuania	11.7%	30.4%	+18.7 pp	+159%
Poland	8.0%	29.9%	+21.9 pp	+274%
Malta	12.6%	29.5%	+16.8 pp	+133%
Luxembourg	13.9%	21.8%	+8.0 pp	+58%
Cyprus	10.0%	20.6%	+10.6 pp	+106%
Other				
Europe (UN)	12.1%	31.2%	+19.1 pp	+159%
World	8.4%	15.4%	+6.9 pp	+82%

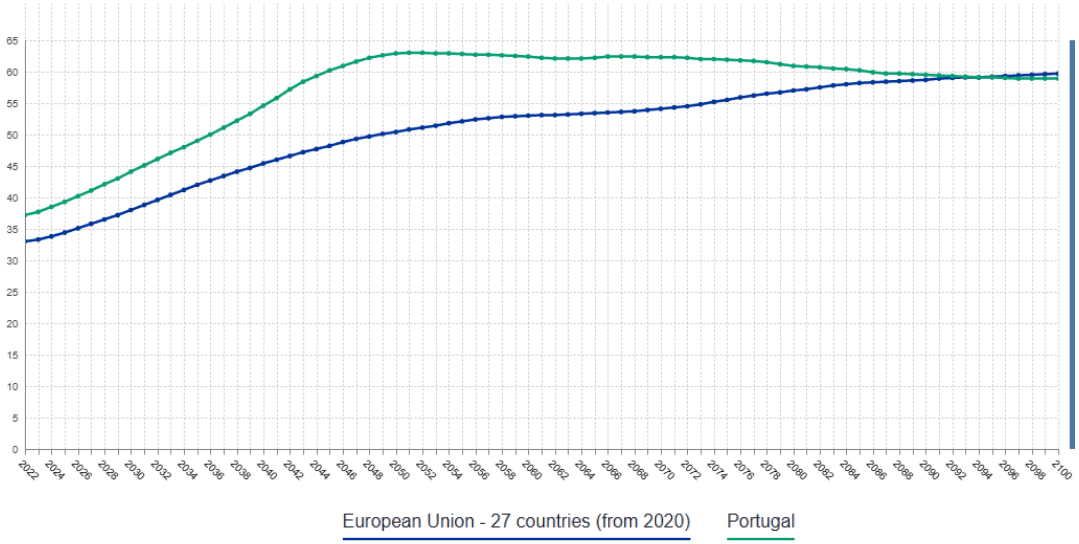

Figure I.5. Old-age dependency ratio projetctions, 1950 to 2100, from Eurostat [17].

These data are even more revealing when we realize that the aging index, which compares the population aged 65 and over (elderly population) with the population aged 0 to 14 (young population), reached the value of 188.1 elderly people for every 100 young people, the 2nd highest in Europe [19].

Furthermore, it is concluded that, today, Portugal has more couples without children, more families' single parents and more single-person families. These data also allow us to understand that the Portuguese people are also more alone: more than a million people live alone and, of these, more than half are elderly. Portugal is the 4th EU country with the highest percentage of elderly people living alone in the total number of people living in this condition [14].

I.2. Physiological, pharmacokinetic and pharmacodynamic changes in aging

I.2.1. Physiology of aging and age-related diseases

Various theories attempt to explain the causes of aging, though it is likely a combination of multiple factors, including both intrinsic processes and external influences, that lead to its clinical manifestations. Aging results in a decline in the function of all body systems, reducing the ability to maintain homeostasis when confronted with stressors. This decline can make it difficult to differentiate between normal age-related changes and pathological conditions [20].

Aging is influenced by genetic factors, environmental exposures, and lifestyle choices. Literature already identified some of the most troubling challenges (Table I.2) that emerge as a result of the natural aging process [21].

Table I.2. Common issues associated with aging by organ system, adapted from [21].

Organ System	Common medical and surgical issues associated with aging
Neurological	Cerebrovascular accident, Alzheimer disease, and other dementias, Parkinson disease
Cardiovascular	Coronary artery disease and atherosclerosis, heart failure, hypertension, hematologic malignancy
Pulmonary	Chronic obstructive pulmonary disease, lung cancer, pneumonia
Musculoskeletal	Osteoporosis, osteoarthritis, fractures, skeletal malignancies
Endocrine	Diabetes mellitus
Urological/Gynecologic	Urinary tract infections, urogenital cancer, cervical cancers, breast cancers, prostate cancer
Special Senses	Presbycusis, presbyopia, cataract, macular degeneration, glaucoma
Gastrointestinal	Malabsorption, gastrointestinal malignancies, bowel obstruction, diverticular disease
Other special considerations	Independence, falls, elder abuse and neglect, psychiatric concerns, skin breakdown, skin tears

Some key physiological processes involved in aging that are associated with age-related diseases are telomere shortening, cellular senescence, stem cells exhaustion, mitochondrial dysfunction, epigenetic modifications, inflammation and immune system decline, proteostasis, and microbiota alterations, as discussed below.

Telomere shortening

Telomeres are repetitive deoxyribonucleic acid (DNA) sequences located at the ends of chromosomes that safeguard them from damage. Telomeres shorten after each cell division, and when they become too short, the cell loses its ability to divide, resulting in cellular senescence or apoptosis. This mechanism is believed to play a role in aging, as tissues depend on cell division for renewal [22]. The rate at which telomeres shorten differs among individuals and is affected by lifestyle factors like stress, smoking, exposure to pollution, a lack of physical activity, obesity, and an unhealthy diet [23]. Many human conditions linked to normal aging are triggered by accelerated telomere dysfunction [24] and the creation of mouse models with short telomeres has shown that telomere attrition is linked to age-associated diseases, such as pulmonary and kidney fibrosis [25,26].

Cellular senescence

Cellular senescence is the process in which cells stop dividing and experience distinct functional changes. This phenomenon is typically triggered by factors like DNA damage, telomere shortening, and oxidative stress. Over time, senescent cells accumulate and release pro-

inflammatory cytokines and growth factors, which play a role in tissue dysfunction and contribute to age-related diseases [27]. Cellular senescence is involved in various non-proliferative diseases, including lung fibrosis, kidney disorders, liver steatosis, obesity-related metabolic syndrome, type 1 and 2 diabetes, atherosclerosis, as well as Alzheimer's and Parkinson's diseases [28].

Stem cells exhaustion

Stem cells are essential for tissue maintenance and repair, as they continuously replace cells lost through damage or wear. However, with aging, the ability of stem cells to regenerate diminishes. This decline is believed to result from intrinsic changes in stem cell function, such as the accumulation of DNA damage, as well as alterations in the tissue microenvironment that impact stem cell niches. As stem cell function declines, tissues and organs age, leading to reduced regeneration and repair capacity [29]. Aging-related features of skin stem cells, hematopoietic stem cells, intestinal stem cells, neural stem cells, and muscle stem cells have already been described [30].

Mitochondrial dysfunction

Mitochondria are the energy generators of cells, and their function deteriorates with age. Mitochondrial dysfunction results in reduced adenosine triphosphate production, elevated reactive oxygen species production, and impaired cellular function. This dysfunction plays a major role in aging, especially in energy-demanding tissues like muscle and the brain. The buildup of reactive oxygen species further causes cellular damage, DNA mutations, and protein misfolding, all of which accelerate the aging process [31,32].

Epigenetic modifications

Epigenetic modifications, including DNA methylation and histone modifications, control gene expression without changing the underlying DNA sequence. As we age, these epigenetic changes gradually accumulate, potentially disrupting the expression of genes responsible for tissue maintenance, repair, and immunity. These modifications have been associated with age-related diseases like cancer, cardiovascular conditions, and neurodegenerative disorders [33].

Inflammation and immune system decline

Chronic low-grade inflammation, commonly known as "inflammaging," is a key feature of aging. This ongoing inflammation is associated with several age-related conditions, such as cardiovascular disease, neurodegeneration, and diabetes. At the same time, the immune system experiences senescence, marked by a diminished ability to respond to infections and an increased

risk of autoimmune diseases. The thymus shrinks with age, leading to a decrease in the production of new T-cells, which are crucial for adaptive immunity [34].

Proteostasis

Proteostasis is the process that governs protein synthesis, folding, and degradation. As we age, the efficiency of proteostasis networks declines, leading to the accumulation of misfolded, oxidized, glycated, or ubiquitinylated proteins that often form aggregates as intracellular inclusion bodies or extracellular amyloid plaques. This accumulation can activate cellular stress responses, like the unfolded protein response, and contribute to several age-related morbidities, such as cataract, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders [35,36].

Microbiota alterations

The gut microbiome plays a significant role in age-related health decline and in the development of various non-communicable diseases across all age groups. Some compositional and functional changes linked to aging and disease overlap, while others are distinct [37]. It has already been reported that age-related changes in gut microbiota composition are associated with frailty, cognition, depression, and inflammation [38].

I.2.2. Pharmacokinetic changes and ageing

Aging leads to a range of physiological changes that can notably affect drug therapy, influencing the absorption, distribution, metabolism, and excretion of drugs. These alterations can modify pharmacokinetics (how the body processes a drug), which, combined with the complex drug regimens of many elderly patients, means that the potential for adverse drug reactions (ADR) is increased in this population [39].

Absorption

Drugs absorption refers to the process by which the unmetabolized drug is transported from the site of administration into the body's circulatory system [40]. Several mechanisms of drug absorption have been identified, including passive diffusion, carrier-mediated membrane transport (such as active and facilitated diffusion), and other nonspecific drug transporters [41].

The percentage of drug absorption varies among different routes of administration, such as oral, subcutaneous, transdermal, intravenous, and intramuscular [41]. This concept refers to bioavailability, which is defined as the relative amount of a drug from a pharmaceutical product that enters the systemic circulation in its unchanged form, along with the rate at which this occurs

[42]. Medications administered intravenously have a bioavailability of 100%, whereas the bioavailability of orally administered drugs depends on the extent of absorption in the intestine and on the extent of first-pass metabolism [39].

Pharmacokinetic studies examining the impact of aging on drug absorption have produced inconsistent results. Several studies found no age-related differences in the absorption rates of various drugs [43,44]. However, several physiological changes occur in the gastrointestinal tract during the aging, including reduced intestinal blood flow [45], decreased gut motility, and delayed gastric emptying, which result from a loss of local neural control [46]. Besides, first-pass metabolism can take place in the gut and in the liver [47]. A reduction in liver mass and blood flow can decrease the first-pass effect, which may impact the extent of absorption of drugs [39].

The absorption rate of subcutaneous or intramuscular administered drugs into the bloodstream can be slowed by decreased tissue blood flow and enhanced by reduced muscle mass, particularly for drugs administered as depot preparations. Additionally, reductions in chest wall compliance, ventilation-perfusion matching, and alveolar surface area may reduce the absorption of drugs delivered through the inhalation route [48]. Table I.3 summarizes some possible changes in older people that can have impact on drug absorption.

Table I.3. Possible changes in drug absorption in older people, adapted from [49].

Changes in absorption	**Impact on drug pharmacokinetics**	**Example(s)**
Decreased gastric emptying rate	Decreased oral absorption	Digoxin, levodopa
Increased gastric pH	Decreased absorption of drugs which are pH-dependent for their release	Enteric-coated drugs
	Increased absorption of weak bases	Methyldopa
	Decreased absorption of strong acids	Amoxycillin
Decreased intestinal absorptive surface	Age-dependent decrease in drug absorption	Indomethacin, prazosin and digoxin
Decreased active transport	Decreased transport of electrolytes and vitamins	Zinc, calcium, folate and B_{12}
Structural changes to stratum corneum	Decreased transcutaneous absorption of hydrophilic substances	Caffeine, aspirin
Poor cutaneous circulation	Decreased transcutaneous absorption	Clonidine
Unpredictable muscle circulation	Erratic intramuscular absorption	Penicillin

Distribution

Volume of distribution is a proportionality constant that relates the total amount of drug in the body to the plasma concentration of the drug at a given time [50]. This is influenced by both drug-

related (such as protein and tissue binding, acidity, lipophilicity, water solubility, charge, and size) and patient-related factors (such as total body water and body fat) [51].

A decrease in muscle mass and an increase in body fat percentage are common with aging [52]. As a result, polar drugs (like gentamicin, digoxin, ethanol, theophylline, and cimetidine) that are primarily water-soluble typically have smaller volumes of distribution, leading to higher serum concentrations in older adults. Instead, nonpolar compounds (like diazepam, lidocaine, and chlormethiazole), which are more lipid-soluble, experience an increase in volume of distribution with age [43]. A greater drug distribution can lead to accumulation during prolonged use, delaying the onset of the therapeutic effects. Additionally, the elimination of the drug may be prolonged after the last dose is taken, meaning that the effects may persist for some time afterwards [52].

A widespread binding to albumin and alpha-1-acid glycoprotein, both plasma proteins, could have a potential impact on drugs disposition (e.g., bioavailability, distribution and clearance), on their innocuity and their efficacy [53]. Acidic drugs (e.g., diazepam, phenytoin, naproxen, warfarin, acetylsalicylic acid) primarily bind to albumin, while basic drugs (e.g., lidocaine, clozapine, propranolol) bind to alpha-1-acid glycoprotein. Although age-related changes in the concentrations of these proteins have not been significant, albumin levels are often reduced in individuals with malnutrition, cachexia, or acute illness, whereas alpha-1-acid glycoprotein levels tend to rise during inflammatory diseases and cancer. An increase in alpha-1-acid glycoprotein could therefore reduce the free fraction of basic drugs such as lidocaine, clozapine, and propranolol. The free (unbound) concentration of a drug is the primary factor influencing its effect. While changes in plasma protein binding might theoretically affect the physiological effects of highly protein-bound drugs, their clinical significance is generally limited for most medications [48].

P-gp, also known as multidrug resistance protein-1, is a transmembrane efflux pump that uses adenosine triphosphate to actively transport substances out of the cell, working against their concentration gradients. P-gp is expressed in several tissues, such as the brain, kidneys, liver, gastrointestinal tract, testis, and placenta [54]. A study examining the P-gp substrate verapamil found reduced P-gp activity in the blood-brain barriers (BBB) of older adults, suggesting that the aging brain may be more vulnerable to higher drug exposure. This is particularly true for drugs actively transported out of the brain by P-gp, including domperidone, loperamide, paclitaxel, ondansetron, and cyclosporine [48]. A recent study focused on drug distribution of metoclopramide, a substrate of the BBB efflux transporter P-gp, used as an antiemetic, but with CNS effects (extrapyramidal symptoms and tardive dyskinesia). It suggests that an age-related decline in the clearance function of the BBB may influence the CNS effects or side effects of clinically used P-gp substrates [55]. Some possible changes in older people that can have impact on distribution are summarized in Table I.4.

Table I.4. Possible changes in drug distribution in older people, adapted from [49].

Changes in distribution	Impact on drug pharmacokinetics	Example(s)
Decrease in 10-15% of total body water	Decreased V_d for hydrophilic drugs	Ethanol, lithium
Increase in 10-15% of total body fat	Increased V_d for lipophilic drugs	Amiodarone, verapamil
Decreased serum albumin	Increased free fraction of albumin-bound drugs	Phenytoin
Increased serum alpha-1-acid glycoprotein levels	Decreased free fraction of alkaline drugs	Metoclopramide, erythromycin
P-gp efflux pump dysfunction	Increased permeability of the BBB and this increased effect-site concentration of CNS drugs	Rifampicin, cyclosporine

CNS, central nervous system; P-gp, P-glycoprotein.

Metabolism

Once a drug is absorbed and distributed throughout the body, it is usually metabolized; a process in which the drug is chemically altered by various body systems to form compounds that can be more easily excreted [56]. Drug metabolism, also known as biotransformation, typically reduces the pharmacological effect of a drug, although it can also produce toxic metabolites or active metabolites. Drugs may be metabolized before they reach systemic circulation (first-pass effect) and the liver is the primary site of drug metabolism in the body, although metabolism can also occur in the kidneys, skin, and gastrointestinal tract. Drug metabolism occurs in two phases: Phase I metabolic reactions and Phase II metabolic reactions [57].

Phase I reactions add reactive or polar groups (e.g., -OH, -COOH, -NH2, -SH) to drugs through processes like oxidation, reduction, and hydrolysis, making the drugs more water-soluble and preparing them for excretion. In Phase II reactions, these modified drugs are conjugated with polar compounds, a process catalyzed by various transferase enzymes, such as uridine diphosphate-glucuronosyltransferases, sulfotransferases, and glutathione S-transferases [58].

During the aging process, anatomically, there is a 20–40% reduction in liver volume, along with thickening of the hepatic sinusoidal endothelium. Physiologically, hepatic blood flow decreases, as does the smooth endoplasmic reticulum, where metabolism takes place. While the activity of drug-metabolizing enzymes generally remains unchanged with aging, it does decline in cases of frailty [59,60].

Drugs metabolized by phase I enzymes experience reduced metabolism with advanced age, particularly those processed by CYP3A isoenzymes [61], while phase II pathways do not seem to be significantly affected [48]. It is clear that hepatic drug clearance is reduced by 10–40% in older individuals for most drugs studied [62], likely due to a decrease in liver volume and hepatic blood flow [59].

For metabolic capacity-limited drugs with low protein binding, such as paracetamol and theophylline, evidence suggests a 30–50% decrease in metabolic clearance in older individuals. For metabolic capacity-limited drugs with high protein binding, like naproxen and valproic acid, total clearance is less reliable, as changes in protein binding can mask the true intrinsic clearance, but there is evidence of a roughly 50% reduction in free clearance in older individuals [63]. Table I.5 summarizes some potential changes in older people that can have impact on drug metabolism.

Table I.5. Possible changes in drug metabolism in older people, adapted from [49].

Changes in metabolism	**Impact on drug pharmacokinetics**	**Example(s)**
Decreased hepatic tissue mass	Decreased clearance by Phase I reactions	Ibuprofen, propranolol, fentanyl
Decreased hepatic blood flow	Decreased clearance of high extraction ratio drugs	Morphine, verapamil, lidocaine
Decreased portal blood flow	Increased oral bioavailability of high extraction ratio drugs	Propranolol, labetalol

Excretion

Excretion is the final stage of a medication's journey within the body. After the drug has been absorbed, distributed, and metabolized, the body needs to handle the remaining substances. The kidneys filter out parent drugs and metabolites from the bloodstream, with some being reabsorbed into the bloodstream and the rest excreted in the urine. The liver also plays a role in excreting byproducts and waste through the bile. Additionally, the lungs can serve as an excretion route, particularly for substances like alcohol and anesthetic gases, which are often eliminated through breathing [56].

The route of renal excretion is of particular importance when discussing age-related changes in pharmacokinetics [39]. Aging impacts the anatomical structure and function of kidney cells, leading to a decline in glomerular filtration rate (GFR), altering permeability of the glomerular capillary wall, and increasing vulnerability to podocyte injury and apoptosis. Additionally, aging affects tubular reabsorption and secretion, disrupts urinary concentration, and modifies the production of kidney-derived hormones and bioactive molecules [64].

There is a decline in endothelium-dependent vasodilation in the kidneys, marked by a reduced response to vasodilators (like acetylcholine, dopamine, and nitric oxide), as well as an increased sensitivity to vasoconstrictors (such as angiotensin, norepinephrine, and endothelin). This shift towards enhanced renal vasoconstriction, due to impaired nitric oxide-dependent responses, contributes to sodium retention and disrupts the pressure-natriuresis response. Additionally, in older adults, the renin-angiotensin system becomes less active. While renin production and release decrease with age, resulting in lower levels of renin and aldosterone, the kidneys' response to these hormones becomes exaggerated [65].

The age-related decline in GFR impacts the clearance of several drugs, including water-soluble antibiotics, diuretics, digoxin, water-soluble beta-blockers, lithium, nonsteroidal anti-inflammatory drugs, and newer anticoagulants like dabigatran and rivaroxaban. Much of this decline seems to be driven by age-related comorbidities, rather than the aging process itself. The clinical significance of reduced renal excretion depends on the drug's therapeutic index and the associated risk of toxicity. Drugs with a narrow therapeutic index (e.g. aminoglycoside antibiotics, digoxin, and lithium) can have serious adverse effects if their levels increase even slightly above the intended therapeutic range [48].

To consider optimize dose in renal impairment is equally important for drugs used in palliative care, such as analgesics [morphine, codeine, tramadol, non-steroidal anti-inflammatory drugs (NSAIDs)], anticonvulsants (gabapentin, pregabalin, topiramate, oxcarbazepine), antidepressants (bupropion, duloxetine, paroxetine, venlafaxine), and drugs that act in gastrointestinal (metoclopramide, famotidine, ranitidine) and cardiovascular [angiotensin-converting enzyme inhibitors (ACEIs), digoxin, diuretics] systems [66].

Recent clinical trials investigated the pharmacokinetic parameters influencing changes in drug exposure in the older population for various drugs (including midazolam, metoprolol, lisinopril, amlodipine, rivaroxaban, repaglinide, atorvastatin, rosuvastatin, clarithromycin, and rifampicin). Drug exposure increased by 0.9% per year starting at age 20 [67].

It is difficult to differentiate the physiological senescence from pathological decline in GFR [68]; however, it is estimated that GFR declines at a rate of 6.3 mL/min/1.73 m^2 per decade [64] and that approximately half of adults over 70 years old have a GFR of less than 60 mL/min/1.73 m^2 [65]. Conditions like hypertension, diabetes, obesity, and others can accelerate kidney aging. Comorbidities, on the other hand, have a far greater impact on the progression of both kidney disease and the aging process [69].

Chronic kidney disease has been defined as a GFR <60 mL/min/1.73 m^2 in the absence of kidney damage, which reflects a mean loss of 50% of kidney function in the healthy adult population. The KDIGO recommendations also define this threshold regardless of age [70]. However, this classification does not account for the normal decline in GFR associated with aging, and some authors considered that it may lead to an overdiagnosis of chronic kidney disease in older adults [71].

On the other hand, due to reduced muscle mass in older patients, serum creatinine levels may fall within the reference range, even though renal function is significantly impaired. Formulas to estimate GFR may be useful, although they were not well validated in frail individuals. Even so, the Cockcroft-Gault, the Modification of Diet in Renal Disease and the Chronic Kidney Disease Epidemiology Collaboration seemed to generally provide accurate estimates of the mean GFR in older populations, but they may misestimate atual kidney function by up to 30 mL/min/1.73 m^2 in individual cases [72].

It is also important to attend to the impact of drugs in kidneys. NSAIDs are commonly prescribed to manage pain in elderly, but they are linked to an increased risk of a ≥30% decline in GFR in individuals with an estimated GFR of less than 60 ml/min/1.73 m² [73]. In addition, the use of iodinated contrast media is another potential cause of kidney damage. Risk factors for developing contrast-induced nephropathy include pre-existing chronic kidney disease, dehydration, diabetes, and the use of ACEIs, diuretics, and NSAIDs [74].

Finally, the so-called "triple whammy" involves the combination of an ACEIs or angiotensin-II receptor blocker (ARBs), a diuretic, and a NSAID. In this drug-drug interaction, NSAIDs inhibit prostaglandin-mediated afferent glomerular tone (preventing vasodilation), while ACEIs and ARBs block angiotensin-mediated efferent control (preventing vasoconstriction), thereby disrupting the glomerulus' autoregulatory response. This leads to a significant reduction in trans-glomerular hydrostatic pressure. When combined with the hypovolemic effect of diuretics and the blood pressure-lowering action of ACEIs/ARBs, the resulting decrease in GFR can increase the risk of renal failure, particularly in vulnerable individuals such as older adults [75].

I.2.3. Pharmacodynamic changes and ageing

Pharmacodynamics refers to the biochemical and physiological response of the body to a drug [75]. As a drug circulates through the bloodstream, it shows affinity for certain drug-receptor sites, which refers to how strongly it binds to them. This interaction between drugs and receptor sites operates like a lock and key system, influencing how drugs function and their presence in the bloodstream after administration [56].

Pharmacodynamic properties are affected by changes in the concentration of the drug at the receptor site, as well as the response at the receptor itself [76]. Compared to pharmacokinetics, there is few data available to support age-related changes in pharmacodynamics. However, these changes can affect a drug's magnitude of effect and increase the likelihood of adverse effects. Differences in pharmacodynamics between youngest and oldest adults may be partly due to age-related changes and partly due to shifts in pharmacodynamic sensitivity, such as alterations in signal transduction, homeostatic mechanisms [66], receptor numbers or concentrations, decreased baroreceptor reflex, and a less effective BBB [77].

The number of cholinergic neurons and receptors also decreases with age, resulting in increased sensitivity to anticholinergic medications. This heightened sensitivity can cause agitation, confusion, memory impairment, and delirium, along with other systemic effects such as reduced salivation, lacrimation, urination, defecation, and gastric emptying and even resulting in the development of an anticholinergic syndrome [78,79]. Some of drugs and herbs associated with anticholinergic syndrome are reported in Table I.6.

Table I.6. Drugs and herbs that may be associated with anticholinergic syndrome, adapted from [79].

Class of compound	**Drugs or herbs**
Antihistamines	H_1 receptor antagonists (hydroxyzine, meclizine, and promethazine)
Antiparkinsonian	Benztropine and trihexyphenidyl
Antimuscarinic, genitourinary system	Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium
Antimuscarinic, spasmolytics	Atropine, belladonna, clidinium-chlordiazepoxide, dicyclomine, hyoscyamine, glycopyrrolate, propantheline, and scopolamine
Antimuscarinic, inhaled bronchodilator	Ipratropium and tiotropium
Antimuscarinic, ophthalmic drugs (mydriatic/cycloplegic)	Atropine, cyclopentolate, homatropine, and scopolamine
Gastrointestinal drugs	Antiemetics (domperidone and loperamide)
Muscle relaxants	Cyclobenzaprine, orphenadrine, and tizanidine
Psychotropic agents	Chlorpromazine, fluphenazine, loxapine, methotrimeprazine, thioridazine, trifluoperazine, clonazepam, tricyclic antidepressants, haloperidol, perphenazine, olanzapine, quetiapine, iloperidone, and risperidone
Analgesics	Opiates: codeine, hydrocodone, fentanyl, meperidine, methadone, morphine, and tramadol
Herbs	Angel's trumpet (Brugmansia species), deadly nightshade (*Atropa belladonna*), henbane, *Datura stramonium*, *Mandragora officinarum*, *Datura inoxia*, clitocybe, inocybe, amanita, entoloma, and mycena

Older adults often exhibit an exaggerated response to CNS-active drugs, which is partly due to the age-related decline in CNS function and an increased ability of drugs to cross the BBB, resulting in higher drug concentrations in the brain compared to younger individuals. In younger individuals, the BBB blocks almost all molecules from leaving the bloodstream to enter the CNS, except substances that are small, lipophilic, or able to cross the barrier via active transport [80]. Regarding serotonin reuptake inhibitors, lower doses are necessary in older patients to achieve the desired exposure [81]. Concerning dopamine, the number of dopamine receptors declines with age, particularly a reduction in D_1 and D_2 receptors, which is associated with impairments in motor functionality, mental function and attention [82]. With antipsychotics, in older patients it was reported an increased risk of sudden death, probably associated with cardiac arrhythmia [83]. Besides, antipsychotics in dementia can be also associated with cerebrovascular events, pneumonia, parkinsonian symptoms, gait disturbance, sedation, venous thromboembolisms, head injuries and traumatic brain injuries, increased mortality risk and accelerated cognitive decline [84]. Regarding adrenergic receptors, there is a heightened activation in the CNS; therefore, it seems that slightly lower doses should be given to older patients in order to achieve the same plasma exposure and effect [81]. Concerning to with benzodiazepine sedative-hypnotics and Z-drugs, which enhance gamma-aminobutyric acid receptor function, there is an increased sensitivity in older adults, which may contribute to severe

adverse events such as hip fractures [85,86]. Regarding to opioid receptors, older individuals exhibit heightened sensitivity to opioid adverse effects, including an increased risk of falls [87,88], and to CNS depression induced by μ-opiate receptor agonists (like fentanyl, alfentanil, and remifentanil) during anesthesia. However, studies on respiratory depression have shown no significant difference in sensitivity to morphine between younger and older individuals [81].

Another clinically significant pharmacodynamic change observed in the elderly is related to alterations in adrenergic responsiveness. Age-related alterations primarily involving a reduction in beta-adrenergic receptor density and abnormalities in the beta-adrenoceptor-G-protein(s)-adenylyl cyclase system [89]. Thus, older adults have reduced sensitivity of their beta-1 and beta-2 adrenergic receptors, resulting in a diminished response to beta-agonists like dobutamine (beta-1 agonist) and salbutamol (beta-2 agonist) [90].

Changes in homeostatic mechanisms also play a role in the pharmacodynamic alterations observed in the elderly, once they increase the susceptibility to the effects of drugs, as there is less attenuation of their impact. The loss of counterregulatory action further increases the risk of ADRs in this population. Clinically significant examples include postural hypotension and the risk of drug-induced orthostatic changes, which can lead to syncope and falls, commonly seen with various cardiovascular and neurological medications. Additionally, older adults may experience heightened sensitivity to warfarin, resulting in a stronger therapeutic response to the anticoagulant effects compared to similar doses in younger patients [76]. In Table I.7 are identified possible changes in pharmacodynamics in older people related to certain drugs ou drugs classes.

Table I.7. Possible changes in pharmacodynamics in older people, adapted from [48].

Drug	**Impact on pharmacodynamics**	**Dose recommendation**
Antipsychotics	Increased sedation	Decrease
	Increased extrapyramidal symptoms	Decrease
Benzodiazepines	Increased sedation	Decrease/re-evaluate necessity and, if necessary, preferably use short-term and select benzodiazepines that are glucoronidized (lorazepam lormetazepam, oxazepam and temazepam)
	Increased postural sway	
	Increased memory impairment	
Beta-agonists	Decreased bronchodilatation	Increase slowly based on effect
Beta-blocking agents	Decreased target tension Antihypertensive effects	Increase slowly based on effect
	Decreased target tension Vasoconstrictive effects (peripheral)	
Vitamin K antagonists	Increased anticoagulant effects	Decrease based on effect (International Normalized Ratio)

Furosemide	Decreased especially in decreased renal function (peak diuretic response)	Increase based on effect
Morphine	Increased especially in decreased renal function (analgesic effect, sedation)	Decrease/switch
Propofol	Increased anaesthesic effect	Decrease
Verapamil	Increased antihypertensive effect	Decrease
	Constipation	Add laxative

I.3. Comorbidity, multimorbidity, disability-adjusted life years and leading causes of death

I.3.1. Comorbidity *versus* multimorbidity

The conditions that commonly co-occur are described using a variety of terms, including diseases, disorders, conditions, illnesses, or health problems. Some of these terms align with classification systems such as the International Classification of Diseases, the Diagnostic and Statistical Manual of Mental Disorders, or the International Classification of Primary Care. However, other terms and concepts do not fit neatly into these classification systems, which makes it challenging to apply them in a consistent and reproducible way [91].

On the one hand, multimorbidity was defined as the co-occurrence of multiple chronic or acute diseases and medical conditions within one person [92], and it is an increasing global issue with significant impacts on individuals, caregivers, and society as a whole [93]. Multimorbidity is a frequent phenomenon among old people [94]. A systematic review revealed that multimorbidity was linked to a higher hospitalization risk, and this risk was not affected by the country's wealth and patient's gender [95]. One the other hand, comorbidity initially was described as "any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study" [96] and, more recently, as "the combined effects of additional conditions in reference to an index chronic condition" [97]. Comorbidity is also an issue of growing importance due to changing demographics [98].

In practice, when a patient with diagnosed chronic kidney disease, type 2 diabetes, and hypertension visits their nephrologist, the specialist considers the patient to have chronic kidney disease along with comorbid type 2 diabetes and hypertension. However, when the patient consults their endocrinologist, the patient is seen as having type 2 diabetes with comorbid chronic kidney disease and hypertension. In contrast, a primary care physician or generalist, such as a geriatrician, would view the patient as having multimorbidity. This perspective takes a holistic approach to care, focusing on the patient's symptoms, preferences, and healthcare priorities, rather than being defined by any specific condition [99].

I.3.2. Disability-adjusted life years, years of life lost and leading causes of death

Disability-adjusted life years

The disability-adjusted life years (DALYs) are calculated by summing years lived with disability and years of life lost (YLLs) [100]. Population ageing can be naturally associated with DALYs and with YLLs [101].

Disorders in individuals aged 60 and older account for 23% of the global disease burden. While the proportion of this burden is highest in high-income regions, DALYs per capita are 40% higher in low- and middle-income regions [102]. Figure I.6 is age-standardized and shows the difference in DALYs worldwide.

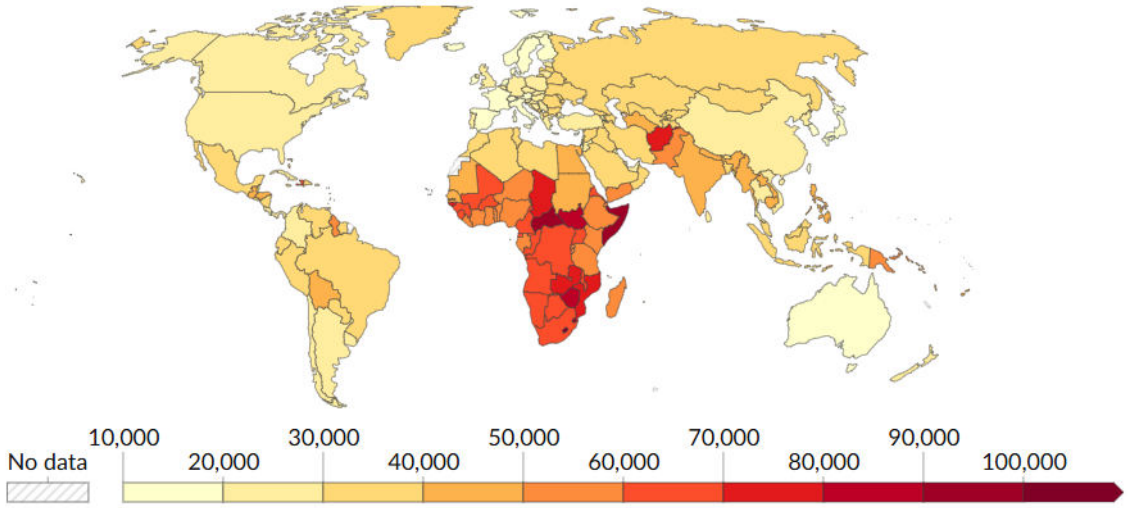

Figure I.6. Disability-adjusted life years per 100,000 individuals from all causes, from [103].

In 2019, the two leading causes of DALYs globally (Figure I.7) were cardiovascular diseases and cancers, which are overlap focusing on Europe (Figure I.8). However, globally, other leading causes are neonatal disorders, respiratory infections and tuberculosis, while in Europe DALYs are also frequently caused by musculoskeletal disorders, neurological disorders and mental disorders, as well in Portugal.

In 2021, global DALYs increased from 2·63 billion in 2010 to 2·88 billion for all causes combined. Coronavirus disease 2019 was the leading cause, followed by ischaemic heart, neonatal disorders, and stroke [104]. DALYs from communicable diseases like human immunodeficiency virus/acquired immune deficiency syndrome and diarrheal diseases have decreased by more than 50% between 2000 and 2021. Meanwhile, DALYs from diabetes and Alzheimer's disease more than doubled [105].

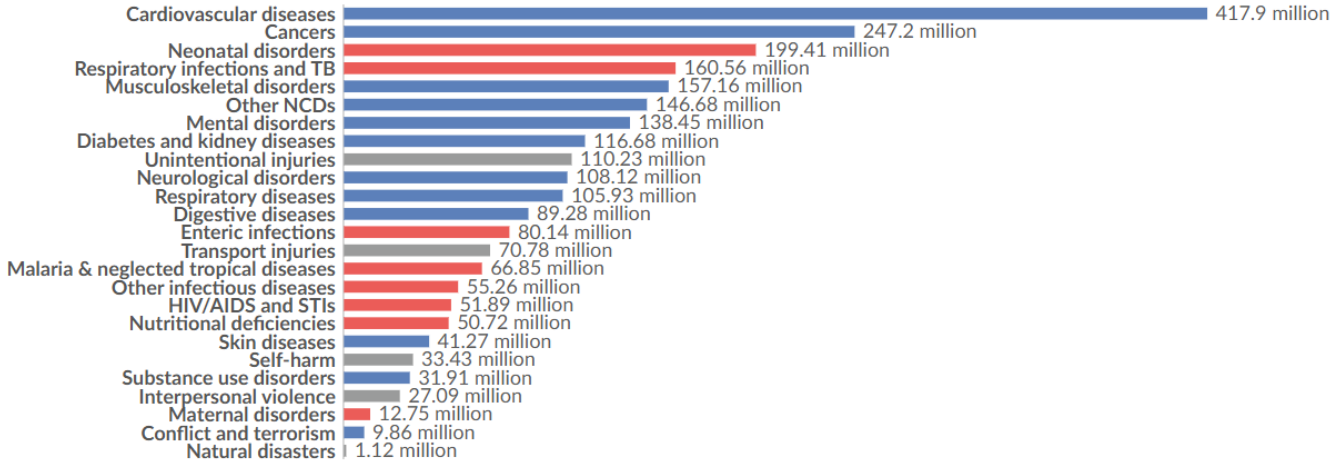

Figure I.7. Burden of disease by cause, World, 2019 [106].

Note: Non-communicable diseases are shown in blue; communicable, maternal, neonatal and nutritional diseases in red; injuries in grey. AIDS: Acquired Immune Deficiency Syndrome; HIV: Human Immunodeficiency Virus; NCDs: non-communicable diseases; STIs: Sexually Transmitted Infections; TB: Tuberkulose

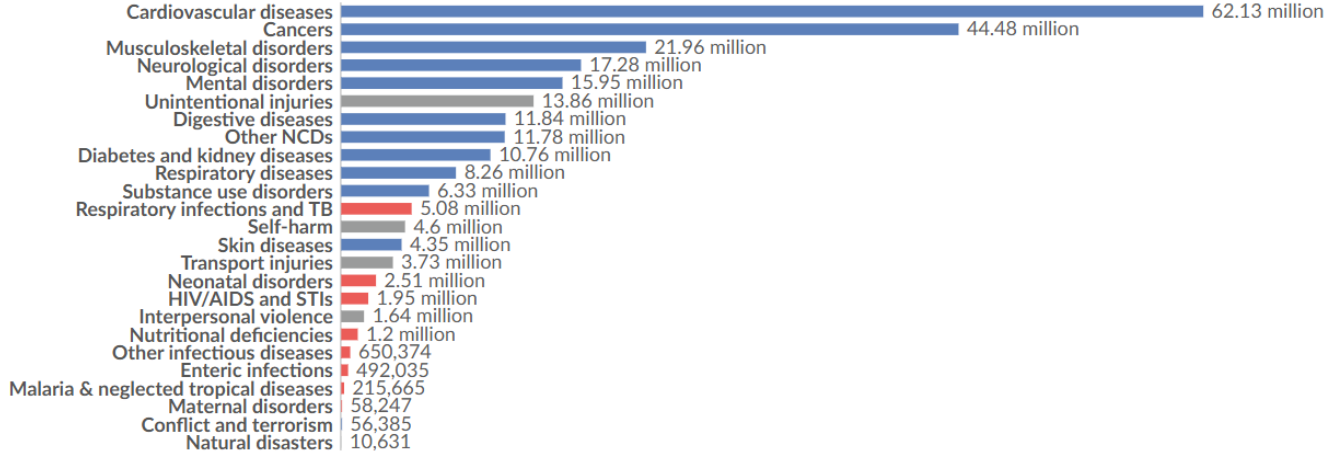

Figure I.8. Burden of disease by cause, Europe, 2019 [106].

Note: Non-communicable diseases are shown in blue; communicable, maternal, neonatal and nutritional diseases in red; injuries in grey. AIDS: Acquired Immune Deficiency Syndrome; HIV: Human Immunodeficiency Virus; NCDs: non-communicable diseases; STIs: Sexually Transmitted Infections; TB: Tuberkulose

Considering DALYs among older people, between 1990 and 2019, the total number of DALYs for all causes increased significantly among older Western Europeans. In Eastern Europe, the absolute DALYs rose from 1990 to 2005 but then declined between 2006 and 2013. However, DALY rates decreased across all European regions over time, with notable variations in the extent of change by region and gender [107].

Focusing on Organization for Economic Cooperation and Development member states, it was found a negative and statistically significant correlation between the age-specific DALY rate with Socio-Demographic Index and with Healthcare Access and Quality Index. Furthermore, the burden of mortality and DALYs in Organization for Economic Cooperation and Development countries is converging, as it has decreased over time in all countries; however, the magnitude and speed of these changes vary [108].

Chang *et al.* (2019) [109] developed a metric that reflects age-related morbidity and mortality, using Global Burden of Disease 2017. For that, it was identified a group of age-related diseases (Table I.8), defined as those with incidence rates among the adult population that increase quadratically with age, and quantified their age-related burden, measured by the total DALYs for these diseases in adults. In terms of proportion, age-related diseases account for 51.3% of the total burden. Globally, the age-related disease burden rate ranged from 137.8 DALYs per 1 000 adults in high Socio-Demographic Index countries to 265.9 DALYs in low Socio-Demographic Index countries. Considering the age-related disease burden rate for global average 65-year-olds in 2017 was 392·9 DALYs per 1 000 adults, but it is important to emphasize that the age to average 65-year-olds globally spanned from 76·1 years (75·6–76·7) in Japan to 45·6 years (42·6–48·2) in Papua New Guinea [109].

Table I.8. Age-related diseases by disease categories, adapted from [109].

Disease categories	**Panel of 92 age-related diseases**
Cardiovascular diseases	Atrial fibrillation and flutter; endocarditis; hypertensive heart disease; intracerebral haemorrhage; ischaemic heart disease; ischaemic stroke; myocarditis; non-rheumatic calcific aortic valve disease; non-rheumatic degenerative mitral valve disease; other cardiomyopathy; other cardiovascular and circulatory diseases; other non-rheumatic valve diseases; peripheral artery disease
Chronic respiratory diseases	Asbestosis; chronic obstructive pulmonary disease; coal worker pneumoconiosis; interstitial lung disease and pulmonary sarcoidosis; other pneumoconiosis; silicosis
Communicable, maternal, neonatal, and nutritional diseases	Diarrhoeal diseases; encephalitis; lower respiratory infections; pneumococcal meningitis; trachoma
Diabetes and kidney diseases	Chronic kidney disease due to type 2 diabetes mellitus; chronic kidney disease due to glomerulonephritis; chronic kidney disease due to other and unspecified causes
Digestive diseases	Cirrhosis due to non-alcoholic steatohepatitis; pancreatitis; paralytic ileus and intestinal obstruction; peptic ulcer disease; vascular intestinal disorders
Injuries	Drowning; environmental heat and cold exposure; falls; foreign body in other body part; other transport injuries; other unintentional injuries

Neoplasms	Acute lymphoid leukaemia; acute myeloid leukaemia; benign and in-situ intestinal neoplasms; bladder cancer; brain and nervous system cancer; breast cancer; chronic lymphoid leukaemia; chronic myeloid leukaemia; colon and rectum cancer; gallbladder and biliary tract cancer; Hodgkin lymphoma; kidney cancer; larynx cancer; lip and oral cavity cancer; liver cancer due to non-alcoholic steatohepatitis; liver cancer due to alcohol use; liver cancer due to hepatitis C; malignant skin melanoma; mesothelioma; multiple myeloma; myelodysplastic, myeloproliferative, and other hematopoietic neoplasms; non-Hodgkin lymphoma; non-melanoma skin cancer (basal-cell carcinoma); non-melanoma skin cancer (squamous-cell carcinoma); oesophageal cancer; other benign and in-situ neoplasms; other leukaemia; other malignant neoplasms; ovarian cancer; pancreatic cancer; prostate cancer; stomach cancer; thyroid cancer; tracheal, bronchus, and lung cancer; uterine cancer
Neurological disorders	Alzheimer's disease and other dementias; motor neuron disease; Parkinson's disease
Other non-communicable diseases	Congenital musculoskeletal and limb anomalies; digestive congenital anomalies; endocrine, metabolic, blood, and immune disorders; other haemoglobinopathies and haemolytic anaemias
Sense organ diseases	Age-related and other hearing loss; age-related macular degeneration; cataract; glaucoma; other sense organ diseases; other vision loss; refraction disorders
Skin and subcutaneous diseases	Cellulitis; decubitus ulcer; fungal skin diseases; other skin and subcutaneous diseases; pyoderma

Years of life lost

The impact of death on population health only becomes completely visible in terms of YLLs [110]. In 2019, ischemic heart disease, stroke, diabetes mellitus, hypertensive heart disease, and chronic kidney disease were the leading causes of YLLs. In addition, prostate cancer in men, breast cancer in women, and tracheal, bronchus and lung cancer in both sexes were also leading causes [111].

Leading causes of death

Leading causes of death differ worldwide (Figure I.9). In 2021, the top 10 causes of death were responsible for 39 million deaths, representing 57% of the total 68 million deaths worldwide. Death causes can be categorized into three groups: communicable (infectious and parasitic diseases, as well as maternal, perinatal, and nutritional conditions), noncommunicable (chronic diseases), and injuries [112].

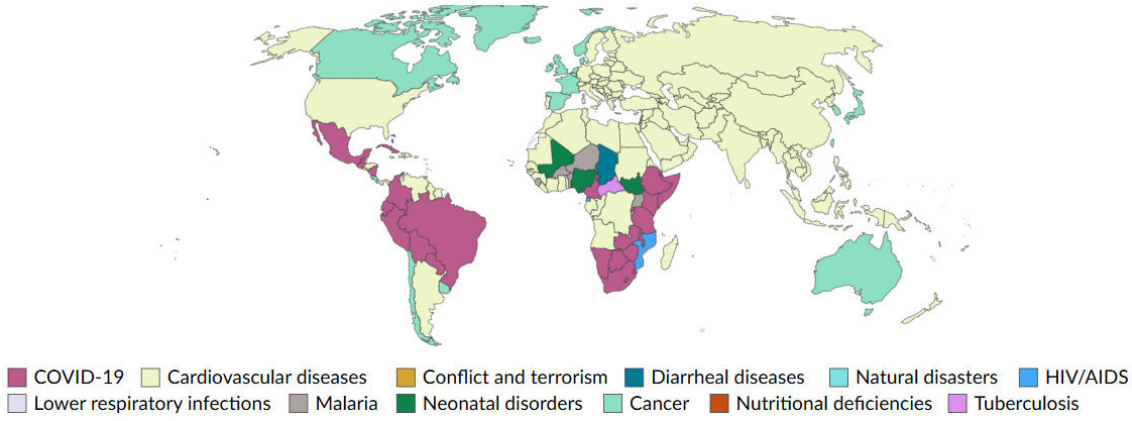

Figure I.9. Leading causes of death, 2021 [113].

Globally, 7 out of the 10 leading causes of death in 2021 were noncommunicable diseases, responsible for 38% of all deaths and 68% of the top 10 causes (Figure I.10), but there are important differences between low, lower-middle, upper-middle and high-income countries. Individuals in low-income countries (Figure I.11) are much more likely to die from a communicable disease than a noncommunicable one (8 out of the top 10). In contrast, in high-income countries (Figure I.12), ischaemic heart disease and stroke remain in the top three causes of death (over 2.6 million deaths in 2021), coronavirus disease 2019 was the second leading cause (with 1.2 million deaths), deaths from Alzheimer's disease and other dementias have surged almost four-fold since 2000 (actually the fourth leading cause), and deaths from hypertensive heart disease have more than doubled in 2021 (rising from the 16th leading cause in 2000 to 10th) [112].

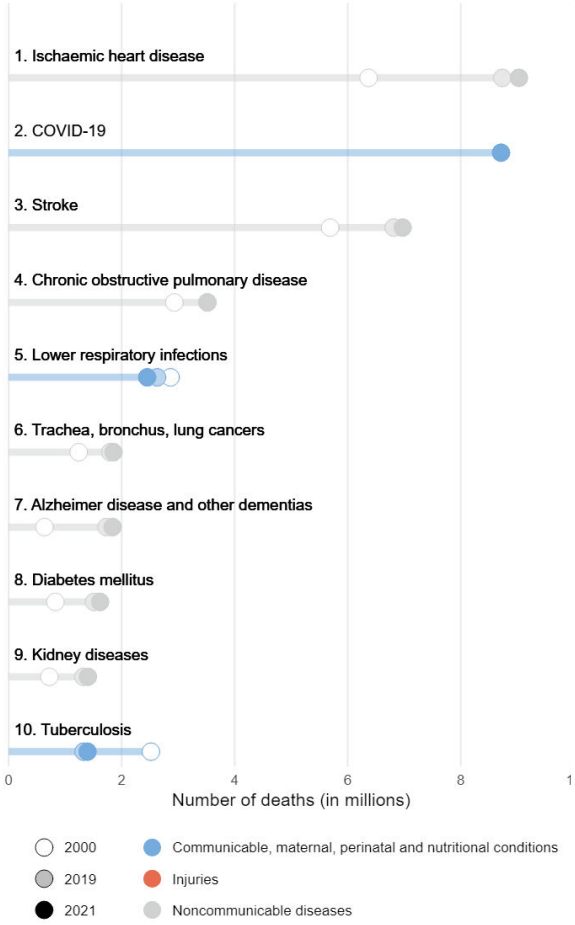

Figure I.10. Leading causes of death in 2000, 2019 and 2021 globally [112].

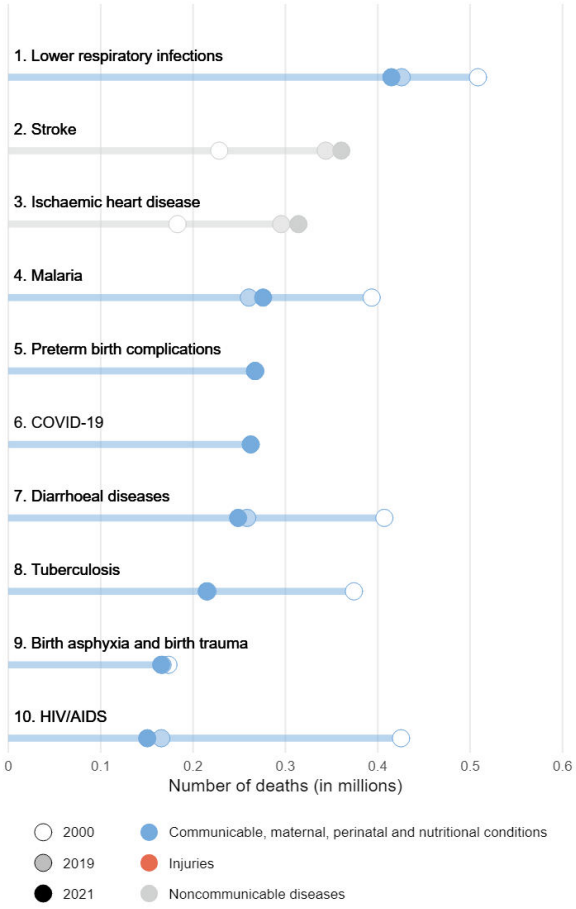

Figure I.11. Leading causes of death in 2000, 2019 and 2021 in low-income countries [112].

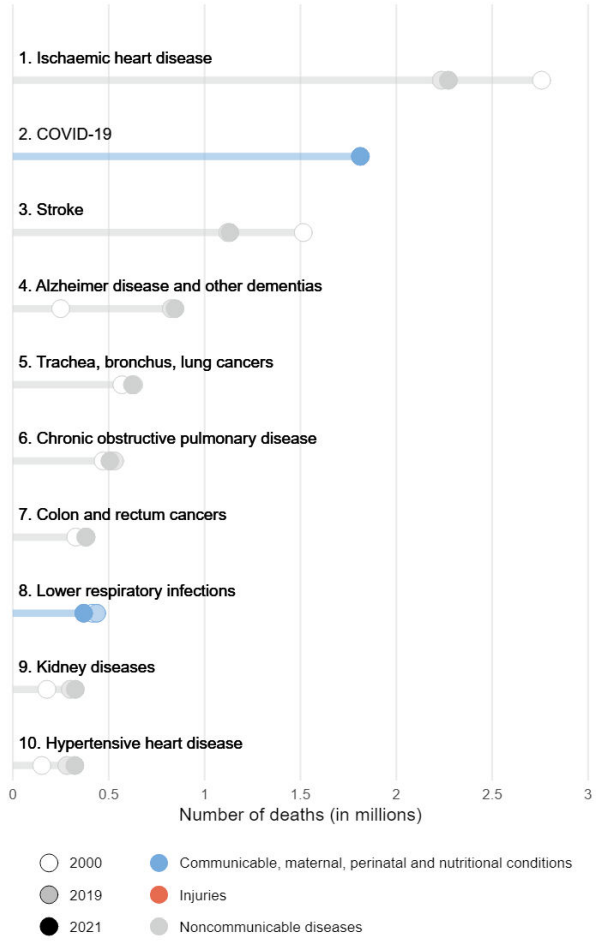

Figure I.12. Leading causes of death in 2000, 2019 and 2021 in high-income countries [112].

I.4. Chronic diseases and geriatric syndromes

The physiological changes associated with aging, along with the resulting alterations in pharmacokinetics and pharmacodynamics, influence medication use in elderly patients overall, making it challenging to achieve an appropriate therapeutic benefit while minimizing associated toxicity.

I.4.1. Chronic diseases

Aging involves various physiological changes that raise the risk of chronic noncommunicable diseases. As the prevalence of these conditions rises, there is a corresponding increase in the use of healthcare services [114].

The primary contributors to the disease burden in older adults are cardiovascular diseases (30.3%), malignant neoplasms (15.1%), chronic respiratory diseases (9.5%), musculoskeletal diseases (7.5%), and neurological and mental disorders (6.6%) [102].

Cardiovascular diseases

Normal aging is associated with multiple changes in cardiovascular structure and function that predispose older adults to coronary artery disease, myocardial ischemia, and acute coronary syndrome [115]. A key characteristic of aging is the increased stiffness of the aorta and large central arteries, primarily due to enhanced collagen deposition and cross-linking, along with the breakdown of elastin fibers. These changes result in greater resistance to left ventricular ejection and a widening of the central aortic pulse pressure, which is reflected in an age-related rise in systolic blood pressure and a decline in diastolic blood pressure, particularly after the age of 75 [116]. In fact, older people (≥ 75 years old) typically exhibit a significant burden of atherosclerotic plaques, anatomical complexities, calcifications, vessel tortuosity, ostial lesions, multivessel disease, and left main stenosis [117].

Among the different cardiovascular diseases, ischaemic heart disease causes the greatest burden in elderly individuals. Most cardiovascular disease burdens increase with age, but stroke and peripheral vascular disease show markedly different distributional characteristics [118].

In older people, the lifetime benefit from cardiovascular disease risk-factor treatment should consider absolute cardiovascular risk, life expectancy, competing (non-cardiovascular) risks, and efficacy and safety data from randomized controlled trials [119]. However, it is crucial to remember that several factors can cause well-intentioned, evidence-based medications to be poorly tolerated by older adults or even lead to harm. For instance, prescribing a statin to a high-risk individual might cause myalgias that hinder their ability to perform daily activities, or an

antihypertensive medication could lead to hypotension[120,121], which may increase the risk of falls and injuries.

Considering myocardial infarction, although survival rates following acute myocardial infarction have significantly improved, older adults continue to face a higher risk of hospital readmissions and death [122]. Myocardial ischemia results from an imbalance between oxygen supply and demand, and it can be identified from the patient's history and electrocardiogram [123]. The pharmacotherapy of post-acute coronary syndrome may involve antiplatelet therapy (aspirin), P2Y12 inhibitor therapy (prasugrel, clopidogrel, ticagrelor), lipid-lowering therapy (atorvastatin, rosuvastatin), beta-blocker therapy and ACEIs/ARBs. Possible side effects are gastrointestinal ulceration, bleeding, skin reactions, myalgia and myopathy, sleep disturbance, liver toxicity, bradycardia, hypotension, fatigue, bronchospasm, claudication, hypotension, hyperkalemia, worsening renal function, angioedema, cough (ACEIs). Thus, in older people it is recommended to continually monitoring bleeding risk, reviewing concurrent comorbidities and medications; myopathies that may impact on physical function, frailty and falls; analyze sleep disturbances that may impact on risk of delirium and falls; hypotension and bradycardia that may increase falls risk; fatigue that may decrease function and independence [124]. Recent studies confirm that the use of guideline-based treatments and outcomes improved simultaneously in older patients with myocardial infarction, regardless of frailty, suggesting that guideline-based management of myocardial infarction may be appropriate for both elderly and frail individuals [125]. Furthermore, 48% of patients were rehospitalized, with half rehospitalized within 2 months and 57% having a cardiovascular diagnosis [126]. In Portugal, the societal costs of productivity losses due to disabilities exceed 10 million euros in the first year following myocardial infarction [127].

Malignant neoplasms

Cancer primarily impacts older adults, and the challenge of determining the most effective treatment for this disease in older patients gave rise to the field of geriatric oncology [128]. The older population represents nearly 60% of new cancer cases and their management presents a complex public health challenge [129].

The incidence and prevalence of cancer rise with age due to the prolonged process of carcinogenesis, which includes the activation of cellular oncogenes and the suppression of anti-proliferative genes [130,131]. Thus, the incidence and mortality rates of various cancers among the elderly and very old are increasing worldwide [132].

According to estimates from the European Commission, new cancer cases increased by 2.3% compared to 2020, reaching 2.74 million in 2022. Similarly, cancer deaths rose by 2.4% compared to 2020. Besides, 31% of men and 25% of women are projected to be diagnosed with cancer before the age of 75 [133].

In 2022, in Europe, it was registered 991 015 new cases of cancer in female and 1 244 428 in males. Most common cancer in female was breast cancer and in male prostate cancer, followed by colorectum, trachea, bronchus and lung cancers for both genders (Figure I.13) [134].

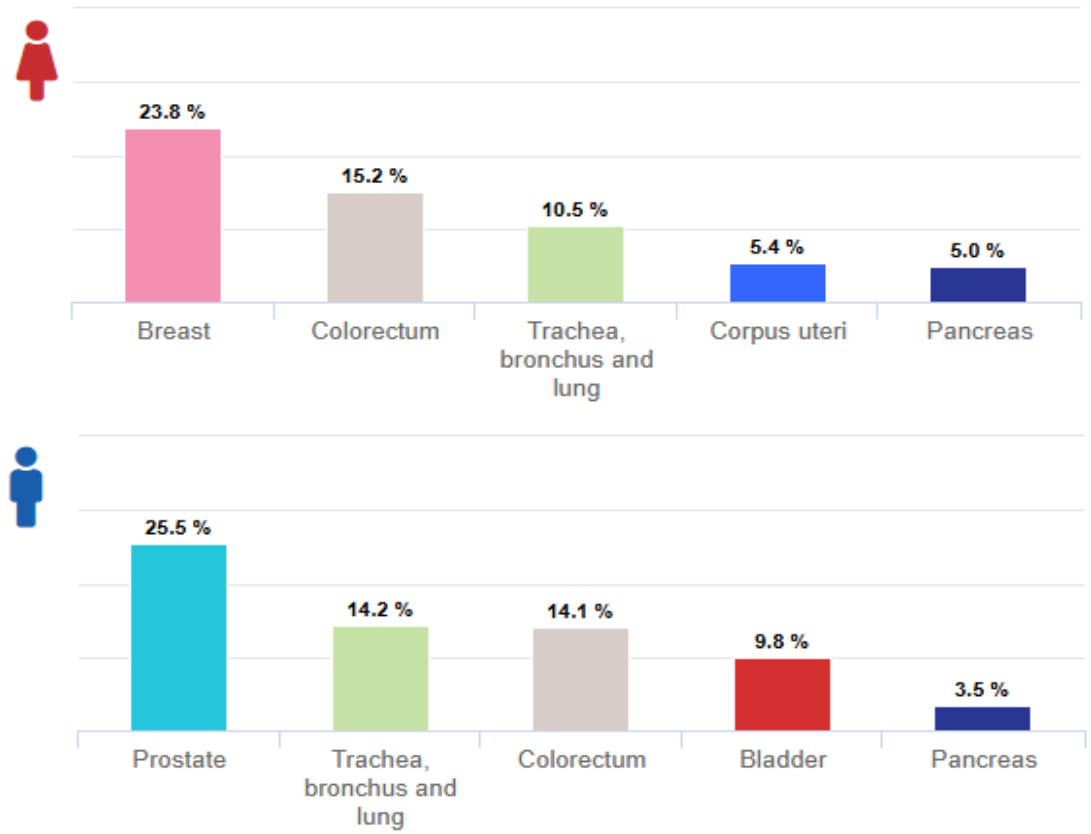

Figure I.13. Estimates of cancer incidence in 2022 in people up to 65 years old, for all cancer sites but non-melanoma skin [134].

European Cancer Information System also registered 1 259 146 deaths from cancer, about 55% in males, whereas the principal cause was breast cancer (15.5%) in females and trachea, bronchus and lung cancer (21.3%) in males [134].

Baseline geriatric impairments and frailty are associated with a range of adverse outcomes, such as complications, toxicity, and mortality, across different cancer types and treatment approaches [135]. A geriatric assessment can influence oncology treatment plans, prompt non-oncologic interventions, and enhance communication regarding care and age-related issues. It can reduce toxicity and complications, improve treatment adherence and patient-centered outcomes [136].

Chronic respiratory diseases

Older adults may exhibit atypical or milder symptoms, with dyspnea often being the most noticeable, while cough and sputum production may be less prominent [137].

Once again, frailty significantly affects the clinical progression and outcomes of pulmonary diseases in older adults. It often leads to more severe symptoms, slower recovery, and a greater risk of complications [138,139].

Aging results in functional decline across various organ systems, driven by physiological, anatomical, and immunological changes. Several factors can accelerate this decline, including smoking, air pollution, and pre-existing respiratory conditions. Changes in lung capacity, elasticity, and ventilation become apparent, with a gradual reduction in vital capacity and forced expiratory volume in one second. Respiratory muscle strength weakens, and gas exchange efficiency declines, particularly after age 40. Structural and anatomical changes include reduced chest wall compliance, leading to a barrel chest, and weakened respiratory muscles. The lung's static elastic recoil decreases, contributing to senile emphysema. Immunological changes involve alterations in bronchoalveolar lavage fluid composition, indicating activated T-cells in the lower respiratory tract. Persistent low-grade inflammation in the lower respiratory tract can cause lung parenchymal damage, impairing gas exchange [140].

Regarding chronic obstructive pulmonary disease, it is a treatable disease with a high prevalence and substantial morbidity, leading to significant socioeconomic costs, primarily associated with moderate to severe stages, as well as the exacerbations and complications that arise [141]. Nearly 384 million people worldwide were diagnosed with chronic obstructive pulmonary disease, and it is estimated that over half of patients may be undiagnosed [137]. Changes in chest anatomy and physiology due to age-related may encounter to diagnostic difficulties in older adults, which can complicate the interpretation of imaging studies and pulmonary function tests. They may also have a reduced tolerance for invasive diagnostic procedures [140]. Bronchodilators and inhaled corticosteroids are the cornerstone of chronic obstructive pulmonary disease treatment. Dual bronchodilation with a long-acting beta-2 adrenergic agonist and a long-acting muscarinic antagonist is recommended for treating patients experiencing dyspnea or exercise intolerance. It has also been proposed that phosphodiesterase 4-related molecular pathways may play a role in both the biology of lung aging and the pathogenesis of chronic obstructive pulmonary disease. Azithromycin, a macrolide recommended to reduce the risk of exacerbations, seems to be particularly effective in older patients (aged over 65), with a significant interaction between age and treatment effect on the risk of exacerbation [142].

Musculoskeletal diseases

Musculoskeletal disorders are disabling conditions that greatly affect health, particularly in older adults. A common pathological triad of interrelated disorders, highly prevalent in the elderly, includes sarcopenia, tendinopathies, and arthritis [143].

In 2017, there were approximately 1.3 billion prevalent cases, 121.3 thousand deaths, and 138.7 million DALYs globally due to musculoskeletal disorders [144].

The most common and debilitating age-related musculoskeletal diseases include osteoarthritis and fragility fractures/osteoporosis [145]. Other conditions may include microcrystal disorders, infections, and tumors [146].

Osteoarthritis is the most prevalent form of arthritis and a major cause of disability among older adults. One in three people over the age of 65, with a higher proportion of women than men, are affected by osteoarthritis. The prevalence of osteoarthritis is increasing due to rising risk factors such as aging and obesity. In older adults, osteoarthritis often coexists with other common chronic conditions, which may heighten the risk of poorer outcomes from these conditions [147].

Osteoporosis is an age-related condition characterized by poor bone microstructure and an increased risk of fragility fractures, often resulting in hospitalization and, eventually, a loss of mobility and independence. By 2050, it is projected that over 30 million people in Europe will be affected by bone diseases, with hospitalizations in Europe alone potentially costing up to 3.5 billion euros annually [148].

Fractures in patients aged 65 and older represent a growing burden on healthcare and social services and are linked to high levels of morbidity and mortality [149]. Classic fragility fractures include fractures of the proximal femur, proximal humerus, pelvis, spine, and distal radius; however, it is likely that other types of fractures are becoming increasingly common [150]. In patients with bone fractures, studies have reported a mean daily cost of hospitalization of R$4,478.64 in a tertiary reference hospital [151]. In the first year following a hip fracture, it was estimated that direct attributable healthcare costs amounted to $282 million in Ontario and $1.1 billion across Canada [152].

Neurological disorders

Neurological disorders, including cerebrovascular, neurodegenerative, autoimmune, and spinal cord diseases, as well as intracranial tumors and craniocerebral trauma, cause substantial cognitive impairment, leading to some of the highest rates of morbidity, disability, and mortality worldwide [153].

Neurological diseases are those that affect the nervous system, including the brain, spine, and nerves. The prevalence of most neurological conditions rises significantly with age, and age also influences the impact of risk factors, clinical presentation, and the progression of these diseases [154].

Stroke led to the highest DALYs loss among all diseases, while within neurological disorders, migraine, meningitis, Alzheimer's disease, autoimmune disorders, Parkinson's disease, other forms of dementia, and epilepsy each caused more than 10 million DALYs [153].

One in two women and one in three men will experience dementia, stroke, or parkinsonism during their lifetime [155].

The age-related remodeling of the immune system (immunosenescence) and vascular aging can contribute to the pathophysiology of several major chronic comorbid conditions, such as age-related diseases of the CNS (e.g., stroke, Parkinson's disease, Alzheimer's disease, and related disorders) and peripheral nervous system (e.g., polyneuropathy). These neurological disorders are major contributors to geriatric syndromes, which are common, chronic conditions of multifactorial origin in older adults, including delirium, falls, incontinence, and frailty [156].

Neurological disorders in older adults lead to numerous acute hospital admissions and significant long-term disability. Diagnosing conditions in complex older patients can be challenging, as clinical features are often atypical, and obtaining a clear history may be more difficult. Neurological signs unrelated to the primary issue are common, and interpreting neurophysiological tests can be more complicated [157].

The costs of neurological disorders are significant and likely to rise; thereby, it is important to focus on how the costs of treating neurological conditions will be funded and explore effective strategies for their prevention and management [158].

Mental disorders

Aging often experiences a gradual increase in disabilities, which may start as minor but eventually lead to significant impairments. Mental disorders play a major role in these disabilities and frequently coexist with one another, such as comorbid depression and cognitive impairment, or with physical conditions, like hearing loss and paranoid thoughts [159].

Mental disorders and cognitive impairments are significant barriers to active aging. More than 20% of adults over the age of 60 experience mental or neurological conditions, excluding headache-related issues, contributing to 6.6% of the total disability in this age group [160].

Globally, between 1990 and 2019, the number of DALYs due to mental disorders increased from 80.8 million to 125.3 million, and the proportion of global DALYs attributed to mental disorders increased from 3.1 to 4.9% [161].

In Europe, a cross-sectional study in primary care revealed that most common disorders were depression (17.1%), panic/anxiety (11.3%), cognitive (5.6%), alcohol (3.8%) and substance use (3.8%) [162].

Depression affected 5.7% of people aged 60 years and over prior to the pandemic and has increased by approximately 28% [163]. In fact, major depression affects 2% of adults aged 55 and older, with its prevalence increasing with age, and 10% to 15% of older adults experience clinically significant depressive symptoms, even without having major depression [164].

Anxiety disorders are more common than depression, with a prevalence of 11.4–12.3%, including 5.8% for phobic disorders and 6.8–9.1% for mood disorders [165]. Anxiety and depression

frequently co-occur, complicating diagnosis. Among older adults, 13% of those with an anxiety disorder also experience depression, while 36% of those with depression have a coexisting anxiety disorder [166].

I.4.2. Geriatric syndromes

Frailty, sarcopenia, weight loss, and dementia are common geriatric syndromes seen in elderly individuals across various care settings. Although they significantly affect quality of life, disability, and mortality in older adults, they are often under-recognized [167].

Frailty

The World Health Organization (WHO) defined frailty as "a clinically recognizable state in which the ability of older people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems" [168]. Thus, frailty may lead to greater vulnerability and a diminished capacity to recover following an acute event (such as an infection) [169].

In addition to changes in body composition, albumin concentration is lower in frail older adults compared to healthy older people [170]. These changes in plasma drug-binding proteins are probably clinically significant for drugs that are highly protein-bound and are either mainly cleared by the kidneys or have a high hepatic extraction ratio [171]. Furthermore, frailty is associated with a rapid decline in kidney function [172].

Another key feature of frailty is non-specific systemic inflammation, partly caused by immune system dysregulation. This inflammation can lead to a downregulation of cytochrome P450 isoenzymes, raising the risk of overdose in older individuals [173]. Aspirin esterase activity is comparable in healthy young and older adults, but it is significantly reduced in frail elderly individuals due to a decrease in the amount of esterase. In turn, paracetamol is extensively metabolized, primarily to the glucuronide and sulphate conjugates, before excretion in the urine. Its clearance, when expressed per unit of body weight, is 21% lower in fit elderly individuals compared to young subjects, but in frail elderly individuals, clearance is further reduced [174].

Besides, frailty index, defined as the proportion of health deficits and serves to measure the progression of unhealthy aging, was identified as a reliable predictor of mortality [175]. It was also considered as a potentially valuable clinical tool for physicians to carefully evaluate a patient's prescription for potentially inappropriate prescribing and help prevent ADRs, particularly when considered alongside the number of medications a patient is taking [176].

Despite the frailty being associated with chronological age [177], biological age was also associated with severe frailty in geriatric rehabilitation inpatients with less comorbidity burden [178]. In fact, chronological age and biological age are not necessarily correlated, since individuals may not

experience at the same rate biological aging, which is most effectively understood clinically as a combination of three factors: frailty, comorbidity, and disability [179]. Compared to chronological age, biological age is being increasingly recognized as a more accurate in determining chronic health outcomes [180] and predicting disease-related mortality [181].

Sarcopenia

Sarcopenia is defined as a progressive, generalized condition of skeletal muscle that frequently develops with aging and is linked to a higher risk of various negative outcomes, such as reduced mobility and increased morbidity and mortality [182]. First introduced just a few decades ago in the fields of nutrition and body composition, the term initially referred to low muscle mass; however, it soon became clear that muscle function is a more reliable predictor of outcomes [183].

Thus, frailty and sarcopenia may overlap, particularly in the physical traits of the frailty phenotype, such as low grip strength, gait speed, and muscle mass. These indicators have been linked to various aging-related outcomes and can be evaluated in a clinical setting [184].

Sarcopenia is linked to, and may partly result from, several chronic diseases that adversely impact the musculoskeletal system and physical activity, such as chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease, diabetes mellitus, human immunodeficiency virus, and cancer [185].

Besides, sarcopenia may serve as a marker of an enhanced cancer-related inflammatory response. In a large-scale study of patients with colorectal cancer, pre-diagnosis inflammation was associated to sarcopenia at the time of diagnosis and the combination of sarcopenia and inflammation nearly doubled the risk of death from colorectal cancer [186].

Older individuals experience an increase in sarcopenia (loss of skeletal muscle mass), often accompanied by higher adiposity, a condition that is further amplified in frailty [187]. These changes in body composition affect the pharmacokinetics of both hydrophilic and lipophilic drugs. They lead to an increased volume of distribution and, consequently, prolonged half-life for lipophilic drugs (i.e., risk of accumulation then re-release), a decreased volume of distribution for hydrophilic drugs (i.e., increasing the risk of overdose), and an elevated free fraction of protein-bound drugs in cases of hypoalbuminemia [188].

Dementia

Dementia is a disorder characterized by progressive memory, thinking, and behavioral impairments, often accompanied by emotional issues, language difficulties, and decreased motivation. About 55 million people are living with dementia, and of the different types of dementia, with different underlying etiologies, the most common is Alzheimer's disease [189].

Before making a diagnosis, a thorough medication review should be conducted to identify if any current medications, such as anticholinergics, benzodiazepines, or narcotics, are contributing to mental status changes. If necessary, these medications should be reduced or stopped, and the patient should be monitored for improvements. If cognitive impairment persists and external causes are ruled out, a neurological workup is needed to determine the underlying cognitive disorder and guide treatment [76].

Actually, treatment strategies for Alzheimer's disease focus on alleviating symptoms, with options like acetylcholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, and the *N*-methyl-D-aspartate antagonist memantine. Currently, the most effective approaches combine both pharmacological and non-pharmacological therapies to enhance cognitive reserve. In the past 20 years, several drugs have been developed targeting key biological features of Alzheimer's disease, and there are already approved two monoclonal antibodies, aducanumab and lecanemab, as disease-modifying therapy [190]. Cholinesterase inhibitors and the *N*-methyl-D-aspartate receptor antagonist memantine may even worsen neuropsychiatric symptoms in patients with frontotemporal dementia [191], while vascular dementia can be prevented by managing vascular risk factors to reduce the likelihood of stroke [192].

Negative effects of acetylcholinesterase inhibitors result from the overstimulation of central and peripheral muscarinic and nicotinic receptors. Most common ADRs are neuropsychiatric (dizziness, dyskinesia, convulsion, muscle cramps, insomnia, and vivid dream), gastrointestinal (abdominal pain, nausea, vomiting, diarrhea, poor appetite, gastrointestinal ulceration and bleeding) and cardiovascular (vagotonic effects, such as bradycardia, heart block, syncope) [193]. On the other hand, common adverse reactions of memantine include hallucinations, confusion, headache, dizziness, high blood pressure, sleepiness, and restlessness [194]. Thus, both strategies require a gradually titrated to improve tolerance to the medication and dose adjustments are advised for those with an estimated creatinine clearance (CrCl) of less than 30 mL/min [76].

Delirium

Delirium is a clinical syndrome resulting from an underlying medical condition, not better explained by an existing or evolving neurocognitive disorder. It is characterized by changes in attention, consciousness, and cognition, with difficulty focusing, sustaining, or shifting attention. Delirium develops rapidly and the underlying causes can be diverse, affecting the patient's baseline homeostasis, such as substance intoxication or withdrawal, medication side effects (Table I.9), infections, surgery, metabolic imbalances, pain, or even conditions like constipation or urinary retention. The diagnosis is often overlooked due to its subtle presentation; however, it is dangerous, often preventable, and linked to increased costs, morbidity, and mortality [195].

Table I.9. Drugs that may induce delirium, adapted from [196].

Type of Drug	System/Organ	Drugs
Prescription drugs	Central acting agents	Sedative hypnotics (e.g., benzodiazepines) Anticonvulsants (e.g., barbiturates) Antiparkinsonian agents (e.g., benztropine, trihexyphenidyl)
	Analgesics	Narcotics (e.g., meperidine*) NSAIDs*
	Antihistamines	First generation (e.g., hydroxyzine)
	Gastrointestinal agents	Antispasmodics H_2 antagonists *
	Antiemetics	Scopolamine Dimenhydrinate
	Antibiotics	Fluoroquinolones*
	Psychotropic medications	Tricyclic antidepressants Lithium*
	Cardiac medication	Antiarrhythmics Digitalis* Antihypertensives (beta-blockers, methyldopa)
	Miscellaneous	Skeletal muscle relaxants Steroids
Over the counter medications and complementary/ alternative medications	Antihistamines	First generation (e.g., diphenhydramine, chlorpheniramine)
	Antinauseants	Dimenhydrinate, scopolamine
	Others	Liquid medications containing alcohol Mandrake Henbane Jimson weed *Atropa belladonna* extract

NSAIDs, Non-steroidal anti-inflammatory drugs; * Requires adjustment in renal impairment.

Medications can both cause and treat delirium, particularly symptoms like agitation and aggression. Antipsychotics, especially haloperidol, are the main treatment for delirium, as haloperidol has minimal side effects and low anticholinergic effects, making it suitable for short-term use. Newer antipsychotic agents have weaker evidence for delirium treatment, with atypical antipsychotics often having greater anticholinergic effects, lack of parenteral formulations, and difficulty in adjusting to smaller doses. Despite not being labeled for delirium, antipsychotics can reduce agitation and combativeness, such as risperidone, that seems to be effective and relatively safe for managing agitation in delirium. Benzodiazepines can be effective in treating delirium caused by benzodiazepine withdrawal, alcohol withdrawal, and seizures. In some cases, specific antidotes, such as physostigmine, may be helpful, along with discontinuing the causative medication [196]. Future studies may clarify the use of other agents, such as melatonin and melatonin receptor agonists, alpha-2 receptor agonists, and antiepileptics [197].

Polypharmacy

A systematic review found approximately 138 definitions of polypharmacy and associated terms, which varies a lot. Generally, polypharmacy can be categorized as: numerical (based solely on the number of medications); numerical with an associated duration of therapy or healthcare setting (such as during a hospital stay); and descriptive (using a brief explanation to define polypharmacy) [198].

For instance, polypharmacy can be defined as the concomitant use of multiple drugs or as the administration of more medications than are indicated clinically [199]. Other definition, characterize polypharmacy as the concomitant use of more than a certain number of drugs, like Rosallon and Vogt [200] or Kaufman *et al.* [201]. In fact, although a standard definition does not exist, polypharmacy is commonly defined as the regular use of five or more drugs, including over-the-counter, prescription, and/or traditional and complementary medicines used by a patient [202].

Other associated terms can be found to assess the extent of polypharmacy, such as minor [203], mild [204], moderate [205], major [203,206] and excessive polypharmacy [207–209].

In practice, polypharmacy can result from the use of different medications as a response to an aging population with comorbities. However, a genuine concern lies in identifying and changing those situations that can be preventable. Vinks *et al.* [210] showed that it is possible to reduce potential drug-related problems (DRPs) in elderly that use six or more drugs concomitantly, through the implementation of an intervention strategy by the community pharmacist.

In addition, it is equally necessary to identify situations of ineffective communication between healthcare practitioners that may result in redundancy or in the use of interaction medications. At transition points of care, preventable adverse drug events (ADEs) account for 46% of all medication errors [211] and the incidence of medication-related adverse events for transitions between hospital and nursing homes is approximately 20% [212].

In Switzerland, studies about community-dwelling population have shown different prevalences of polypharmacy, revealing that 25.5% and 41.2% of older people take five or more drugs daily [213,214].

In Scotland, a cross-sectional analysis of adult electronic primary healthcare records revealed that the prevalence of polypharmacy (defined as the use of 4–9 medications) was found to be 28.6% in adults aged 60–69 years and 51.8% in those aged 80 and older. Additionally, the prevalence of patients taking ten or more medications was 7.4% in those aged 60–69 years and 18.6% in those aged 80 and older [215].

In United States of America (USA), a cross-sectional study of the Centers for Disease Control and Prevention's National Ambulatory Medical Care Survey from 2009 to 2016, revealed that

polypharmacy (2 or more drugs) was common (65.1%) among older people: 16.2% of minor polypharmacy (2 to 3 drugs); 12.1% of moderate polypharmacy (4 to 5 drugs), and 36.8% of major polypharmacy (more than 5 drugs) [216].

Considering the need to enhance polypharmacy, several programs have already been developed. In Europe, it was created the SIMPATHY Project, "Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly". This project sets out to develop numerous strategies to improve the management of polypharmacy and adherence in the elderly, but also alerted that deprescribing cannot be an automated, robotic process [217].

Falls

In 1988, Tinetti *et al.* [218] defined a fall as an incident where an individual unintentionally ends up on the ground or another lower surface, not due to a major medical event (like a stroke) or an overwhelming external hazard.

In older adults, the presence of medical comorbidities increases the likelihood of falls, which also raises the risk of injury. Falls are a leading cause of disability, particularly among older adults, and they are strongly linked to higher mortality rates, morbidity, and reduced functional capacity [219].

One in four older adults reports having a fall each year [220] and approximately 10% experiencing multiple falls each year [221]. Based on data from the Centers of Disease Control, annually, among older adults, approximately 3 million emergency department visits occur due to falls and there are around 1 million fall-related hospitalizations [222]. Additionally, in 2021, 38 742 (78.0 per 100 000 population) older adults died as the result of unintentional falls [220].

Literature shows that falls among community-dwelling older adults are associated with factors such as age, female gender, fear of falling, history of falls, unclear vision, depression, and balance disorders [223].

The use of screening tools to identify at-risk individuals in hospitals is no longer recommended due to their lack of proven effectiveness; instead, they should be replaced with multifactorial risk assessments [224]. Most guidelines strongly recommended risk stratification, gait and balance assessments, management of fractures and osteoporosis, multifactorial interventions, medication reviews, exercise promotion, environmental modifications, vision and footwear corrections, referrals to physiotherapy, and cardiovascular interventions. The recommendations for vitamin D supplementation, addressing cognitive factors, and falls prevention education were less consistent in terms of strength. Guidance on the use of hip protectors, digital technology, or wearables was often absent [225]. A systematic review and meta-analysis found strong evidence and large effect sizes for the associations between falls and factors such as older age (65-79 years), certain comorbidities (Parkinson's disease, diabetes mellitus, hyponatremia), the use of specific

medications (antidepressants, benzodiazepines, sedative-hypnotics, antipsychotics, unspecified psychotropics, and anticonvulsants), and functional limitations (history of falls, mobility disorders, and cognitive impairment). Additionally, there was strong evidence of associations, with small effect sizes, for increasing age (as a continuous variable) and male sex [226].

Comorbid diseases and Charlson comorbidity index

The Charlson comorbidity index (CCI), developed in 1987 by Charlson and colleagues, is a tool used to classify comorbid conditions that may impact mortality risk. It is the most widely used index for assessing survival rates (1-year and 10-year) in patients with multiple comorbidities. Initially designed for use in longitudinal studies, the CCI is a weighted index that considers both the number and severity of comorbid diseases. It was developed based on a cohort of 559 medical patients. The 1-year mortality rates for various scores were as follows: "0" – 12% (181 patients), "1-2" – 26% (225 patients), "3-4" – 52% (71 patients), and "≥5" – 85% (82 patients). The index was later tested on a second cohort of 685 patients over a 10-year follow-up period to evaluate its ability to predict mortality from comorbid diseases. The mortality rates for the second cohort were: "0" – 8% (588 patients), "1" – 25% (54 patients), "22 – 48% (25 patients), and "≥3" – 59% (18 patients). As the CCI score increased, there was a corresponding rise in cumulative mortality due to comorbid conditions. The index includes 19 conditions, such as diabetes with complications, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, liver disease (both mild and severe), hemiplegia, renal disease, leukemia, lymphoma, metastatic cancer, and acquired immune deficiency syndrome, with each condition assigned a weight based on its potential impact on mortality. Over time, the CCI has been adapted and validated as an effective tool for predicting the outcomes and risks associated with various comorbid conditions [227].

Malnutrition/anorexia

Malnutrition is commonly defined as a deficiency, excess, or imbalance in a person's intake of energy and/or nutrients. Despite its strong association with increased morbidity, mortality, and healthcare costs, malnutrition frequently goes undiagnosed in both clinical and community environments [228]. The global prevalence of malnutrition among older adults was estimated at 18.6%, with the highest rates observed in Africa at 35.7%, followed by the Americas at 20.3%. Subgroup analysis based on malnutrition assessment tools showed the highest prevalence, 39.9%, when using the nutritional risk screening 2002 index [229].

Instead, anorexia of aging is a prevalent geriatric syndrome characterized by diminished appetite and/or reduced food intake, often leading to undernutrition, unintentional weight loss, weakened immunity, frailty, sarcopenia, functional decline, loss of independence, reduced quality of life, and other negative health outcomes. It can lead to serious and wide-ranging consequences, yet it

is frequently overlooked by healthcare professionals and even mistakenly regarded as a normal and unavoidable aspect of aging [230].

A recent systematic literature review showed that in individuals aged 65 and older, anorexia or appetite loss is linked to a higher risk of malnutrition, mortality, and other adverse outcomes across community, care home, and hospital settings, which highlight the need for improved and standardized approaches to screening, identifying, assessing, and managing anorexia or appetite loss in older adults [231].

Dependency in activities of daily living

The term of "activities of daily living" (ADL) was first introduced by Sidney Katz, in 1950, and refers to the basic skills needed for independent self-care, which include ambulating, feeding, dressing, personal hygiene, continence and toileting [232]. Each question on both scales was categorized into four levels: "no difficulty" = 0, "difficulty but able to complete" = 1, "difficulty and requires help" = 2, and "unable to complete" = 3 [233].

The ability to perform ADLs is a key indicator for assessing the independence of older adults in daily living. These activities serve as a vital indicator of the health status of older adults. Research has demonstrated that factors such as socioeconomic status, physical health, depression, and health insurance affect ADL function [234].

Obesity

The WHO defines "overweight" as having a body mass index (BMI) between 25 and 29,9 kg/m^2, while "obesity" is defined as a BMI of 30 kg/m^2 or higher [235].

Obesity is a chronic, multifaceted disease characterized by excessive body fat accumulation and is recognized as a major public health challenge in both developed and developing nations. Globally, the prevalence of obesity among older adults is estimated at 25.3%, in continental Europe with 33.6% and the highest rates observed in South America (40.4%). Additionally, meta-regression analysis revealed a significant upward trend in obesity prevalence with larger sample sizes, and a downward trend associated with more recent study years [236].

Older adults with BMI <25 and >35 kg/m^2 are at a higher risk of a decrease in functional capacity, and experienced gait and balance problems, fall risk, decrease in muscle strength, and malnutrition. Data available in literature suggest that the optimum range of BMI levels for older adults is 31–32 and 27–28 kg/m^2 for female and male, respectively [237].

However, waist circumference may serve as a more accurate measure of obesity in older adults than BMI. Weight loss is generally not recommended for overweight older individuals due to evidence of reduced mortality in this group – a phenomenon known as the "obesity paradox".

Although weight loss can offer benefits for older obese adults, it also carries significant risks, including muscle loss, reduced bone mineral density, and the onset of sarcopenic obesity. For older adults with a BMI over 30 kg/m² who present metabolic disorders, cardiovascular disease, or functional limitations, weight loss interventions may be considered but only after carefully evaluating the potential risks and benefits, as well as the intervention's impact on quality of life [238].

Sarcopenic obesity is defined by the simultaneous loss of muscle mass and function alongside an increase in body fat. This condition is an emerging concern among older adults due to its serious health implications, including higher mortality risk, increased comorbidities, and a greater likelihood of developing geriatric syndromes. Its pathophysiology is complex, involving interactions among muscle and fat tissue, hormonal shifts, inflammation, oxidative stress, and lifestyle factors. Management includes a combination of lifestyle changes, targeted exercise, nutritional strategies, and medical treatments. Additionally, novel therapies — originally developed for other conditions — such as new pharmacological agents and personalized approaches like precision medicine, show potential for treating sarcopenic obesity [239]. In 2022, a consensus statement introduced updated definitions and diagnostic criteria for sarcopenic obesity [240].

Pressure ulcers

A pressure ulcer (bedsore or decubitus ulcer) is defined as skin damage resulting from prolonged and continuous pressure on a specific area. The incidence of pressure ulcers ranges from approximately 4% to 38%, depending on the clinical setting. Among the elderly, complications from pressure ulcers contribute to a mortality rate of around 68%. These ulcers are most frequently observed in patients who are confined to bed for extended periods [241].

According to the national pressure injury advisory panel system, the most widely used classification system for pressure ulcers in the USA, ulcers can be categorized based on their depth: stage I for intact skin with non-blanchable redness (erythema); stage II for partial-thickness skin loss involving the epidermis and dermis; stage III for full-thickness skin loss extending into the subcutaneous tissue, without penetrating the underlying fascia, slough or eschar may be present, and the wound can emit an unpleasant odor; stage IV for full-thickness skin loss that extends through the fascia, often involving extensive tissue damage and exposure of muscle, bone, tendon, or joint structures; and unstageable when the depth of the ulcer cannot be determined due to the presence of slough or eschar that obscures the wound [242].

Patients at risk of developing new pressure ulcers can be identified based on their total Braden score and age, with older age also being associated with deeper ulcers [243]. Besides, it is also true that the incidence of pressure ulcers is highest among older people with frailty [244].

Individuals with pressure ulcers frequently experience intense pain and may engage in social withdrawal. Effective prevention and treatment strategies focus on optimizing hydration, circulation, and nutrition. Ensuring sufficient nutrient intake helps to reduce the risk of malnutrition and supports the healing process of existing ulcers [245].

The recent guidelines from the Wound Healing Society offer clear, concise, and unbiased recommendations that physicians can follow to guide patient care, and it also introduces a new section titled *"Palliative Wound Care for Seriously Ill Patients with Pressure Ulcers",* reflecting shifts in demographic trends [246].

History of recent fractures

Fragility fractures are common among the elderly. The lifetime risk of osteoporotic fractures is between 40–50% for women and 13–22% for men [247,248]. The WHO predicts that these cases will triple over the next 50 years [249]. It is estimated that approximately one in three women and one in twelve men will experience a hip fracture during their lifetime [250], with mortality rates being higher in men [251].

Fragility fractures also have a significant economic impact. In 2005, the USA experienced over 2 million osteoporosis-related fractures, with 71% occurring in women and 29% in men, resulting in a total cost of nearly $17 billion. By 2025, both the number of fractures and the associated costs are expected to increase by more than 48% [252].

A significant concern regarding quality of life is that after a fragility fracture, between 25% and 75% of individuals with an independent gait may experience a severe functional decline, becoming unable to walk without assistance within a year [253].

Some countries have already developed strategies to improve care for older fractured patients. The "fast track" in Canada enables patients suspected of having a fracture to receive priority pain relief, a quick diagnosis, and prompt treatment [254]. The "Blue Book" of the United Kingdom outlines six standards for high-quality hip fracture care. These standards include arrival at the orthopedic department within 4 hours, surgery within 48 hours, minimizing the risk of pressure ulcers, early management, and ongoing fall prevention after the incident [255]. This approach is regarded as one of the most effective strategies for treating older patients with hip fractures, leading to improved mortality outcomes [256].

Following the first minimal trauma fracture, the risk of experiencing another fracture increases by up to 25% within the next 2 years, especially in women, and this risk continues to rise in the years that follow [257]. On the one hand, there is no evidence that osteoporosis treatment affects bone callus formation in treated fractures. In fact, early initiation of therapy has demonstrated better outcomes, even before hospital discharge, highlighting the importance of educating the medical team to enhance the implementation of this recommendation. Therefore, it is crucial to

begin pharmacological therapy for osteoporosis early to prevent new fractures in both the short and long term [254].

I.5. Drug-related problems

I.5.1. Definition and classification

DRPs, which have been defined as events or circumstances related to drug therapy that actually or potentially interferes with desired health outcomes [258], represent an important issue with high prevalence and rising incidence worldwide. Despite some efforts to prevent them, it is still a major cause of morbidity and mortality, particularly among elderly [259]. Thus, recently, there are a lot of studies about this matter, but the definition and classification of DRPs is still unclear and not universal, which leads to some difficulties when trying to compare them.

Therefore, DRPs can be classified according to their toxicity, in intrinsic or extrinsic. Intrinsic toxicity is related to the interaction of human biosystem and both pharmaceuticals, chemical and/or pharmacological characteristics of the drug itself [260].

Consequently, ADRs can be considered as DRPs with intrinsic toxicity, since they comprise unintended and prejudicial effects that are consequence of dosages generally employed for prophylaxis, diagnosis or therapy, in humans, or for the modification of a physiological function [261]. ADRs may be divided into six types (with mnemonics): type A, dose-related (Augmented); type B, non-dose-related (Bizarre); type C, dose-related and time-related (Chronic); type D, time-related (Delayed); type E, withdrawal (End of use); and type F, failure of therapy (Failure) [262].

On the other hand, extrinsic toxicity is related to the management of the drug by the patient or by the healthcare professional. In this way, a medication error can be classified as a DRP with extrinsic toxicity, due to the fact that it is preventable and can cause or lead to improper medication use or patient harm [263].

In spite of this, other definitions have been proposed. Marcum *et al.* [259] employed the term "medication misadventures" and divided it into medication errors and medication-related adverse patients events (MRAPEs). They also considered that adverse drug withdrawal events (events that result from the removal of a drug, which origin clinically significant sets of signs or symptoms) and therapeutic failure (consequence of inadequate or inappropriate drug therapy, which is not related to the natural progression of disease [264]) are examples of medication-related adverse patients events [259].

Considering DRPs classification, ADRs can be classified using the WHO terminology [265] and its severity can be analyzed by the WHO Critical Terms List [266]. The Medical Dictionary for Drug regulatory Affairs is another tool widely used as ADR terminology coding system [267]. Instead, medical errors can be categorized into prescribing, transcription, dispensing, administration and "across-settings" errors [268].

Besides, the Pharmacological Care Network Europe (2020) suggested a classification for DRPs too and identified their principal consequences: treatment effectiveness, treatment safety and others [258].

I.5.2. Drug-related problems consequences

In fact, the expenditure of treatments more costly than necessary or even unnecessary has been constantly referred to in a variety of studies. A study about the costs of a nursing home sitting alone calculates that DRPs may cause a loss of $4 billion per year [269]. Later, Goodman *et al.* [270] (2011) estimates that adverse medical advents may lead to 187.000 deaths in USA hospitals each year as well as 6.1 million injuries, in and outside hospitals. This can result in an annual social cost of $393 billion to $958 billion, which represents 18 to 45% of total USA healthcare expenditure in 2006. However, reviewing the literature, it is evident that these studies are mainly made in the USA and few exhibit concrete calculations. This fact complicates the comparison between countries and their different health systems and the achievement of a generalized and more precise conclusion as well.

In spite of this, it is certain that elderly patients (≥ 65 years) are the most affected. It has been estimated that about 50 ADEs take place among 1 000 ambulatory people ≥ 65 years, and that hospitalization rates due to ADEs are 4 to 7 times higher in elderly than in younger patients [271].

I.5.3. Elderly: Risk factors for drug-related problems

First of all, elderly suffer aged-related changes in pharmacodynamics and pharmacokinetics. Slower absorption rates lead to longer remaining of medication in the body and poor circulation cause higher concentration of drugs in discrete parts. In addition, drug excretion and metabolism are affected by decreased renal function and liver shrinkage (with consequent decreased cardiac output), respectively [272].

Furthermore, it is generally consensual that elderly adults take more medication than younger people, which directly increases the chance of error medication or ADRs occurrence. Qato *et al.* [273] studied 3,500 community-residing elderly and concluded that 81% used at least one prescription medication, 42% took over-the-counter medication, 49% had a dietary supplement and 29% used at least five prescription medications. Thus, polypharmacy is a leading cause of DRPs among elderly.

I.6. Screening tools for detection of potentially inappropriate medications

Potentially inappropriate medication (PIM) prescribing has been considered as a concern and delicate subject, especially in the last two decades. In 1991, Beers described it as medications or medication classes that should be avoided in the elderly (65 years or older), since they are ineffective or carry unnecessarily high risk and a safer alternative can be chosen [274]. A lot of studies have shown the prevalence, and some have analyzed the incidence of PIM prescribing among nursing homes, ambulatory settings and emergency departments and that inappropriate prescribing is associated with increased ADEs and, consequently, with more morbidity, mortality and healthcare resource utilization [275]. Furthermore, there are also studies regarding the problematic of DRPs in older people after hospital discharge [276], the importance of defining strategies to reduce its occurrence [277], and the increased risk for hospital readmission [278].

Over the years, many tools have been developed to help healthcare professionals to identify and avoid PIM prescribing. Appropriateness of prescribing can be evaluated based on the criteria applied, which can be explicit or implicit [275]. The explicit criteria are mostly developed from expert opinions and published reviews and can be used with little or no clinical judgment. For this reason, it may not consider all quality indicators of healthcare defined for each patient and their particularities. On the other hand, implicit criteria consider all patient information and published evidence, focusing on the patient instead on drugs or diseases. These are more sensitive methods, but also time-consuming and dependent on the users' knowledge and attitudes [279]. Both strategies (explicit or implicit) have their advantages and limitations, and some authors have already tried to combine them, in order to achieve a better and more complete tool [280].

I.6.1. Implicit criteria

Medication appropriateness index

Medication appropriateness index (MAI) was developed by Hanlon and his colleagues and consider ten components of prescribing: indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost [281]. This validated measure of prescribing appropriateness combines implicit and explicit criteria [281] and has been proved to be a consistent method in evaluating drug therapy appropriateness [282]. It consists in a scheme where each drug obtains a score from 0 (no inappropriate ratings) to 18 (only inappropriate ratings) [283] and the ratings originate a weighted score that provides a summary measure of prescribing appropriateness. One of the studies that used this tool was developed by Crotty *et al.* [284] and demonstrated that it is possible to reduce the use of inappropriate medication in residential care through multidisciplinary case conferences, since the change in MAI mean was 4.1 in the intervention group against 0.4 in the control group. The MAI for benzodiazipines also suffered a significant reduction (mean control -

0.38, 95% CI -1.02-0.27 *versus* intervention 0.74, 95% CI 0.16-1.30; $p = 0.017$). Later, Bergkvist *et al.* [285] have the same opinion, achieving a significant decrease in the number of inappropriate drugs for the intervention group compared with the control group ($p = 0.049$). They also demonstrated that the MAI dimensions with the most inappropriate ratings were indication, duration and expenses, and anxiolytics, hypnotics and sedatives were the drugs with the most inappropriate ratings. This method has the advantage of assessing diverse dimensions of prescribing appropriateness, evaluates any medication considering the particular characteristics of the patient and reveals good intra-rater and inter-rater reliability as well. Nevertheless, it requires more time and does not appraise underprescribing [283], and it needs to be applied in additional studies, especially with more patients, and the results obtained should be compared with other tools.

I.6.2. Explicit criteria

PRISCUS

The PRISCUS list is a method that was developed by Holt *et al.* [286], which embraces 83 drugs in 18 drug classes and contains recommendations for clinical practice and therapeutic alternatives. This was primarily created to be use in German, but Gorzoni *et al.* [287] used it in 100 brazilian elderly people at their first outpatient geriatric visit. In this study, they obtained a mean of 0.7 ± 0.8 PIMs/patient with PRISCUS and a mean of 0.5 ± 0.7 PIMs/patient with Beers-Fick criteria, with no statistical significance found in the number of PIMs achieved with both criteria [287].

Norwegian General Practice criteria

The Norwegian General Practice criteria are also explicit criteria that were created through a three-round Delphi process with the aim of detecting pharmacological inappropriate prescriptions to older patients (≥ 70 years). The results were 37 explicit criteria of which 19 are related to a particular drug, 2 regarding drug dosage limits and the others involved various drug combinations. The highest agreement between a panel of specialists in general practice, clinical pharmacology and geriatrics was related to flunitrazepam, carisoprodol and the simultaneous use of three or more psychotropic drugs. Instead, the lowest agreement respected to the concomitant use of a NSAID and a selective serotonin reuptake inhibitor or a glucocorticoid [288].

Beers criteria

Based on various healthcare professional and expert's opinions, in 1991, Beers and colleagues published a list of 30 medications that should be avoided in nursing home residents [274]. In 1997 was published a revision of these explicit criteria for potentially inappropriate drug use in ambulatory elderly [289], considering not only the age, but doses, frequencies or durations of

specific therapies, and drugs that should be avoid in combination with a specific comorbidity as well. Later, Fick *et al.* [290] updated these criteria, resulting in 48 individual medications or classes of medications and 20 diseases/conditions and medications to be avoided in older adults.

Currently, there are a variety of studies performed in hospitals, outpatient settings, nursing homes and other healthcare centers that exploit this method to obtain some pertinent data, helping to understand the real dimension of this issue.

The prevalence of PIM ranged between 18.20% and 62.50%. The variety of data can be explained by the differences in drug availability, prescription practices, settings and even by cultural differences. Lai *et al.* [291], based on ambulatory care visits, revealed that 62.50% of the elderly patients were exposed to such medication, the highest prevalence found in this article. They also revealed that the most prescribed types of PIMs were antihistamines (4.8% of all prescriptions in 48.3% of elderly patients), muscle relaxants/antispasmodics (4.0% and 40.3%, respectively), and long-acting benzodiazepines (2.4% and 21.4%). Other authors distinguished the results obtained with explicit 1997 and 2003 criteria. Van der Hooft *et al.* [292] studied a population from 1997 to 2001, with 18,030 and 29,605 elderly, respectively, and the 1-year risks at least one potenttially inappropriate prescription varied between 16.8% and 18.5% according to the 1997 criteria and between 19.1% and 20.0% according to 2003 criteria. In this case, the most frequently prescribed potentially inappropriate medications were nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine and cimetidine; the mostly prescribed in supratherapeutic dose were temazepam and zolpidem; and the most frequently prescribed contraindicated drugs were conventional NSAIDs in persons with a history of gastric/duodenal ulcer. Finally, a study performed by Jones [293] evaluated elderly patients with chronic kidney disease and found that 56% of patients had one or more PIMs prescribed and 13% of all drugs prescribed were PIM, where antibiotics and antihypertensives contributed for the majority of PIMs.

Furthermore, there were studies that followed the patients for a certain period of time. Fick *et al.* [294] analyzed 17,330 patients for 18 months and 355 physicians that were separated into the treatment or usual-care groups. The number of patients with at least one PIM decreased from 19.4% to 17.9%. Besides, physicians made some change considering PIM use on 15.4% of the medication. Regarding to drug classes, the most likely to be discontinued were antihistamines (32.3%), analgesics (16.2%) and muscle relaxants (13.9%) and the PIM most likely to be changed were methocarbamol (46.7%), reserpine (42.9%), hydroxyzine (37.6), barbiturates (37.5%) and promethazine hydrochloride (37.1%). On the other hand, Laroche *et al.* [295] investigated the effect of hospitalization on potential inappropriate drug use and found a decreased of prevalence of PIM use from 66% at admission to 43.6% at discharge. In fact, all studies demonstrate improvements in some aspects such as PIM prevalence, risk of ADEs, underuse, change in medication or number of hospitalizations.

Zhan criteria

Zhan criteria were another tool based on 1997 Beers criteria that only divides drugs into three categories: drugs that always should be avoided, drugs that are rarely appropriate and drugs that are sometimes appropriate but often misused [296]. Therefore, Steinman *et al.* [297] compared both criteria analyzing 256 patients and concluded that 53% of the patients were taking at least one Beers-criteria drug against 28% Zhan-criteria drug.

Assessing care of vulnerable elders

As an underuse explicit tool, Spinewine and colleagues [298] used Assessing Care of Vulnerable Elders (ACOVE) to measure patients' outcomes after providing appropriate pharmaceutical care from admission to discharge. The study showed that the intervention group had improvements regarding to ACOVE underuse criteria and MAI as opposed to Beers' criteria.

Healthcare effectiveness data and information set

Pugh *et al.* [299] applied Health Effectiveness Data and Information Set (HEDIS) of 2006 that results from the addition of 2003 Beers criteria's drugs classified as always to be avoided (according to the National Committee on Quality Assurance). More than one million of outpatient visits were included and the results showed that 19.6% of older veterans were exposed to HEDIS 2006 drugs, a similar result to those obtained with 1997 Beers' criteria.

Screening tool of older people's prescriptions and screening tool to alert to right treatment criteria

Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) were developed and validated by a multidisciplinary team to respond to some inherent problems of Beers' criteria. These two methods are based on physiological systems, but while STOPP criteria suggest a list of explicit rules to avoid certain drugs or drug classes, START criteria reflect on patients with particular medical conditions and list frequent PPOs of beneficial drugs [300]. Recently, both criteria have been converted into software algorithms and implemented in a clinical decision support system to facilitate their use in clinical practice [301].

Ryan *et al.* [302] developed a study with 1 329 patients and 6 684 drugs prescribed; the results indicated 21.4% and 18.3% of PIM using STOPP and Beers' criteria respectively, and 22.7% of PPO prevalence using START criteria. The application of Beers' criteria classified 61.8% of the PIM as being of "high severity" and also described the prescribing benzodiazepines as one of the main contributors to the PIMs identified from both lists of Beers' criteria in which were defined the medications that should be avoided independent of diagnosis and considering diagnosis, accounting for 31.9% and 74.3% of the cases, respectively.

Afterward, Gallagher *et al.* [303] performed a prospective study with 900 older patients from six different European hospitals. STOPP criteria found 51.3% of PIM prevalence against 30.4% using Beers' criteria, and START criteria revealed 59.4% of PPO prevalence, concluding a high prevalence of PIM prescribing and omission of beneficial drugs.

I.6.3. Other tools

Drug Burden Index (DBI) is a tool that permits the calculation of an individual's total exposure to anticholinergic or sedative medications, considering pharmacological principles, through Hilmer *et al.* equation [304]. According to literature, DBI medicines, in older people, ranged from 29% to 70%. In a study of 226 elderly diagnosed with dementia, 56.90% were exposed to at least one PIM and 78.80% to medications leading to a DBI>0 [305]. Besides, Gnjidic *et al.* [306] in a study performed with 115 residents living in low care facilities found that 44% were exposed to DBI medications, 44% received at least one PIM and 26% were exposed to both.

I.7. The National Health Service, the National Network for Long-term Integrated Care and the pharmacist

I.7.1. Healthcare system in Portugal and organization

In Portugal, the National Health Service (*Serviço Nacional de Saúde*, SNS) predominantly provides primary care as well as acute general and specialized hospital services. However, dental consultations, diagnostic services, renal dialysis, and rehabilitation are more commonly offered by the private sector, often with significant public funding through contractual agreements with the SNS [307].

About primary care, Portugal had a noteworthy progress since the 1960s. Numerous studies conducted at that time revealed that the health situation in Portugal was "catastrophic", with the country ranking at the bottom for all health indicators [308]. The social pressure to reduce the significant inequities in the country's population's health led to the establishment of a SNS, funded by taxes and supplemented by public and private insurance schemes and direct payments. SNS was established starting in 1979 and fully implemented by 1983, organized explicitly around the principles of primary healthcare. It consisted of a network of health centres, staffed with family physicians and nurses, which gradually expanded to cover the entire country [309]. To qualify for SNS benefits, patients must register with a family physician at a health center, which serves as the primary point of contact. Later, in 2007, in order to turn these centers more efficient and better attuned to patient needs, the Family Health Units (*Unidades de Saúde Familiar*) reforms were introduced [308]. In 2008, local groups of primary healthcare centers (*Agrupamentos de Centros de Saúde*) emerge as a feasible alternative, providing administrative autonomy and enhancing the efficiency of primary healthcare [310]. Later, the Portuguese

primary healthcare system was divided into five mainland regions *(Administração Regional de Saúde*), which supervise 55 local groups of primary healthcare centers (*Agrupamento de Centros de Saúde*) [311]. At the ent of 2024, those five mainland regions were extinguished, transferring its powers and duties to different public entities, namely to the Executive Directorate of the SNS I. P. *(Direção Executiva do Serviço Nacional de Saúde, DE-SNS, I. P.),* the Directorate-General of Health *(Direção Geral da Saúde, DGS),* the National Institute of Health Doutor Ricardo Jorge I. P. *(Instituto Nacional de Saúde Doutor Ricardo Jorge, INSA, I. P.),* and the Central Administration of the Health System *(Administração Central do Sistema de Saúde, ACSS)* [312].

Secondary and tertiary care is primarily provided in hospitals, which are organized into Hospital Centres that serve specific geographical regions. At the beginning of the 21st century, one of the government's goals was to enhance capacity and improve cost-effectiveness in the SNS by increasing private sector involvement in the construction, maintenance, and operation of healthcare facilities through public-private partnerships, inspired by the British model. However, the results of these partnerships have been mixed, and no further public-private partnerships are currently planned. Another initiative to promote vertical integration in healthcare was the creation of Local Health Units (*Unidades Locais de Saúde*), which aim to combine hospitals and primary healthcare units within the same organization [313].

I.7.2. National Network for Long-term Integrated Care

Although the health status of the Portuguese population has improved, there continue to be gaps in long-term and palliative care due to the rising prevalence of chronic disabling diseases. As a result, new health and social needs are emerging, necessitating diverse and innovative responses to address the expected rise in demand from elderly individuals with functional dependencies, patients with multiple chronic conditions, and those with advanced, incurable diseases nearing the end of life [314].

In response to the need for new policies to (re)shape health and social care, the Portuguese authorities established the National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI) in 2006. RNCCI is an integrated network of post-acute care and long-term care units developed through collaboration between public, private, and third-sector organizations [315,316]. These services are offered in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCIs) and patient information is recorded and shared on GestCare CCI, an online web-based system of data management for RNCCI [317]. The primary objectives of RNCCI are to facilitate smoother transitions for patients from hospital to home care, reduce hospital stay durations, prevent hospital readmissions, and provide support for individuals who need long-term care to manage their mental, social, and physical limitations [315,318].

Actually, the general scope of the RNCCI includes the following response typologies: Convalescence Units (*Unidades de Convalescença*, UC); Medium-Term and Rehabilitation Units (*Unidades de Média Duração e Reabilitação*, UMDR); Long-Term and Maintenance Units (*Unidades de Longa Duração e Manutenção*, ULDM); and Integrated Continued Care Teams – Home (*Equipas de Cuidados Continuados Integrados*, ECCI) [316].

UC is a standalone inpatient facility, either integrated within an acute hospital or another institution, if linked to an acute hospital, providing ongoing intensive clinical treatment, supervision, and clinical rehabilitation care after a hospital admission due to an acute clinical condition, recurrence, or decompensation of a chronic illness. This kind of units is designed for hospital admissions that are expected to last up to 30 consecutive days per admission, and it aims to achieve clinical and functional stabilization, assessment, and comprehensive rehabilitation for individuals with a temporary loss of potentially recoverable autonomy who do not require acute hospital care [314,316].

UMDR is an inpatient facility with dedicated space, connected to an acute hospital, providing clinical care, rehabilitation, and psychosocial support for individuals recovering from an acute illness or experiencing decompensation of a chronic condition, and who have a temporary loss of potentially recoverable autonomy. The expected duration of hospitalization is more than 30 and fewer than 90 consecutive days per admission and the principal goal of UMDR is to achieve clinical stabilization, assessment, and complete rehabilitation and may offer specialized clinical, rehabilitation, and social care for individuals with specific pathologies [314,316].

In turn, ULDM is an inpatient facility, either temporary or permanent, with dedicated space to offer social support and ongoing healthcare for individuals with chronic illnesses or conditions, varying levels of dependency, and who cannot receive care at home. ULDM may offer care for a shorter period, in temporary situations such as family support challenges or the need for the primary caregiver to rest, for up to 90 days per year. The goal is to provide care that prevents or delays the progression of dependency, while promoting comfort and quality of life, for hospital stays lasting longer than 90 consecutive days [314,316].

Concerning to home care, ECCI is a multidisciplinary group, coordinated by primary healthcare and social support organizations, that provides home-based services, because these individuals have a social support network and do not require hospitalization but are unable to move autonomously. These services are based on a comprehensive assessment and include medical, nursing, rehabilitation, and social support care, among others, for individuals experiencing functional dependency, terminal illness, or recovering from illness. The team of ECCI utilizes local resources available within each health center's scope, working in conjunction with community services, including local authorities [314,316].

The RNCCI covers 10 190 patients hospitalized, 6 824 in home care and 231 in ambulatory. Regarding to UCCI, there are almost ten thousand places available nationally (1 391 in UC, 3 333 in UMDR and 5 260 in ULDM) [319].

I.7.2. The Role and Intervention of Pharmacist

The general objective of the RNCCI is to "*provide continued care to people who, regardless of age, are in a situation of dependency, namely elderly people with functional dependence, patients with multiple chronic pathologies and people with incurable diseases in an advanced state and in the final stages of life"* [314]. To achieve this, UCCIs (either UC, UMDR or ULDM) offer, among other services, prescription and medication administration [316]; therefore, and being inpatients institutions, it is crucial that UCCIs have medicines available for both consumption and own use.

However, industry (manufacturers, importers, or wholesalers) can only sell medications to healthcare establishments and services, whether public or private, and to non-profit social solidarity institutions, provided they have a medical and pharmaceutical service, as well as an inpatient care system. The medications must be for their own use, and these establishments, services, and institutions must be properly authorized for this purpose by National Authority of Medicines and Health Products (*Autoridade Nacional do Medicamento e Produtos de Saúde*, INFARMED I.P.) [320]. Thus, direct acquisition from industry requires a license for direct acquisition, which is only possible if there is a pharmacist duly authorized and registered in the INFARMED.

Recently, a new concierge allowed UCCI to acquire medication from community pharmacies [321], however there are medications, some of them lifesaving, such as some types of antibiotics, fluids, opioids and emergency medication (such as diazepam, midazolam or morphine injectable), whose acquisition is only possible via industry and, therefore, the existence of a pharmacist is still indispensable. In addition, this orientation does not refer to medicinal gases (e.g. oxygen and medicinal air), considered medicines, which acquisition also requires the existence of a license and whose circuit is also a responsibility of the pharmaceutical service. Furthermore, the control and registration of controlled substances (narcotics and psychotropic drugs) is the responsibility of the pharmacist and is governed by specific legislation.

Despite any bureaucratic issues, the pharmacist is essential for a safe, traceable, effective and efficient medication circuit. In fact, in 2010, INFARMED highlighted the importance of having a responsible pharmacist for each entity, who should ensure individualized monitoring and traceability of medication batches, as well as the proper handling and storage of medications, and report safety and quality alerts to INFARMED [322].

According to the Statute of the Order of Pharmacists, the pharmacist is responsible for, among others, the "*preparation, control, selection, acquisition, storage, and dispensing of human and*

veterinary medications, as well as medical devices, in public pharmacies, hospital pharmacy services, and pharmacy services of any other public or private entities" [323]. Thus, the existence of a responsible pharmacist is essential.

In 2007, UCCIs without a pharmacist were almost universally present, partly due to the lack of specific mention of pharmacists in the initial legislation and even more recent legislation regulating the RNCCI (Table I.10), even though the same legislation recognized UCCIs as inpatient units. However, of the 253 UCCI with UC, UMDR and/or ULDM listed in the latest Central Administration of the Health System (*Administração Central do Sistema de Saúde*) update (dated November 30, 2024) [324], at least 53 are not registered on the INFARMED portal "*Licenciamento +*" [325], which indicate that they do not have a license for direct acquisition, and therefore, from the outset they will not have a pharmacist responsible for the Pharmaceutical Services.

Table I.10. Recommended human resources for Units for Integrated Continuous Care, considering the capacity of 30 beds, adapted from [326].

Professional profile	**UC**	**UMDR**	**ULDM**	**Frequency**
	Weekly hours (a)			
Physician (includes physiatrist)	40	30	20	Daily presence (b)
Psychologist	20	20	20	Weekday presence
Nurse (includes coordinator and rehabilitation nurse)	480	360	240	Permanent presence
Physiotherapist	80	80	20	Daily presence
Social worker	40	40	40	Weekday presence
Speech therapist	8	8	0	Weekday presence
Socio-cultural animator	20	20	40	Weekday presence
Nutritionist	5	5	4	Weekday presence
Occupational therapist	40	40	20	Weekday presence
Auxiliary staff	560	480	320	Permanent presence

UC, Convalescence Units; ULDM, Long-Term and Maintenance Units; UMDR, Medium-Term and Rehabilitation Units. (a) The weekly hours correspond to the recommended minimum of contracted hours per professional group, with the possibility of flexible teams if there is more than one type in the same facility; (b) At ULDM the presence of a physician should be considered throughout the week.

The need for a pharmacist became consensual and, to help resolve this situation, the Union of Portuguese Mercies (*União das Misericórdias Portuguesas*) formed a working group consisting, among others, of pharmacists who developed procedures on various key issues for better management of the medication circuit, based on Good Hospital Pharmacy Practices [327,328] and generic and area-specific national legislation. The procedures carried out and respective

annexes focus on critical issues of pharmaceutical services and should be implemented in UCCI with the necessary adaptations.

Acquisition

This procedure defines the guiding principles to ensure proper acquisition of medications, as well as the correct execution of all technical tasks involved in this area. Thus, it outlines the responsibilities, proposes the kind (from the industry, distributors, and community pharmacies) and frequency of the acquisition, and also suggests when and how urgent or periodic acquisition should be made. This document also includes examples of purchase orders and templates for exceptional purchase orders.

Storage

This procedure aims to define the guiding principles and practices to be implemented in order to ensure the correct and safe storage of medicines. It describes the physical structure that must be followed for general storage, as well as how the medication should be organized and identified. In addition, it also focuses on specific aspects relating to the storage of medicines with special characteristics, such as flammables [329], medicinal gases, controlled substances, medicines that require refrigeration and emergency medication. In addition to the proposed template for recording temperature and humidity, Look-alike, Sound-alike medicines [330] and their own signage are also listed.

Identification, repackaging and splitting of medications

This procedure defines the guiding principles and practices to be implemented in order to ensure correct and safe identification, repackaging and fractionation of medicines. Identification applies to all medicines that do not display a unit dose, i.e. international nonproprietary name, dosage, batch and expiry date. Repackaging applies to medicines that are removed from their primary packaging [e.g. medicines whose identification is not possible on the blister itself, those sold in bottles (multi-dose) or those subject to fractionation]. Tablet fractionation, when applicable (automatically excluding controlled or prolonged release forms, modified release, with a special coating, or gastro-resistant, among others) implies repackaging with the assignment of a new batch and adjusted expiry date (validity reduced to 6 months or 25% of the original expiry date, whichever is shorter). This document includes examples of forms that can be used to record repackaging and/or fractionation processes.

Daily individual distribution in unit dose

This procedure focuses on daily individual unit dose dispensing, the main objective of which is to minimize medication-related errors and consequently the associated costs. In a hospital setting, medication should be prepared daily in individual unit doses for a 24-hour period. Medications to support individual preparation must be prepared for distribution, i.e. they must be previously identified/fractionated/packaged so that they can be placed daily and individually in the drawer module/medication trolley in each of the places designated for each patient and differentiated by dose.

Stock management and replenishment

This procedure focuses on the guiding principles and practices to be implemented in order to ensure efficient stock management and the correct and safe replenishment of drug stocks. Stock management must comply with a Medicines Formulary previously approved by the institution, in which medicines are designated by the National Hospital Medicines Code (*Código Hospitalar Nacional do Medicamento*) or a single internal reference, which should include only the international nonproprietary name, dosage and pharmaceutical form, regardless of the commercial brand or laboratory of origin. All entries, exits and stock losses must be duly recorded in a tool adopted for this purpose and the stock periodically inventoried. Addicionatly, it includes templates that may be used in this issue.

Control of expiry dates and disposal of medications

This procedure provides information on how to ensure correct and safe management of medicine expiration dates as well as the guidelines for the safe disposal of expired drugs, according to the type of medication, which may require the adoption of specific protocols.

Control and record of narcotics and psychotropic substances

Procedure that applies to all narcotic and psychotropic drugs listed in tables I, II and IV of Decree-Law No. 15/93, of 22 January. This procedure intends to ensure the control and registration of this medication, in concordance with the legislation [331–333]. This procedure focuses on the various stages of the circuit, explaining how these medicines should be acquired and what precautions and requirements should be taken into account when receiving and storing them. In addition, it also describes how the dispensing and administration of these medicines are planned, as well as the procedure for the destruction and recording of breakages of these types of medicines. For the key stages of the circuit, templates are suggested for registration, identification or conference of this medication.

Donation management

As a health institution, the UCCI can only accept donations made within the legal limits and the rules of INFARMED, the medicine authority. Thus, this was a procedure created for accepting donated medicines from institutions that must guarantee the quality of the donated product, namely by having a pharmacist responsible for the entire journey of the medicine and by complying with basic rules regarding, e.g., storage and packaging.

Medicinal gases

This procedure establishes the guiding principles and practices to be implemented in the selection, acquisition, stock management, reception storage, handling, security, monitoring and quality control of medical gases. According to Decree-Law no. 176/2006 of August 30 (Medicines Statute) [320], medical gases are considered medicines and must therefore be used under pharmaceutical supervision, covering the entire medical gas circuit, from the selection of the gas to be used to post-administration monitoring. There must be a safe distribution network, without interchangeability and with an adequate alarm system.

Emergency trolley/bag

This procedure suggests the composition of the emergency trolley/bag, as well as the guiding principles and practices to be implemented in order to ensure the correct and safe storage of medicines and medical devices. Thus, after the selection and acquisition of medicines and medical devices, it is necessary to ensure their correct identification and organization, taking into account the care to be taken with look-alike/sound-alike medicines, and to guarantee an adequate periodic review.

Cleaning and disinfection of surfaces and equipment

This procedure sets out to define the guiding principles for cleaning, so that equipment and surfaces used in all procedures related to medicines can be properly sanitized. This involves classifying the different areas according to the risk of infection, selecting the products to be used according to the type of material, type of surface and objective (disinfection or cleaning) and defining the cleaning frequency.

Medication at admission, transfer, or discharge of patients

This procedure defines the guiding principles and practices to be implemented in order to ensure the continuous administration of medication when a patient is admitted, transferred or discharged.

Risk management of medication and medical devices

This procedure establishes the surveillance system to be implemented to ensure the detection and reporting of ADRs/adverse events resulting from the use of medicines and medical devices, and to report these events to the National Pharmacovigilance System (*Serviço Nacional de Farmacovigilância*), while managing the clinical risks associated with their use. It is essential to implement a protocol for monitoring and tracking safety and quality alerts issued by INFARMED, which will permit to reduce the clinical risks linked to the use of medicines and medical devices.

Medication errors

This procedure intends to establish the core principles to guarantee the detection, documentation, and analysis of medication errors, with the goal of identifying their underlying causes and implementing preventive measures. Notifications resulting from this process focus solely on fostering the ongoing improvement of the medication process.

I.8. Aims of this thesis

As previously discussed, the progressive ageing of the population is the result of several factors. On the one hand, the increase in average life expectancy should be recognised as a testament to effective public health initiatives. However, this demographic shift has changed morbidity patterns, leading to a higher prevalence of chronic diseases and increased pressure on health and social care systems. This tendency has created new societal challenges and raised concerns about the long-term sustainability of patient care and health infrastructures. In this context, and in view of the need for new policies to (re)structure health and social care, the Portuguese government established the RNCCI in 2006.

In addition, the literature indicates that several age-related conditions are more common in older adults, often leading to multimorbidity and polypharmacy, which in turn increase the risk of DRPs. In particular, ADRs - a major cause of hospital admissions, healthcare costs, morbidity and mortality - are thought to be preventable in about 50% of cases.

A significant cause of ADRs is inappropriate prescribing which, in turn, has been associated with other negative clinical outcomes such as risk of hospitalisation, hospital readmission, reduced quality of life and even mortality. On the other hand, inappropriate prescribing can also be associated with significant and unnecessary expenditure, raising another concern: cost. All of this is likely to have contributed to the increasing global focus on inappropriate prescribing.

Of all the tools developed, the STOPP/START criteria have proved to be a useful tool, with a double benefit. On the one hand, the STOPP criteria can play an important role in reducing PIM rates; on the other hand, the START criteria aim to reduce under-prescribing by identifying PPOs.

Thus, this thesis has as principal goals in a first phase:

- To understand the concept of ageing in Portugal and in the world, mentioning the physiological, pharmacokinetic and pharmacodynamic changes involved and their implications for pharmacotherapy;
- To explore the concepts of comorbidity, multimorbidity, DALYs and leading causes of death;
- To recognize the chronic diseases and geriatric syndromes that are more common in the elderly, to explore their prevalence and their economic, health and social implications;
- To contextualize, define and classify DRPs, according to different authors and guidelines, as this topic is rather controversial and not universal, which leads to some difficulties when trying to compare different studies;
- To explore the existing screening tools to detect PIMs (Beers' criteria, MAI, STOPP/START and others less used) and evaluation of their prescription appropriateness, advantages and limitations;
- To describe the healthcare system in Portugal and focus on Portuguese RNCCI;
- To explore the role of the pharmacist in continuous care.

In the second phase, a study will be carried out on the prevalence of PIM in the Portuguese elderly, through the application of the STOPP and START criteria, with the following objectives:

- To assess and analyse the relationship between patients' demographic and medical characteristics and their medication use patterns, the prevalence of polypharmacy and associated factors in different UCCIs among Portuguese RNCCI patients;
- To determine the prevalence of PIMs and PPOs, both overall and according to individual STOPP and START criteria, respectively, in patients aged 65 years and older;
- To explore potential demographic and clinical predictors of PIMs and PPOs in older RNCCI patients;
- To determine and compare the prevalence of PIMs and PPOs and their predictors in patients aged 75-84 years and those aged 85 years and over admitted to the RNCCI.

At the end of this work, we hope to improve knowledge about the dynamics between ageing, multimorbidity, polypharmacy and inappropriate prescribing. In addition to the international panorama, we hope to conclude on the prevalence of inappropriate prescribing and its potential predictors in the Portuguese population. This information will certainly contribute to the development of future health policies and clinical practices adapted to Portugal's growing elderly population.

Chapter II

Patients' characterization, pattern of medication use, and factors associated with polypharmacy: a cross-sectional study focused on eight units of the Portuguese National Network for Long-Term Integrated Care

Chapter II – Patients' characterization, pattern of medication use, and factors associated with polypharmacy: a cross-sectional study focused on eight units of the Portuguese National Network for Long-Term Integrated Care

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II.1. Introduction

The progressive aging of the population is the result of multiple factors, two of the most important being the growth of average life expectancy and the increasingly low birth rate [334–336]. The increase in average life expectancy must necessarily be seen as a reflection of successful public health policies. However, it is true that these measures have also brought new challenges to society, which raises concerns about the sustainability of patient management and healthcare systems [336,337]. In fact, the aging of the population has led to changes in patients' morbidity profiles, with a higher incidence of chronic diseases and a consequent greater demand on health and social care systems [336]. In this context, Portugal is no exception, presenting an average life expectancy of 81.3 years, which is slightly higher than the European Union average (80.9 years) [336,338]. Thus, considering the need for new policies to (re)configure health and social care, in 2006, the Portuguese authorities launched the RNCCI. RNCCI is an integrated network of post-acute and long-term care units that resulted from a partnership between public, private, and third-sector entities [315,316] and that are currently available in UCCIs. Its main goals are to help healthcare services improve patients' transitions from hospital to home care, reduce the length of patients' hospitalizations and avoid hospital readmissions, and also support people who require long-term care to deal with their mental, social, and physical limitations [315,318,339].

Epidemiologic studies suggest that multiple age-related diseases tend to be more prevalent in older people, leading to multimorbidity, polypharmacy, and a greater likelihood of developing ADRs and DRPs [340–344]. In particular, the ADRs are one of the foremost DRPs responsible for hospital admissions [345–348], healthcare costs [349,350], morbidity, and mortality [350–356], with many of them being associated with specific drug classes [351,353,357]. Still, it must be considered that around 50% of all ADRs could be prevented [348,352,358], including those associated with polypharmacy, an undesirable and expensive problem with potential negative clinical outcomes [359–361]. Although there is still a lack of consensus on the definition of polypharmacy, it is generally referred to as the concurrent use of multiple medications (i.e., ≥5 drugs) by the same individual [343,362]. Due to the progressive increase in the number of drugs concomitantly prescribed, several studies distinguish polypharmacy (defined as 5–9 drugs) from excessive polypharmacy (defined as ≥10 drugs) [363–365]. Furthermore, factors associated with polypharmacy and excessive polypharmacy have been explored [340,366,367]. Some studies on polypharmacy and patterns of medication use have been performed in different settings, such as nursing homes [368,369], hospital settings [366,370,371], and post-acute and long-term care settings [372–376]. However, despite the global tendency toward better healthcare for the population, no study to evaluate the patterns of medication use and the predictor factors such as the demographic and medical characteristics of polypharmacy have been conducted in Portugal, focusing on data from post-acute and long-term care residents from different UCCIs of the RNCCI.

Thus, this study aimed to evaluate and correlate the patients' demographic and medical features with the pattern of medication use, prevalence of polypharmacy, and factors associated with patients from different UCCIs of the Portuguese RNCCI.

II.2. Materials and methods

II.2.1. Study design, setting, and population

An observational, retrospective, cross-sectional, and multicenter study was performed in UCCIs inserted in the Portuguese RNCCI. According to specific features, UCCIs of the RNCCI are currently divided into three different response typologies of hospitalization: (i) UC that provide medical, nursing, and rehabilitation care for stays up to 30 consecutive days; (ii) UMDR that offer less intensive nursing and rehabilitation care, with an expected length of stay between 30 and 90 consecutive days; and (iii) ULDM that provide social support and maintenance healthcare for more than 90 consecutive days. This last response typology is specially intended for people with chronic diseases with different levels of dependency who are unable to be cared for at home, thus preventing and delaying the worsening of the dependency situation and favoring comfort and quality of life [314,315]. Different patients from UC, UMDR, and ULDM response typologies of hospitalization in the central region of Portugal were included in this study. To reduce bias associated with the type of hospitalization and the healthcare team, data were collected from one UC, four UMDR, and seven ULDM belonging to eight different UCCIs (A to H). The same number of patients (fifteen) from each UC, UMDR, or ULDM selected with a consecutive discharge date in the defined time period were selected. Data were collected considering the clinical processes at discharge.

The retrospective nature of this study did not affect healthcare provision to patients, and informed consent was not required. Patients' data were anonymized through the attribution of an alphanumeric code, and access were restricted to the person who collected the data. The subsequent analysis was performed exclusively using the encoded data.

II.2.2. Data sources

Data were mainly collected through the RNCCIs platform, which is an online tool that integrates multiple pieces of information about patients, such as medical, nursing, and social evaluations. This data system is regularly updated by the healthcare team, so it were used to collect most of the data on patients' demographic records, medical history, diagnoses, and prescribed drugs; whenever available, additional internal records were also accessed to obtain information about the prescribed drugs.

II.2.3. Data collection

For the eligible patients with the complete information records of the UCCIs selected, the following characteristics were collected by a pharmacist from the RNCCIs platform: demographic characteristics (age and gender), general information related to medical history (provenance/origin, length of stay, and type of feed), prescribed medications, and comorbidities. All pharmaceutical dosage forms, including oral, parenteral, topical, ophthalmological, and inhaled medications, taken on a regular basis (excluding only SOS medications), were considered. If a fixed-dose combination of drugs was used in the same medication, it was only counted as one. To describe the most frequently prescribed medications, drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification system [377]: the first level of ATC classification (anatomical main group) and the second level of ATC classification (therapeutic subgroup); in both cases, whenever possible, the last update available (i.e., the prescription at discharge) was used. The polypharmacy status was classified as non-polypharmacy (≤4 drugs) and polypharmacy (≥5 drugs). Comorbidities were also investigated using the encoded diagnoses presented on the *GestCare CCI* platform. For this assessment, only diagnoses based on the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) were considered. Only the three ICD-9-CM codes existing in the patients' profiles were collected, and only those that affected at least 5% of the total study population were reported. For the CCI, all medical records were investigated [227].

II.2.4. Statistical analysis

Continuous variables (age, length of stay, number of dispensed prescribed drugs, and CCI) were expressed as mean ± standard deviation (SD), median, and interquartile range (P25; P75), and in the specific case of age, it also indicated the range. As for categorical variables, the number of observations (absolute frequency) and percentages (relative frequency) are explicitly shown. Logistic regression was performed to investigate the relationship between the main outcome (polypharmacy status) and the other variables [facilities (UCCIs, encoded from A to H); response typologies of hospitalization (UC, UMDR, and ULDM), demographic characteristics (age and gender), medical history (provenance/origin, length of stay, and type of feed), and CCI]. The existence of associations between the dependent variable and the evaluated independent variables was initially tested using bivariate logistic regression (an unadjusted model). The respective odds ratios (ORs) were also estimated and adjusted for possible confounding variables in a multivariate logistic regression (in which all the previously indicated variables were taken into account except the response typology of hospitalization). Logistic regression analysis with the logit link function was performed using the forward selection method based on the Wald test to find independent predictors associated with polypharmacy status. Also, ORs were adjusted for possible confounding variables. The Hosmer–Lemeshow test was performed to assess the goodness of fit, whereas the area under the receiver operating characteristic curve allowed the evaluation of the discriminatory power of the model and its sensitivity/specificity. The ORs were calculated

considering a 95% confidence interval (CI). A *p*-value less than 0.05 ($p < 0.05$) was used as the significance level. Data analysis was performed using the statistical package IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism software version 8.0 (San Diego, CA, USA).

II.3. Results

II.3.1. Characteristics of this study population

A total of 180 patients who received post-acute and long-term care at different response typologies from eight UCCIs of the RNCCI were included and extensively characterized. The characteristics of this study population are summarized in Table II.1. Regarding demographic characteristics, this study population had a mean age of 78.4 ± 12.3 years in the range of 23–102 years, with the majority (59.4%) being female. Before being admitted to UCCIs, patients' provenance was mainly from hospital facilities (53.3%). For 53.3% of patients, the length of stay was longer than 90 days, and for 31.1%, it was between 31 and 90 days. Overall, 12.8% of patients had to be fed by enteral nutrition using a nasogastric tube or percutaneous endoscopic gastrostomy.

Regarding the number of dispensed prescribed drugs, patients had a median value of 8 (P25: 6; P75: 11) medications, with 38.9% having ten or more medications prescribed (Table II.1).

To evaluate the most frequently prescribed drugs, 1594 prescriptions were initially considered. However, in some patients, there were repeated observations of drug prescriptions belonging to the same therapeutic subgroup, so it was considered that these should only be counted once, meaning that in the end, there were considered 1350 prescriptions. According to the ATC classification system, the main therapeutic subgroups prescribed were psycholeptics (67.2%), drugs for acid-related disorders (66.7%), antithrombotic agents (66.1%), psychoanaleptics (57.8%), diuretics (46.7%), agents acting on the renin-angiotensin system (40.0%), and lipid modifying agents (38.9%) (Table II.1).

Concerning comorbidities, a total of 124 different ICD-9-CM codes were identified, with only those that affected at least 5% of this study population being selected. In addition, in 6 cases in which the ICD-9 code 436 (Acute, but ill-defined cerebrovascular disease) and the ICD-9-CM code 437 (Other and ill-defined cerebrovascular disease) were used, only the most recent diagnosis was considered. Thus, of the 234 comorbidities identified, only 228 were eligible for the final analysis. Overall, the results showed that approximately 29% of patients had essential hypertension, 26% had diabetes mellitus, and 13% were diagnosed with heart failure. The other prevalent identified conditions were acute (but ill-defined) cerebrovascular diseases, other cerebral degeneration, other and ill-defined cerebrovascular disease, fracture of the femoral neck, osteoarthrosis and related disorders, cardiac dysrhythmias, chronic kidney disease, and prostate hyperplasia (5%) (Table II.1). Regarding CCI, patients had a median value of 5 (P25: 4; P75: 7) (Table II.1).

Table II.1. Characteristics of this study population (N = 180) that received post-acute care and long-term care in Units for Integrated Continuous Care (UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (RNCCI).

	Total (*N* = 180)	**UC (*n* = 15)**	**UMDR (*n* = 60)**	**ULMD (*n* = 105)**
Demographic characteristics				
Age (years)				
Mean ± SD (range)	78.4 ± 12.3 (23–102)	70.5 ± 13.6 (44–82)	77.3 ± 10.5 (34–94)	80.1 ± 12.6 (23–102)
Median (P25; P75)	81 (74.25; 86.00)	75 (62; 81)	79 (74; 83)	83 (75; 87)
< 65, *n* (%)	19 (10.6)	4 (21.1)	7 (36.8)	8 (42.1)
65–74, *n* (%)	26 (14.4)	2 (7.7)	9 (34.6)	15 (57.7)
75–84, *n* (%)	79 (43.9)	9 (11.4)	32 (40.5)	38 (48.1)
≥ 85, *n* (%)	56 (31.1)	0 (0.0)	12 (21.4)	44 (78.6)
Gender, n (%)				
Male	73 (40.6)	6 (8.7)	24 (32.9)	43 (58.9)
Female	107 (59.4)	9 (8.1)	36 (33.7)	62 (57.9)
Medical history				
Provenance/origin, *n* (%)				
Residence or other	84 (46.7)	1 (1.2)	23 (27.4)	60 (71.4)
Hospital	96 (53.3)	14 (14.6)	37 (38.5)	45 (46.9)
Length of stay				
Mean ± SD	145.3 ± 189.5	30.5 ± 11.0	94.7 ± 49.3	190.7 ± 234.5
Median (P25; P75)	93 (59.25;150.00)	30 (30; 38)	92.5 (68; 115)	117 (86; 184)
≤ 30, *n* (%)	28 (15.6)	11 (39.3)	7 (25.0)	10 (35.7)
31–90, *n* (%)	56 (31.1)	4 (7.1)	22 (39.3)	30 (53.6)
> 90, *n* (%)	96 (53.3)	0 (0.0)	31 (32.3)	65 (67.7)
Type of feed				
Enteral nutrition, *n* (%)				
No	157 (87.2)	15 (9.6)	54 (34.4)	88 (56.1)
Yes	23 (12.8)	0 (0.0)	6 (26.1)	17 (73.9)
Nasogastric tube, *n* (%)	20 (11.1)	0 (0.0)	6 (30.0)	14 (70.0)
Percutaneous endoscopic gastrostomy, *n* (%)	3 (1.7)	0 (0.0)	0 (0.0)	3 (1.7)
Number of dispensed prescribed drugs				
Mean ± SD	8.8 ± 3.6	5.9 ± 3.0	9.3 ± 3.0	8.9 ± 3.8

Median (P25; P75)	8 (6; 11)	6 (4; 8)	8.5 (7; 11)	9 (6; 11)
≤4, *n* (%)	19 (10.6)	5 (26.3)	4 (21.0)	10 (52.6)
5–9, *n* (%)	91 (50.6)	8 (8.8)	29 (31.9)	54 (59.3)
≥10, *n* (%)	70 (38.9)	2 (2.9)	27 (38.6)	41 (58.6)
Most frequent prescribed therapeutic subgroups [†], *n* (%)				
Psycholeptics (N05)	121 (67.2)	9 (7.4)	42 (34.7)	70 (57.9)
Drugs for acid-related disorders (A02)	120 (66.7)	11 (9.2)	42 (35.0)	67 (55.8)
Antithrombotic agents (B01)	119 (66.1)	10 (8.4)	42 (35.3)	67 (56.3)
Psychoanaleptics (N06)	104 (57.8)	9 (8.7)	33 (31.7)	62 (59.6)
Diuretics (C03)	84 (46.7)	4 (4.8)	32 (38.1)	48 (57.1)
Agents acting on the renin-angiotensin system (C09)	72 (40.0)	5 (6.9)	30 (41.7)	37 (51.4)
Lipid-modifying agents (C10)	70 (38.9)	5 (7.1)	25 (35.7)	40 (57.1)
Analgesics (N02)	59 (32.8)	4 (6.8)	19 (32.2)	36 (61.0)
Drugs for constipation (A06)	58 (32.2)	0 (0.0)	22 (37.9)	36 (62.1)
Beta-blocking agents (C07)	53 (29.4)	2 (3.8)	24 (45.3)	27 (50.9)
Drugs used in diabetes (A10)	51 (28.3)	1 (2.0)	24 (47.1)	26 (51.0)
Antiepileptics (N03)	47 (26.1)	2 (4.3)	14 (29.8)	31 (66.0)
Antianemic preparations (B03)	41 (22.8)	0 (0.0)	15 (36.6)	26 (63.4)
Cardiac therapy (C01)	39 (21.7)	0 (0.0)	14 (35.9)	25 (64.1)
Most common/significant comorbidities (ICD-9-CM codes[‡]), *n* (%)				
Essential hypertension (401)	52 (28.9)	4 (7.7)	20 (38.5)	28 (53.8)
Diabetes mellitus (250)	47 (26.1)	0 (0.0)	23 (48.9)	24 (51.1)
Heart failure (428)	23 (12.8)	0 (0.0)	11 (47.8)	12 (52.2)
Acute, but ill-defined, cerebrovascular disease (436)	20 (11.1)	0 (0.0)	11 (55.0)	9 (45.0)
Other cerebral degenerations (331)	16 (8.9)	0 (0.0)	4 (25.0)	12 (75.0)
Other and ill-defined cerebrovascular diseases (437)	14 (7.8)	0 (0.0)	1 (7.1)	13 (92.9)
Fracture of the neck of the femur (820)	14 (7.8)	4 (28.6)	5 (35.7)	5 (35.7)
Osteoarthrosis and allied disorders (715)	12 (6.7)	6 (50.0)	0 (0.0)	6 (50.0)
Cardiac dysrhythmias (427)	11 (6.1)	0 (0.0)	6 (54.5)	5 (45.5)
Chronic kidney disease (585)	10 (5.6)	0 (0.0)	4 (40.0)	6 (60.0)
Hyperplasia of the prostate (600)	9 (5.0)	0 (0.0)	2 (25.0)	6 (75.0)
CCI				
Mean ± SD	5.5 ± 2.1	3.3 ± 1.9	5.5 ± 1.9	5.8 ± 2.0
Median (P25; P75)	5 (4; 7)	4 (2; 5)	5.5 (4; 7)	6 (5; 7)

CCI, Charlson Comorbidity Index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; SD, Standard deviation; UC, Convalescence Units; ULDM, Long-Term and Maintenance Units; UMDR, Medium-Term and Rehabilitation Units; † the therapeutic subgroups present in more than 20% of patients; ‡ ICD-9-CM codes affected at least 5% of the total study population.

II.3.2. Factors associated with polypharmacy status

Table II.2 summarizes the data related to polypharmacy status. Approximately 89.4% were subjected to polypharmacy (≥ 5 drugs), and only 10.6% of patients were prescribed less than 5 drugs. Among the different UCCI facilities (A to H), non-polypharmacy ranged from 0% to 33.3%, and polypharmacy varied between 66.7% and 100% (Figure II.1 and Table II.2). Considering the response typologies of hospitalization, 66.7%, 93.3%, and 90.5% of patients in the UC, UMDR, and ULDM, respectively, were subjected to polypharmacy regimens. In relation to age, the prevalence of polypharmacy was higher (92.4%) in the age group between 75 and 84 years old. Furthermore, 95.7% of patients fed by the enteral route were also subjected to polypharmacy. Regarding CCI, patients with higher scores were also more polymedicated.

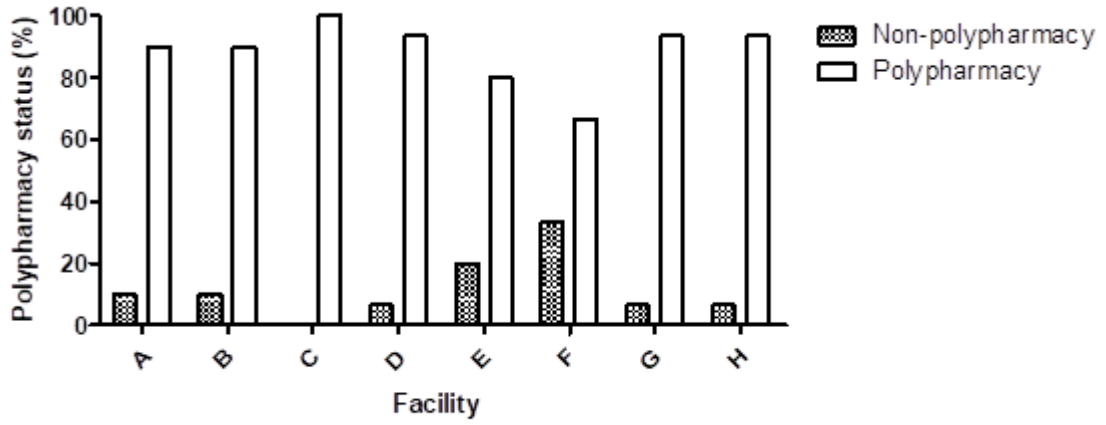

Figure II.1. Polypharmacy status (non-polypharmacy and polypharmacy) according to the different facilities.

Bivariate analysis identified as potential predictor factors of polypharmacy status: UCCIs [facility F when compared with H (OR = 0.143, 95%CI: 0.024–0.857; p = 0.033)]; response typologies of hospitalization [UMDR when compared to UC (OR = 7.000, 95%CI: 1.598–30.657; p = 0.010); ULDM when compared with UC (OR = 4.750; 95%CI: 1.353–16.675; p = 0.015)]; and CCI (OR = 1.424, 95%CI: 1.120–1.812; p = 0.004).

After multivariate logistic regression analysis (Table II.3), a significant association was found between polypharmacy status and the unit of internment (facility) when facility E is compared with facility H (OR = 0.035, 95%CI: 0.003–0.417; p = 0.008). Polypharmacy status was also significantly associated with the CCI (OR = 1.914, 95% CI: 1.128–3.246; p = 0.016). However, no significant association was found with age, gender, or other factors assessed.

Table II.2. Factors associated with polypharmacy status (non-polypharmacy and polypharmacy) were subjected to a bivariate logistic regression (unadjusted model).

	Total *N* (%)	**Non-Polypharmacy *n* (%)**	**Polypharmacy *n* (%)**	**OR [†] (95% CI)**	***p* [*]**
	180	19 (10.6)	161 (89.4)		
Facilities					
UCCI					0.290
A	30 (16.7)	3 (10.0)	27 (90.0)	0.643 (0.100; 4.153)	0.643
B	30 (16.7)	3 (10.0)	27 (90.0)	0.643 (0.100; 4.153)	0.643
C	15 (8.3)	0 (0.0)	15 (100.0)	-	-
D	30 (16.7)	2 (6.7)	28 (93.3)	1.000 (0.131; 7.605)	1.000
E	15 (8.3)	3 (20.0)	12 (80.0)	0.286 (0.042; 1.935)	0.199
F	15 (8.3)	5 (33.3)	10 (66.7)	**0.143 (0.024; 0.857)**	**0.033**
G	15 (8.3)	1 (6.7)	14 (93.3)	1.000 (0.083; 11.998)	1.000
H	30 (16.7)	2 (6.7)	28 (93.3)	1	
Response typology of hospitalization					**0.020**
UC	15 (8.3)	5 (33.3)	10 (66.7)	1	
UMDR	60 (33.3)	4 (6.7)	56 (93.3)	**7.000 (1.598; 30.657)**	**0.010**
ULDM	105 (58.4)	10 (9.5)	95 (90.5)	**4.750 (1.353; 16.675)**	**0.015**
Demographic characteristics					
Age (years)					
Mean ± SD (range)	78.4 ± 12.3 (23–102)	75.7 ± 18.0 (44–102)	78.7 ± 11.4 (23–99)	1.018 (0.983; 1.053)	0.322
Median (P25; P75)	81 (74; 86)	79 (58; 91)	81 (75; 86)		
< 75, *n* (%)	45 (25.0)	7 (15.6)	38 (84.4)	1	
75–84, *n* (%)	79 (43.9)	6 (7.6)	73 (92.4)	2.241 (0.703; 7.141)	0.172
≥ 85, *n* (%)	56 (31.1)	6 (10.7)	50 (89.3)	1.535 (0.477; 4.962)	0.472
Gender					
Male	73 (40.6)	11 (15.1)	62 (84.9)	1	
Female	107 (59.4)	8 (7.5)	99 (92.5)	2.196 (0.837; 5.760)	0.110
Medical history					
Provenance / origin					
Residence or other (%)	84 (46.7)	11 (13.1)	73 (86.9)	1	
Hospital (%)	96 (53.3)	8 (8.3)	88 (91.7)	1.658 (0.633; 4.338)	0.303

Length of stay:					
Mean ± SD	145.3 ± 189.5	96.0 ± 76.4	151.1 ± 198.0	1.003 (0.998; 1.009)	0.248
Median (P25; P75)	93 (59; 150)	90 (30; 162)	94 (64.5; 150)		
≤ 30, *n* (%)	28 (15.6)	6 (21.4)	22 (78.6)	1	
31–90, *n* (%)	56 (31.1)	4 (7.1)	52 (92.9)	3.545 (0.910; 13.811)	0.068
> 90, *n* (%)	96 (53.3)	9 (9.4)	87 (90.6)	2.636 (0.848; 8.194)	0.094
Type of feed					
Enteral nutrition (%)					
Yes	23 (12.8)	1 (4.3)	22 (95.7)	2.849 (0.362; 22.426)	0.320
No	157 (87.2)	18 (11.5)	139 (88.5)	1	
CCI					
Mean ± SD	5.5 ± 2.1	4.2 ± 2.5	5.6 ± 1.9	**1.424 (1.120; 1.812)**	**0.004**
Median (P25; P75)	5 (4; 7)	5 (1; 6)	6 (4; 7)		

CCI, Charlson Comorbidity Index; SD, Standard deviation; UC, Convalescence Units; UCCI, Units for Integrated Continuous Care; ULDM, Long-Term and Maintenance Units; UMDR, Medium-Term and Rehabilitation Units; † Not adjusted odd ratio; * Wald test; All significant variables are in bold.

Table II.3. Factors associated with polypharmacy status (non-polypharmacy and polypharmacy) were subjected to multivariate logistic regression (adjusted model).

	aOR † **(95% CI)**	***p*** *
Facilities		
UCCI		0.109
A	0.686 (0.096; 4.895)	0.707
B	0.818 (0.110; 6.060)	0.844
C	-	-
D	1.073 (0.121; 9.553)	0.949
E	**0.035 (0.003; 0.417)**	**0.008**
F	0.133 (0.012; 1.409)	0.094
G	1.081 (0.078; 15.078)	0.954
H	1	
Demographic characteristics		
Age (years)	0.931 (0.867; 1.000)	0.051
Gender		
Male	1	
Female	2.253 (0.681; 7.458)	0.183
Medical History		
Provenance/origin		
Residence or other (%)	1	
Hospital (%)	4.369 (0.969; 19.698)	0.055
Length of stay	1.003 (0.997; 1.009)	0.310
Type of feed		
Enteral nutrition (%)		
Yes	1.739 (0.136; 22.269)	0.671
No	1	
CCI	**1.914 (1.128; 3.246)**	**0.016**

CCI, Charlson Comorbidity Index; † aORs, adjusted odd ratio with all the variables of Table II.2, except with the response typology of hospitalization; $p < 0.05$ is significant; all significant variables are in bold. Omnibus test: $p = 0.004$; Hosmer and Lemeshow test: $p = 0.683$; Cox and Snell $r^2 = 0.16$, Nagelkerke $r^2 = 0.32$; AUC = 0.842 (95% CI (0.759; 0.925), $p < 0.001$); Sensitivity = 59.6%; Specificity = 94.7% (cut-off probability = 0.945); * Wald test.

II.3.3. Distribution of drug users according to the most prescribed drugs and polypharmacy status

Table II.4 shows the distribution of drug users according to the most prescribed drugs and polypharmacy status, taking into consideration the anatomical main groups and therapeutic subgroups.

Regarding the anatomical main groups analysis, 751 drugs were considered to avoid the repetition of the counting of the same code in the same patient; of these, 98.0% (736 drugs) were included in the ten groups most frequently prescribed, and 93.5% (702 drugs) were reported by 10% of the total study population. In general, nervous system-active medications were the most chronically prescribed drugs (90.6%); drugs that act in the alimentary tract and metabolism and in the cardiovascular system had a similar prevalence (85.0% and 83.3%, respectively); and drugs belonging to the blood and blood-forming organs group also represented a significant part of the prescribed drugs (75.6%). When comparing the non-polypharmacy group with the polypharmacy

group, the same trend can be seen between them, since the same main anatomical groups were those prescribed to the less medicated patients.

Table II.4. Distribution of drug users according to the most prescribed drugs and polypharmacy status.

	ATC Code	Total *N* (%)	Non-Polypharmacy *n* (%)	Polypharmacy *n* (%)
		180 (100%)	19 (10.6)	161 (89.4)
Anatomical main groups †				
Nervous system	N	163 (90.6)	13 (8.0)	150 (92.0)
Alimentary tract and metabolism	A	153 (85.0)	10 (6.5)	143 (93.5)
Cardiovascular system	C	150 (83.3)	10 (6.7)	140 (93.3)
Blood and blood forming organs	B	136 (75.6)	9 (6.6)	127 (93.4)
Respiratory system	R	40 (22.2)	2 (5.0)	38 (95.0)
Musculo-skeletal system	M	34 (18.9)	0 (0.0)	34 (100)
Genito urinary system and sex hormones	G	26 (14.4)	0 (0.0)	26 (100)
Systemic hormonal preparations	H	15 (8.3)	0 (0.0)	15 (100)
Anti-infectives for systemic use	J	12 (6.7)	0 (0.0)	12 (100)
Dermatologicals	D	7 (3.9)	0 (0.0)	7 (100)
Therapeutic subgroups ‡				
Psycholeptics	N05	121 (67.2)	8 (6.6)	113 (93.4)
Drugs for acid related disorders	A02	120 (66.7)	8 (6.7)	112 (93.3)
Antithrombotic agents	B01	119 (66.1)	8 (6.7)	111 (93.3)
Psychoanaleptics	N06	104 (57.8)	5 (4.8)	99 (95.2)
Diuretics	C03	84 (46.7)	4 (4.8)	80 (95.2)
Agents acting on the renin-angiotensin system	C09	72 (40.0)	2 (2.8)	70 (97.2)
Lipid modifying agents	C10	70 (38.9)	4 (5.7)	66 (94.3)
Analgesics	N02	59 (32.8)	2 (3.4)	57 (96.6)
Drugs for constipation	A06	58 (32.2)	2 (3.4)	56 (96.6)
Beta blocking agents	C07	53 (29.4)	0 (0.0)	53 (100)
Drugs used in diabetes	A10	51 (28.3)	0 (0.0)	51 (100)
Antiepileptics	N03	47 (26.1)	2 (4.3)	45 (95.7)
Antianemic preparations	B03	41 (22.8)	1 (2.4)	40 (97.6)
Cardiac therapy	C01	39 (21.7)	1 (2.5)	38 (97.4)

† the ten most frequently prescribed anatomical main groups; ‡ the therapeutic subgroups present in more than 20% of patients.

Regarding the therapeutic subgroup analysis, 1039 drugs belonging to the main 14 therapeutic subgroups were present in more than 20% of patients (Table II.4). All of these therapeutic subgroups belong to the most commonly prescribed anatomical main groups (N, A, C, and B). Psycholeptics were prescribed to 42.1% of patients belonging to the non-polypharmacy group and to 70.2% of patients in the polypharmacy group. More than half of the patients with polypharmacy were prescribed at least a psycholeptic, a drug for acid-related disorders, an antithrombotic agent, or a psychoanaleptic drug.

II.4. Discussion

RNCCI in Portugal provides healthcare and social support to all patients in situations of dependency [316]. This support is given to patients in post-acute care that present a predictable end and, in an increasing way, to patients that may need lifelong, long-term care. Thus, this study analyzed patients from different UCCIs (A to H) that comprise the three response typologies (UC, UMDR, and ULMD), with a focus on their demographic and medical features, their pattern of medication use, the prevalence of polypharmacy, and other factors associated with these features.

This study population consisted of a representative sample of patients with a mean age of 78.4 ± 12.3 years, mostly female, with the majority having undergone long periods of hospitalization in the UCCIs. It was found that 8.3% of patients stayed in the UC (response typology for less than 30 days), 33.3% in the UMDR (response typology between 30 days and 90 days), and 58.4% stayed in the ULMD (response typology for more than 90 days). According to recent data, this obtained proportion are very close to the 10.3%, 28.5%, and 57.7% of the patients of national reality reported to be admitted to the UC, UMDR, and ULMD, respectively [378].

The described sample of patients was also analyzed in relation to the prescribed drugs. Around 90% of patients were found to be subject to polypharmacy (≥ 5 drugs), with a median value of 8 drugs per patient being prescribed. Regarding the classification of the prescribed drugs according to their anatomical main groups and therapeutic subgroups, it was found that the most frequently prescribed drugs belong to the nervous system (psycholeptics and psychoanaleptics), alimentary tract and metabolism (drugs for acid-related disorders), cardiovascular system (diuretics, agents acting on the renin-angiotensin system, and lipid-modifying agents), and also blood and blood-forming organs (antithrombotic agents). Our results are in agreement with the findings of other studies performed in nursing homes and in long-term care homes, in which the most prevalent therapeutic groups also involved the nervous system, alimentary tract, metabolism, and cardiovascular system [368,379]. Still, it is also important to note that other drugs such as nonsteroidal anti-inflammatory drugs [345,348,353,356,380] and antibiotics [380–382] have also been highly reported in the literature. However, those were not prevalent in our study, maybe because the data collected in our study refers to the period of discharge when patients are clinically stable. According to the literature, some of these therapeutic groups (e.g., cardiovascular agents [356,380,383,384], antidiabetics [356,357,380,383], analgesics [383], psycholeptics [356,380], diuretics [345,356,381], antithrombotics [351,353], and psychotropic drugs [351]) are described as predictors for ADRs.

The comorbidities (ICD-9-CM codes) most frequently found in our study (hypertension, heart failure, diabetes, osteoarthrosis, and allied disorders) have also been regularly reported in the literature: hypertension [385–387], heart failure [346,384,385], diabetes [346,384], renal and rheumatic diseases [346].

Our study calculated a polypharmacy prevalence of 66.7%, 93.3%, and 90.5% in the patients admitted to the UC, UMDR, and ULDM, respectively. These prevalence values were slightly higher than those found in the literature for older people in residence (67.4%), older outpatients (70%) [388], and nursing home residents (74%) [369], but similar to residents in long-term care homes [389], hospital patients (87.5%) [390], older patients discharged from hospital (85.9%) [391], and even older patients with urgent ADR-related hospital admissions (86%) [392]. Still, according to the literature, the prevalence of polypharmacy can differ widely between facilities [379,389], a statement that our results also recognized by observing that UCCIs themselves act as predictors for polypharmacy and high levels of polypharmacy. Therefore, it is suggested that periodic monitoring and drug prescription reviews could play an important role in reversing this trend.

By comparing facility E with facility H, we were able to identify a significant association between polypharmacy status and the unit of internment (facility). In addition to that, CCI was identified as a polypharmacy status predictor, probably because patients with more severe comorbid diseases may require more complex pharmacotherapeutic regimens to control their health status. In contrast, the other factors evaluated, such as age or gender, did not show statistically significant differences. Thus, healthcare professionals must pay special attention to patients with more comorbidities, which include pharmacists who are part of multidisciplinary teams where they could play an important role in medication reconciliation, preventing or reducing polypharmacy.

The present study also had some limitations, particularly the small size of the patient sample. Thus, to understand if the same medication pattern is maintained in the future, similar studies must be conducted in more healthcare centers. To identify the most frequent comorbidities, only diagnoses based on ICD-9-CM were considered, and only the three ICD-9-CM codes available were collected from patient profiles. It should also be considered that Portuguese UCCIs have a type of prescription policy that prefers the use of single-drug formulations instead of fixed-dose combinations of drugs and aims for easy dose adjustment whenever necessary. This practice can overestimate the results and contribute to a higher prevalence of polypharmacy.

II.5. Conclusions

Our investigation expands the knowledge on demographical and medical characteristics, patterns of medication use, and polypharmacy, as well as its predictor factors, in the Portuguese RNCCI, where data in this field are scarce. Our findings suggest that the studied population (patients with a mean age of 78.4 ± 12.3 years, a range of 23–102 years, and 59% female) was prescribed a median of 8 medications. Around 90% of patients were found to be subject to polypharmacy (≥ 5 drugs), and the most frequent anatomical main groups were the nervous system, alimentary tract and metabolism, cardiovascular system, and also blood and blood-forming organs. In addition, this study demonstrates that polypharmacy is highly prevalent in Portuguese RNCCI residents and is significantly associated with the facility (E vs. H) and with CCI. The higher prevalence of

polypharmacy and its associated factors may indicate that, to achieve an optimal risk-benefit relationship in each patient's therapeutic list, it is urgent to improve patients' pharmacotherapy regimens through periodic monitoring and review of their therapeutic lists, an area in which pharmacists are in a unique position within the multidisciplinary healthcare teams belonging to the RNCCI. Hence, further research on drug use in which interventions by health professionals are performed as well as the impact of these interventions on post-acute and long-term care patients is needed to improve drug therapy.

Chapter III

Potentially inappropriate medications and potential prescribing omissions in elderly patients receiving post-acute and long-term care: application of STOPP/START criteria

Chapter III – Potentially inappropriate medications and potential prescribing omissions in elderly patients receiving post-acute and long-term care: application of STOPP/START criteria

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III.1. Introduction

Potentially inappropriate prescribing refers either to (i) PIMs, the use of drugs where no clear clinical indication exists (overprescribing) or the use of an indicated drug where the risk outweighs the benefit or when a safer or more effective alternative is available (misprescribing) or (ii) PPOs, not prescribing a beneficial medicine for which there is a clear clinical indication (underprescribing) [393–395]. In older people, this subject has been increasingly explored because of the relationship between potentially inappropriate prescribing and negative clinical outcomes, namely the occurrence of ADRs [396,397], risk of hospitalization, hospital readmission, lower quality of life and even mortality [398–402]. This may be related to polypharmacy, which has been identified as a determinant factor for potentially inappropriate prescribing [398,403,404]. Another concern is the cost, since the total expenditure on potentially inappropriate prescribing has been reported to be 9% of the global expenditure on pharmaceuticals in people aged 70 or over [403]. Moreover, in PIM users it was found an increase of 33% in healthcare medical costs comparatively with nonusers [398]. Besides, it is also important to consider the potential impact of aging in drug elimination, because aging involves progressive impairments in the functional reserve of multiple organs such as liver and kidneys [405]. Considering that the number of people aged 65 years or over is projected to double, from 703 million to 1.5 billion, between 2019 and 2050, reaching a proportion of 16% worldwide [406] the high prevalence of PIMs in the elderly [398,400,407] is a current problem that will likely to be even worse in the future in this age group. Therefore, potentially inappropriate prescribing is a major concern that claims for measures that allow the detecting and reducing of its occurrence.

In order to improve prescribing, screening tools based on explicit criteria have been extensively used, being the earliest the Beers list [274], which was mainly applicable in the USA and has been updated in 2019 [408]. Although this list was undoubtedly important to the advances in the study of PIMs, the criteria used could not be easily applied in European countries. Therefore, in the last decade, a European-based tool was also developed to detect PIMs and PPOs, respectively: i) the STOPP; and ii) START [301,409]. The STOPP and START criteria consist of a list of PIMs and a list of PPOs, respectively, which complement each other. STOPP criteria can play an important role in reducing PIMs rates [410], while START criteria aim to reduce underprescribing [411] by identifying PPOs. Meanwhile, Corsonello *et al.* [412] reported that the STOPP/START criteria, compared to the Beers criteria, show a greater ability to predict ADRs and prevent potentially inappropriate prescribing. In addition, the STOPP/START criteria seemed to afford a good inter-rater reliability when the evaluations carried out by pharmacists from different sectors were compared [413]. However, for that, it is important to have full access to clinical information; otherwise, PIMs and PPOs detection can be overestimated and underestimated, respectively [414].

The STOPP/START criteria have been applied to different target populations of different settings (such as hospital, nursing homes, community-dwelling, primary care and post-acute care and

long-term care). For instance, a meta-analysis of 28 studies in elderly patients showed that the prevalence of PIMs and PPOs was high, with the highest values observed in hospitalized patients and nursing homes, compared to community dwelling-individuals for national outpatient databases small community studies [410,415]. In another meta-analysis, including both post-acute care and long-term care patients, it was demonstrated that the STOPP/START criteria may be effective in improving prescribing quality, clinical, humanistic and economic outcomes [410]. However, while Hill-Taylor *et al.* [410] reported less falls, delirium episodes, hospital length-of-stay, care visits, and medication costs, they found no association with improvements in quality of life or mortality. More recently, Thomas *et al.* [402] suggests that both PIMs and PPOs were significantly associated with hospital readmission and mortality within six months.

In Portugal, there are few examples of investigations using the START/STOPP criteria [416,417]. However, no one to the best of our knowledge has included the UCCIs inserted in the Portuguese RNCCI. Therefore, the present study was carried out to: (i) determine the prevalence of PIMs and PPOs (overall and per individual STOPP and START criteria, respectively); and (ii) potential predictors of PIMs and PPOs among demographic and clinical features of elderly patients who received post-acute care and long-term care in UCCIs of the RNCCI.

III.2. Patients and methods

III.2.1. Study design, setting, and participants

An observational, retrospective, cross-sectional, multicenter study was performed in 161 patients aged ≥ 65 years from UCCIs in the central region of Portugal, between June 2015 and April 2016. The UCCIs belong to the category of patient units and provide continuous support to frail people, for rehabilitation in post-acute care and for people with mental, social, and physical limitations who need long-term care. According to each patient needs and goals established, the length of stay usually varied between 30 and 180 consecutive days. All patients are monitored by a multidisciplinary team of various professionals, such as physicians, nurses, pharmacists, physiotherapists, social workers, psychologists, speech therapists, occupational therapists, and nutritionists. To reduce bias associated with the type of hospitalization and healthcare team, the data were collected from eight UCCIs.

The retrospective nature of the study did not affect healthcare provision to patients, and informed consent was not required. Patients' data were anonymized through the attribution of an alphanumeric code and access restricted to the first author. The subsequent analysis was performed exclusively using the encoded data.

III.2.2. Data sources

Data were mainly collected from RNCCI's platform, which is an online tool implemented in the RNCCI in Portugal. In this platform, all relevant patient information is recorded, namely, discharge summaries, periodic evaluations performed by different professionals (such as physicians, nurses, physiotherapists, psychologists, social workers, and nutritionists), diagnoses, prescribed drugs, medical exams, nutrition status, dependence in ADL, products spent (e.g., ostomy, wound or incontinence products), identification of need for social support and results of medical scales application (e.g., risk of falls, pressure ulcer risk assessment, calculation of the risk of developing type 2 diabetes mellitus in the next 10 years and pain evaluation). In addition, patient clinical history was complemented with other existent documents (e.g., patient diary) whenever possible and necessary.

III.2.3. Data collection and analysis

A detailed analysis was used for each patient by a pharmacist, including demographic and clinical data, namely, all current diagnoses (not only those coded through ICD-9-CM), relevant clinical information reported from the first medical evaluation (before to the actual internment) until discharge and an update on the latest therapeutic list. All pharmaceutical dosage forms including oral, parenteral, topical, ophthalmological and inhaled medications, taken on a regular basis (excluding SOS medications) were considered. If a fixed-dose combination of drugs was used in the same medication, it was only counted as one. Polypharmacy (intake of ≥ 5 drugs per day), comorbid diseases, CCI [227] (CCI ≥ 4 and CCI ≥ 6), dependency in ADL, risk of falls (medium to high), malnutrition/anorexia, obesity, pressure ulcers and history of recent fractures were also considered as geriatric syndromes. Continuous variables were expressed as mean ± SD, median and inter-quartile range (P25; P75), and categorical variables as the number of observations (absolute frequency) and percentages (relative frequency). To identify the determinants of PIMs and PPOs, variables with a significant association with PIMs or PPOs at the univariate level were tested using a multivariate analysis. Logistic regression analysis, with logit link function, was performed using the forward selection method based on the Wald test to find independent predictors associated with PIMs or PPOs. Also, ORs were adjusted for possible confounding variables, and results were reported only for variables with a $p < 0.1$. The Hosmer-Lemeshow test was performed to assess the goodness of fit, whereas the area under the receiver operating characteristic curve allowed the evaluation of discriminatory power of the model and its sensitivity/specificity. Differences were considered statistically significant when $p < 0.05$ and the CI was set at 95%. IBM SPSS Statistics version 23 was used to analyse all the data.

III.3. Results

III.3.1. Characteristics of the study population

Table III.1 details patients' demographic characteristics and medical history. From 161 patients 103 were female (64.0%). The average age of patients was 81.6 years and the medical history demonstrated higher provenance from the hospital (50.9%). The median length-of-stay in UCCIs was 93 days and 61 patients returned home (37.9%; Table III.1). Of the remaining 100, the highest number either died during the internment (28 patients) or has been transferred to another RNCCI response (28 patients; Table III.1). Table III.2 demonstrates that inpatients frequently took a median of 9 [P25: 6; P75: 11] drugs per day, totaling a median of 10 [P25: 7; P75: 13] daily oral doses, a CCI median of 6 [P25: 5; P75: 7] and 21 patients were fed by enteral nutrition (13.0%). Regarding geriatric syndromes, 147 patients had polypharmacy, 143 had high levels of dependency and 131 presented risk of falls (91.3%, 88.8% and 81.4%, respectively; Table III.2). Most common comorbidities were hypertension (68.3%), cerebrovascular disease (34.8%), depression (34.2%), diabetes mellitus (33.5%) and constipation (33.5%; Table III.3).

Table III.1. Demographic characteristics and medical history of study population (*N*=161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

		STOPP criteria				START criteria			
	Total	**PIMs**	**No PIMs**	**Not adjusted OR (95% CI)**	**P** [a]	**PPOs**	**No PPOs**	**Not adjusted OR (95% CI)**	**P** [a]
Demographic characteristics									
Age (years)				1.01 (0.95; 1.07)	0.827			1.04 (0.99; 1.10)	0.123
Mean ± SD	81.6 ± 7.4	81.7 ± 7.0	81.3 ± 9.8			82.0 ± 7.4	79.7 ± 7.6		
Median (P25; P75)	82 (76.5; 86.5)	82 (77; 86)	80.5 (74; 88.5)			82 (78; 87)	78.5 (75; 85)		
Gender, n (%)									
Male	58 (36.0)	43 (31.4)	15 (62.5)	1		48 (36.6)	10 (33.3)	1	
Female	103 (64.0)	94 (68.6)	9 (37.5)	3.64 (1.48; 8.98)	0.005	83 (63.4)	20 (66.7)	0.87 (0.37; 2.00)	0.734
Medical history									
Provenance/Origin, n (%)									
Hospital	82 (50.9)	74 (54.0)	8 (33.3)	2.74 (1.09; 6.87)	0.031	65 (49.6)	17 (56.7)	0.79 (0.35; 1.80)	0.575
Residence	70 (43.5)	54 (39.4)	16 (66.7)	1		58 (44.3)	12 (40.0)	1	
Nursing home	5 (3.1)	5 (3.6)	0 (0.0)	-		4 (3.1)	1 (3.3)	0.83 (0.09; 8.07)	0.871
Primary care	2 (1.2)	2 (1.5)	0 (0.0)	-		2 (1.5)	0 (0.0)	-	
Other	2 (1.2)	2 (1.5)	0 (0.0)	-		2 (1.5)	0 (0.0)	-	
Provenance/Origin, n (%)									
Hospital	82 (50.9)	74 (54.0)	8 (33.3)	2.35 (0.94; 5.85)	0.067	65 (49.6)	17 (56.7)	0.75 (0.34; 1.68)	0.487
Residence or other	79 (49.1)	63 (46.0)	16 (66.7)	1		66 (50.4)	13 (43.3)	1	
Length of stay				1.00 (1.00; 1.01)	0.182			1.00 (1.00; 1.00)	0.652
Mean ± SD	146.1 ± 190.7	154.8 ±	96.0 ± 62.3			149.3 ±	131.8 ± 221.1		
Median (P25; P75)	93 (65; 163.5)	204.0	90 (68.5; 95)			183.9	90 (42.5; 112)		
Discharge to, n (%)		98 (65; 167.5)				97 (79; 168)			
Residence	61 (37.9)		14 (58.3)	0.26 (0.05; 1.23)	0.088		17 (56.7)	0.52 (0.06; 4.76)	0.561
Death	28 (17.4)	47 (34.3)	2 (8.3)	1.00 (0.13; 7.64)		44 (33.6)	1 (3.3)	5.40 (0.29; 101.28)	0.260
Another RNCCI	28 (17.4)	26 (19.0)	2 (8.3)	1	1.000	27 (20.6)	6 (20.0)	0.73 (0.07; 7.53)	0.794
response	20 (12.4)	26 (19.0)	4 (16.7)	0.31 (0.05; 1.88)	0.201	22 (16.8)	3 (10.0)	1.13 (0.10; 13.44)	0.921
Social option/response	17 (10.6)	16 (11.7)	2 (8.3)	0.58 (0.07; 4.53)	0.601	17 (13.0)	1 (3.3)	3.20 (0.17; 61.02)	0.439
Nursing home	6 (3.7)	15 (10.9)	0 (0.0)	-		16 (12.2)	1 (3.3)	1	
Other or not referred	1 (0.6)	6 (4.4)	0 (0.0)	-		5 (3.8)	1 (3.3)	-	
Emergency department		1 (0.7)				0 (0.0)			

CI, confidence interval; OR, odd ratio; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; SD, Standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions; [a] Wald test.

Table III.2. Clinical features of study population (*N*=161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

		STOPP criteria				START criteria			
	Total	**PIMs**	**No PIMs**	**Not adjusted OR (95% CI)**	**P** [a]	**PPOs**	**No PPOs**	**Not adjusted OR (95% CI)**	**P** [a]
Clinical features									
Enteral Nutrition, n (%)									
Yes	21 (13.0)	19 (13.9)	2 (8.3)	1.77 (0.39; 8.15)	0.463	19 (14.5)	2 (6.7)	2.38 (0.52; 10.80)	0.263
No	140 (87.0)	118 (86.1)	22 (91.7)	1		112 (85.5)	28 (93.3)	1	
Medication per patient				1.30 (1.11; 1.53)	0.002			1.12 (0.98; 1.27)	0.086
Mean ± SD	8.84 ± 3.32	9.20 ± 3.19	6.79 ± 3.40			9.06 ± 3.38	7.90 ± 2.93		
Median (P25; P75)	9 (6; 11)	9 (7; 11)	7 (4.5; 8)			9 (6; 11)	8 (5; 10)		
Number of doses				1.51 (1.02; 1.30)	0.024			1.04 (0.94; 1.15)	0.407
Mean ± SD	10.20 ± 4.14	10.51 ± 4.03	8.42 ± 4.41			10.33 ± 4.22	9.63 ± 3.79		
Median (P25; P75)	10 (7; 13)	10 (8; 13)	8 (6; 11)			10 (7; 13)	10 (6; 12)		
Comorbid diseases				0.99 (0.68; 1.46)	0.976			2.10 (1.35; 3.29)	0.001
Mean ± SD	1.70 ± 1.14	1.70 ± 1.16	1.71 ± 1.04			1.85 ± 1.15	1.07 ± 0.83		
Median (P25; P75)	2 (1; 2)	2 (1; 2)	2 (1; 2)			2 (1; 3)	1 (0; 2)		
CCI				1.13 (0.87; 1.47)	0.376			1.56 (1.17; 2.06)	0.002
Mean ± SD	5.83 ± 1.71	5.88 ± 1.71	5.54 ± 1.69			6.03 ± 1.66	4.93 ± 1.64		
Median (P25; P75)	6 (5; 7)	6 (5; 7)	5 (4; 6.5)			6 (5; 7)	5 (4; 6)		
Geriatric syndromes, n (%)									
Polypharmacy (≥5 drugs/day)									
Yes	147 (91.3)	129 (94.2)	18 (75.0)	5.38 (1.67; 17.28)	0.005	121 (92.4)	26 (86.7)	1.86 (0.54; 6.40)	0.324
No	14 (8.7)	8 (5.8)	6 (25.0)	1		10 (7.6)	4 (13.3)	1	
Comorbid diseases ≥ 2									
Yes	86 (53.4)	73 (53.3)	13 (54.2)	0.97 (0.40; 2.30)	0.936	77 (58.8)	9 (30.0)	3.33 (1.42; 7.82)	0.006
No	75 (46.6)	64 (46.7)	11 (45.8)	1		54 (41.2)	21 (70.0)	1	
CCI ≥ 4									
Yes	149 (92.5)	127 (92.7)	22 (91.7)	1.16 (0.24; 5.63)	0.859	124 (94.7)	25 (83.3)	3.54 (1.04; 12.07)	0.043
No	12 (7.5)	10 (7.3)	2 (8.3)	1		7 (5.3)	5 (16.7)	1	
CCI ≥ 6									
Yes	85 (52.8)	74 (54.0)	11 (45.8)	1.39 (0.58; 3.32)	0.460	76 (58.0)	9 (30.0)	3.22 (1.37; 7.58)	0.007
No	76 (47.2)	63 (46.0)	13 (54.2)	1		55 (42.0)	21 (70.0)	1	
Dependency in ADL									
Yes	143 (88.8)	120 (87.6)	23 (95.8)	0.31 (0.04; 2.42)	0.262	120 (91.6)	23 (76.7)	3.32 (1.17; 9.46)	0.025
No	18 (11.2)	17 (12.4)	1 (4.2)	1		11 (8.4)	7 (23.3)	1	

Fall Risk (medium or high)									
Yes	131 (81.4)	113 (82.59	18 (75.0)	1.57 (0.56; 4.37)	0.388	109 (83.2)	122(73.3)	1.80 (0.71; 4.57)	0.215
No	30 (18.6)	24 (17.5)	6 (25.0)	1		22 (16.8)	8 (26.7)	1	
Malnutrition/anorexia									
Yes	7 (4.3)	5 (3.6)	2 (8.3)	0.42 (0.08; 2.28)	0.313	5 (3.8)	2 (6.7)	0.56 (0.10; 3.01)	0.495
No	154 (95.7)	132 (96.4)	22 (91.7)	1		126 (96.2)	28 (93.3)	1	
Obesity									
Yes	22 (13.7)	19 (13.9)	3 (12.5)	1.13 (0.31; 4.15)	0.857	17 (13.0)	5 (16.7)	0.75 (0.25; 2.21)	0.597
No	139 (86.3)	118 (86.1)	21 (87.5)	1		114 (87.0)	25 (83.3)	1	
Pressure ulcers at discharge									
Yes	27 (16.8)	25 (18.2)	2 (8.3)	2.46 (0.54; 11.13)	0.244	24 (18.3)	3 (10.0)	2.02 (0.57; 7.21)	0.279
No	134 (83.2)	112 (81.8)	22 (91.7)	1		107 (81.7)	27 (90.0)	1	
History of recent fractures									
Yes	46 (28.6)	39 (28.5)	7 (29.2)	0.97 (0.37; 2.51)	0.944	44 (33.6)	2 (6.7)	7.07 (1.61; 31.09)	0.010
No	115 (71.4)	98 (71.5)	17 (70.8)	1		87 (66.4)	28 (93.3)	1	

ADL, dependency in activities of daily living; CCI, Charlson Comorbidity Index; CI, confidence interval; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; OR, odd ratio; SD, Standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions; [a] Wald test.

Table III.3. Most common/significant comorbidities of study population (*N*=161) that received post-acute care and long-term care in Units for Integrated Continuous Care (*Unidades de Cuidados Continuados*, UCCI) inserted in the Portuguese National Network for Long-term Integrated Care (*Rede Nacional de Cuidados Continuados Integrados*, RNCCI).

		STOPP criteria				START criteria			
	Total	**PIMs**	**No PIMs**	**Not adjusted OR (95% CI)**	**P** [a]	**PPOs**	**No PPOs**	**Not adjusted OR (95% CI)**	**P** [a]
Most common/significant comorbidities, n (%)									
Hypertension									
Yes	110 (68.3)	96 (70.1)	14 (58.3)	1.67 (0.69; 4.07)	0.257	92 (70.2)	18 (60.0)	1.57 (0.69; 3.57)	0.280
No	51 (31.7)	41 (29.9)	10 (41.7)	1		39 (29.8)	12 (40.0)	1	
Cerebrovascular disease									
Yes	56 (34.8)	42 (30.7)	14 (58.3)	0.32 (0.13; 0.77)	0.011	47 (35.9)	9 (30.0)	1.31 (0.55; 3.08)	0.543
No	105 (65.2)	95 (69.3)	10 (41.7)	1		84 (64.1)	21 (70.0)	1	
Depression									
Yes	55 (34.2)	52 (38.0)	3 (12.5)	4.28 (1.22; 15.07)	0.023	45 (34.4)	10 (33.3)	1.05 (0.45; 2.43)	0.916
No	106 (65.8)	85 (62.0)	21 (87.5)	1		86 (65.6)	20 (66.7)	1	
Diabetes mellitus									
Yes	54 (33.5)	45 (32.8)	9 (37.5)	0.82 (0.33; 2.01)	0.656	46 (35.1)	8 (26.7)	1.49 (0.61; 3.61)	0.379
No	107 (66.5)	92 (67.2)	15 (62.5)	1		85 (64.9)	22 (73.3)	1	
Constipation									
Yes	54 (33.5)	51 (37.2)	3 (12.5)	4.15 (1.18; 14.61)	0.027	47 (35.9)	7 (23.3)	1.84 (0.73; 4.61)	0.194
No	107 (66.5)	86 (62.8)	21 (87.5)	1		84 (64.1)	23 (76.7)	1	
Dementia									
Yes	47 (29.2)	43 (31.4)	4 (16.7)	2.29 (0.74; 7.10)	0.152	43 (32.8)	4 (13.3)	3.18 (1.04; 9.68)	0.042
No	114 (70.8)	94 (68.6)	20 (83.3)	1		88 (67.2)	26 (86.7)	1	
Urinary incontinence									
Yes	45 (28.0)	42 (30.7)	3 (12.5)	3.10 (0.88; 10.94)	0.080	41 (31.3)	4 (13.3)	2.96 (0.97; 9.04)	0.056
No	116 (72.0)	95 (69.3)	21 (87.5)	1		90 (68.7)	26 (86.7)	1	
Rheumatic Disease									
Yes	38 (23.6)	31 (22.6)	7 (29.2)	0.71 (0.27; 1.87)	0.488	29 (22.1)	9 (30.0)	0.66 (0.27; 1.60)	0.362
No	123 (76.4)	106 (77.4)	17 (70.8)	1		102 (77.9)	21 (70.0)	1	
Congestive heart failure									
Yes	36 (22.4)	32 (23.4)	4 (16.7)	1.52 (0.49; 4.78)	0.471	34 (26.0)	2 (6.7)	4.91 (1.11; 21.70)	0.036
No	125 (77.6)	105 (76.6)	20 (83.3)	1		97 (74.0)	28 (93.3)	1	
Arrhythmia									
Yes	29 (18.0)	26 (19.0)	3 (12.5)	1.64 (0.46; 5.91)	0.450	29 (22.1)	0 (0.0)	-	-

No	132 (82.0)	111 (81.0)	21 (87.5)	1		102 (77.9)	30 (100.0)		
Benign prostatic hypertrophy									
Yes	28 (48.3)	21 (48.8)	7 (46.7)	1.09 (0.34; 3.54)	0.885	27 (56.3)	1 (10.0)	11.57 (1.36; 98.67)	0.025
No	30 (51.7)	22 (51.2)	8 (53.3)	1		21 (43.8)	9 (90.0)	1	
Renal disease									
Yes	23 (14.3)	21 (15.3)	2 (8.3)	1.99 (0.44; 9.11)	0.375	20 (15.3)	3 (10.0)	1.62 (0.45; 5.86)	0.461
No	138 (85.7)	116 (84.7)	22 (91.7)	1		111 (84.7)	27 (90.0)	1	
Chronic pulmonary obstructive disease									
Yes	20 (12.4)	15 (10.9)	5 (20.8)	0.47 (0.15; 1.43)	0.184	19 (14.5)	1 (3.3)	4.92 (0.63; 38.29)	0.128
No	141 (87.6)	122 (89.1)	19 (79.2)	1		112 (85.5)	29 (96.7)	1	
Non-metastatic solid tumor									
Yes	20 (12.4)	19 (13.9)	1 (4.2)	3.70 (0.47; 29.05)	0.213	16 (12.2)	4 (13.3)	0.90 (0.28; 2.93)	0.867
No	141 (87.6)	118 (86.1)	23 (95.8)	1		115 (87.8)	26 (86.7)	1	
Hemiplegia									
Yes	15 (9.3)	12 (8.8)	3 (12.5)	0.67 (0.18; 2.58)	0.563	13 (9.9)	2 (6.7)	1.54 (0.33; 7.23)	0.582
No	146 (90.7)	125 (91.2)	21 (87.5)	1		118 (90.1)	28 (93.3)	1	
Parkinson's disease									
Yes	6 (3.7)	3 (2.2)	3 (12.5)	0.16 (0.03; 0.83)	0.029	3 (2.3)	3 (10.0)	0.21 (0.04; 1.10)	0.065
No	155 (96.3)	134 (97.8)	21 (87.5)	1		128 (97.7)	27 (90.0)	1	
Metastatic solid tumor									
Yes	5 (3.1)	5 (3.6)	0 (0.0)	-	-	4 (3.1)	1 (3.3)	0.91 (0.10; 8.48)	0.936
No	156 (96.9)	132 (96.4)	24 (100.0)			127 (96.9)	29 (96.7)	1	
Angina									
Yes	4 (2.5)	3 (2.2)	1 (4.2)	0.52 (0.05; 5.17)	0.573	3 (2.3)	1 (3.3)	0.68 (0.07; 6.77)	0.742
No	157 (97.5)	134 (97.8)	23 (95.8)	1		128 (97.7)	29 (96.7)	1	
Osteoporosis									
Yes	3 (1.9)	3 (2.2)	0 (0.0)	-	-	2 (1.5)	1 (3.3)	0.45 (0.04; 5.13)	0.520
No	158 (98.1)	134 (97.8)	24 (100.0)			129 (98.5)	29 (96.7)	1	
Glaucoma									
Yes	3 (1.9)	3 (2.2)	0 (0.0)	-	-	2 (1.5)	1 (3.3)	0.45 (0.04; 5.13)	0.520
No	158 (98.1)	134 (97.8)	24 (100.0)			129 (98.5)	29 (96.7)	1	

CI, confidence interval; PIMs, potentially inappropriate medications; PPOs, potential prescribing omissions; OR, odd ratio; SD, Standard deviation; START, Screening Tool to Alert to Right Treatment; STOPP, Screening Tool of Older People's Prescriptions; [a] Wald test.

III.3.2. Potentially inappropriate medications

According to STOPP criteria, patients had a median of 3 [1; 4] PIMs (range 0-10), with 85.1% of them presenting at least one and about a fifth had 5 or more PIMs in their list of prescriptions (Table III.4). Sections with higher frequency of PIMs were found in "central nervous system (CNS) and psychotropic drugs" (66.5%) and "drugs that predictably increase the risk of falls in older people" (65.8%). Among "CNS and psychotropic drugs" section, the most common PIMs in patients were benzodiazepines for ≥ 4 weeks (D5; 51.6%; Table III.5), tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (D1; 15.5%; Table III.5), and anticholinergics/antimuscarinics in patients with delirium or dementia (D7; 13.7%; Table III.5). Among "drugs that predictably increase the risk of falls in older people" were benzodiazepines (K1; 54.0% Table III.5) and neuroleptics (K2; 24.8%; Table III.5).

Table III.4. Number of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs), according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria, respectively (*N*=161).

Number of PIMs/PPOs	STOPP criteria (*n*, %)	START criteria (*n*, %)
0	24 (14.9)	30 (18.6)
1	23 (14.3)	36 (22.4)
2	32 (19.9)	47 (29.2)
3	33 (20.5)	28 (17.4)
4	16 (9.9)	13 (8.1)
5	16 (20.5)	6 (3.7)
6	10 (6.2)	1 (0.6)
≥ 7	7 (4.3)	0 (0.0)
Total	137 (85.1)	131 (81.4)
Mean ± SD	2.8 ± 2.1	1.9 ± 1.4
Median (P25; P75)	3 [1; 4]	2 [1; 3]

SD, Standard deviation.

In the multivariate analysis (Table III.6), PIMs were found to be significantly associated with gender (F/M) (OR=4.04, 95%CI: 1.27; 12.84), hospital provenance (OR=3.43, 95%CI: 1.10; 10.69), number of medications (OR=1.32, 95%CI: 1.09; 1.60), cerebrovascular disease (OR=0.29, 95%CI: 0.10; 0.89) and Parkinson's disease (OR=0.06, 95%CI: 0.00; 0.84).

Table III.5. Frequency of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria respectively (*N*=161).

			n (%)
STOPP criteria	A	Indication of medication	27 (16.8)
	A1	Any drug prescribed without an evidence-based clinical indication.	15 (9.3)
	A3	Any duplicate drug class prescription.	15 (9.3)
	B	Cardiovascular System	28 (17.4)
	B9	Loop diuretic for treatment of hypertension with concurrent urinary incontinence.	10 (6.2)
	B12	Aldosterone antagonists with concurrent potassium-conserving drugs without monitoring of serum potassium.	7 (4.3)
	C	Antiplatelet/Anticoagulant Drugs	9 (5.6)
	C7	Ticlopidine in any circumstances.	5 (3.1)
	D	CNS and Psychotropic Drugs	107 (66.5)
	D1	Tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention.	25 (15.5)
	D2	Initiation of tricyclic antidepressants as first-line antidepressant treatment.	11 (6.8)
	D5	Benzodiazepines for ≥ 4 weeks.	83 (51.6)
	D7	Anticholinergics/antimuscarinics in patients with delirium or dementia.	22 (13.7)
	D9	Neuroleptic antipsychotic in patients with behavioural and psychological symptoms of dementia unless symptoms are severe and other treatments have failed.	8 (5.0)
	D11	Acetylcholinesterase inhibitors with a known history of persistent bradycardia heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate.	6 (3.7)
	D14	First-generation antihistamines.	8 (5.0)
	E	Renal System	0 (0.0) [a]
	F	Gastrointestinal System	22 (17.7)
	F2	Proton-pump inhibitors for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for > 8 weeks.	10 (6.2)
	F3	Drugs likely to cause constipation in patients with chronic constipation where non-constipating alternatives are appropriate.	12 (7.5)
	G	Respiratory System	14 (8.7)
	G5	Benzodiazepines with acute or chronic respiratory failure.	13 (8.1)
	H	Musculoskeletal System	1 (0.2)
	I	Urogenital System	1 (0.2)
	J	Endocrine System	0 (0.0) [a]
	K	Drugs that predictably increase the risk of falls in older people	106 (65.8)
	K1	Benzodiazepines	87 (54.0)
	K2	Neuroleptic drugs	40 (24.8)
	K4	Hypnotic Z-drugs	9 (5.6)
	L	Analgesic Drugs	18 (11.2)
	L2	Use of regular (as distinct from *pro re nata*) opioids without concomitant laxative.	12 (7.5)
	L3	Long-acting opioids without short-acting opioids for break-through pain.	8 (5.0)
	N	Antimuscarinic/Anticholinergic Drug Burden	8 (5.0)

START criteria	A	Cardiovascular System	64 (39.8)
	A1	Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation.	5 (3.1)
	A3	Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.	22 (13.7)
	A5	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.	15 (9.3)
	A6	Angiotensin Converting Enzyme inhibitor with systolic heart failure and/or documented coronary artery disease.	28 (17.4)
	A8	Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.	18 (11.2)
	B	Respiratory System	12 (7.5)
	B1	Regular inhaled 2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or chronic obstructive pulmonary disease.	10 (6.1)
	C	CNS and Eyes	19 (11.8)
	C2	Non-tricyclic antidepressant drug in the presence of persistent major depressive Symptoms.	12 (7.5)
	D	Gastrointestinal System	0 (0.0) [a]
	E	Musculoskeletal System	89 (55.3)
	E3	Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores, more than -2.5 in multiple sites.	44 (27.3)
	E5	Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia.	74 (46.0)
	F	Endocrine System	6 (3.7)
	F1	Angiotensin Converting Enzyme inhibitor or Angiotensin Receptor Blocker (if intolerant of Angiotensin Converting Enzyme inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria (>30mg/24 hours) with or without serum biochemical renal impairment.	6 (3.7)
	G	Urogenital System	22 (13.7)
	G1	Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary.	12 (7.5)
	G2	5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary.	18 (11.2)
	H	Analgesics	12 (7.5)
	H2	Laxatives in patients receiving opioids regularly.	12 (7.5)
	I	Vaccines	0 (0.0) [a]

CNS, central nervous system; [a] not applicable.

Table III.6. Predictors of potentially inappropriate medications (PIMs), according to Screening Tool of Older People's Prescriptions (STOPP) criteria, in the study population (*N*=161).

	Total	PIM	No PIM	Adjusted OR (95% CI)	P [a]
Gender, n (%)					
Male	58 (36.0)	43 (31.4)	15 (62.5)	1	
Female	103 (64.0)	94 (68.6)	9 (37.5)	4.04 (1.27; 12.84)	0.018
Provenance/Origin, n (%)					
Hospital	91 (56.5)	83 (60.6)	8 (33.3)	3.43 (1.10; 10.69)	0.034
Residence or other	70 (43.5)	54 (39.4)	16 (66.7)	1	
Medication per patient				1.32 (1.09; 1.60)	0.005
Mean ± SD	8.84 ± 3.32	9.20 ± 3.19	6.79 ± 3.40		
Median (P25; P75)	9 (6; 11)	9 (7; 11)	7 (4.5; 8)		
History of recent fractures					
Yes	46 (28.6)	39 (28.5)	7 (29.2)	0.31 (0.09; 1.06)	0.062
No	115 (71.4)	98 (71.5)	17 (70.8)	1	
Cerebrovascular disease					
Yes	56 (34.8)	42 (30.7)	14 (58.3)	0.29 (0.10; 0.89)	0.030
No	105 (65.2)	95 (69.3)	10 (41.7)	1	
Depression					
Yes	55 (34.2)	52 (38.0)	3 (12.5)	4.02 (0.88; 18.42)	0.073
No	106 (65.8)	85 (62.0)	21 (87.5)	1	
Dementia					
Yes	47 (29.2)	43 (31.4)	4 (16.7)	4.62 (0.98; 21.85)	0.054
No	114 (70.8)	94 (68.6)	20 (83.3)	1	
Parkinson's disease					
Yes	6 (3.7)	3 (2.2)	3 (12.5)	0.06 (0.00; 0.84)	0.037
No	155 (96.3)	134 (97.8)	21 (87.5)	1	

CI, confidence interval, OR, odd ratio; SD, Standard deviation; [a] Wald test; OR's adjust with all the variables of tables III.1, III.2 and III.3 without null frequencies, but we only show the results for the variables that $p < 0.1$; Omnibus test: $p < 0.001$; Hosmer and Lemeshow test: $p = 0.291$; area under the receiver operating characteristic curve = 0.866 (95% CI: (0.801; 0.931), $p < 0.001$); Sensitivity = 79.6% and Specificity = 87.5% are simultaneously maximized for the cut-off probability 0.8109.

III.3.3. Potential prescribing omissions

According to START criteria, patients had a median of 2 [1; 3] PPOs (range 0-6), with 81.4% of them having at least one PPO and more than half of patients had one or two PPOs (Table III.4). Most associated systems with PPOs were "Musculoskeletal System" (55.3%) and "Cardiovascular System" (39.8%). In the "Musculoskeletal System", the highest frequency of PPOs was associated with "vitamin D supplementation in elderly people who are housebound or experiencing falls or with osteopenia" (E5; 46%; Table III.5) followed by "vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than -2.5 in multiple sites" (E3; 27.3%; Table III.5). Among "Cardiovascular System" the highest frequency of PPOs was associated with "ACEI with systolic heart failure and/or documented coronary artery disease" (A6; 17.4%; Table III.5), and "antiplatelet therapy (aspirin, clopidogrel, prasugrel or ticagrelor, with a documented history of coronary, cerebral or peripheral vascular disease)" (A3; 13.7%; Table III.5).

In the multivariate analysis (Table III.7), PPOs were found to be independently associated with the number of CCI (OR=2.14, 95%CI: 1.46; 3.14), history of recent fractures (OR=13.90, 95%CI: 2.83; 68.36), Parkinson's disease (OR=0.08, 95%CI: 0.01; 0.61) and metastatic solid tumor (OR=0.03, 95%CI: 0.00; 0.59).

Table III.7. Predictors of potential prescribing omissions (PPOs), according to Screening Tool to Alert to Right Treatment (START) criteria, in the study population (*N*=161).

	Total	PPOs	No PPOs	Adjusted OR (95% CI)	P [a]
Gender, n (%)					
Male	58 (36.0)	48 (36.6)	10 (33.3)	1	
Female	103 (64.0)	83 (63.4)	20 (66.7)	0.38 (0.14; 1.05)	0.063
CCI				2.14 (1.46; 3.14)	<0.001
Mean ± SD	5.83 ± 1.71	6.03 ± 1.66	4.93 ± 1.64		
Median (P25; P75)	6 (5; 7)	6 (5; 7)	5 (4; 6)		
History of recent fractures					
Yes	45 (28.0)	41 (31.3)	4 (13.3)	13.90 (2.83; 68.36)	0.001
No	116 (72.0)	90 (68.7)	26 (86.7)	1	
Non-metastatic solid tumor					
Yes	20 (12.4)	16 (12.2)	4 (13.3)	0.29 (0.07; 1.26)	0.099
No	141 (87.6)	115 (87.8)	26 (86.7)	1	
Parkinson's disease					
Yes	6 (3.7)	3 (2.3)	3 (10.0)	0.08 (0.01; 0.61)	0.015
No	155 (96.3)	128 (97.7)	27 (90.0)	1	
Metastatic solid tumor					
Yes	5 (3.1)	4 (3.1)	1 (3.3)	0.03 (0.00; 0.59)	0.021
No	156 (96.9)	127 (96.9)	29 (96.7)	1	

CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odd ratio; SD, Standard deviation; [a] Wald test; OR's adjust with all the variables of tables III.1., III.2. and III.3. without null frequencies, but we only show the results for the variables that $p < 0.1$; Omnibus test: $p < 0.001$; Hosmer and Lemeshow test: $p = 0.744$; area under the receiver operating characteristic curve = 0.826 (95% CI: (0.747; 0.905), $p < 0.001$); Sensitivity = 77.9% and Specificity = 76.7% are simultaneously maximized for the cut-off probability 0.7631.

III.4. Discussion

III.4.1. Main findings

The prevalence among inpatients was similar for PIMs (85.1%) and PPOs (81.4%), considering the application of the STOPP and START criteria, respectively. The most involved drugs in PIMs were from the CNS group, while PPOs were associated with drugs from the musculoskeletal and cardiovascular system groups. The most common overuses were associated with benzodiazepines as a predictable increase in the risk of falls and when used for longer than 4 weeks. Omissions were more frequently related to the lack of vitamin D supplements, calcium-vitamin D supplements, ACEIs and antiplatelet agents. Female gender, hospital provenance and a higher number of prescription drugs were found to be associated with a higher risk for PIMs. In contrast, patients with cerebrovascular disease and Parkinson's disease had the lowest risk of PIMs. On the other hand, patients with a higher value of CCI and with recent fractures had a higher risk for PPOs, while Parkinson's disease and metastatic solid tumors were shown to be protective diagnoses for PPOs.

Considering the main findings obtained in our study, it should be highlighted that the number of PIMs per patient (2.8) is lower, but the number of PPOs per patient is higher (1.9), than the reported in a recent study focused on patients admitted to acute care hospitals (3.55 and 0.72, respectively) [418]. On the other hand, the prevalence of PIMs detected in our study (85.1%) is higher than that reported in the literature, in which it ranges from patients 35% to 77% in patients ≥ 65 years old [303,419–427]. A higher prevalence of PPOs was also found in our study (81.4%),

since the reported values in literature ranged from 34% to 65% [303,420–424,428]. However, PIM rates varies according to each setting: 15%-46% in community-dwelling [397,425,429], 21%-38% in primary care [302,403,404,430–432], and 48%-79% in nursing homes [433–435]; and the same pattern was reported for PPO rates: 30% in community-dwelling [429], 23%-51% in primary care [302,431,432], and 42-74% in nursing homes [433–435]). Regarding national data, the application of the STOPP/START criteria is scarce. However, Borges *et al.* [436] have already identified PPOs in 68% of 91 elderly patients admitted to a stroke unit, Moraes *et al.* [437] reported a prevalence of PIMs and PPOs of 74% and 29% respectively, in 100 patients admitted to a hospital and Costa *et al.* [417] reported PIMs and PPOs of 75% and 43% respectively, in 161 elderly patients in nursing homes.

Although the prevalence of PIMs and PPOs is generally higher than that reported in the literature, some underlying aspects of existing studies could make this comparison difficult. For instance, Gallagher *et al.* [303] found a total PIMs prevalence of 51.3% and a global PPOs prevalence of 59.4% considering six European hospitals, but individually different results were observed, for instance a PIMs prevalence of 77.3% in Geneva and a PPOs prevalence of 72.7% in Perugia. In addition, some studies only applied a subset of the STOPP/START criteria [427,429,430], which can result in lower prevalence [430] and misleading direct comparisons. Thus, pulling out the three most frequent PIMs (D5, K1 and K2) and PPOs (A6, E3 and E5) the results would be substantially lower (69% and 60%, respectively). Moreover, of the 81 STOPP criteria, the three most prevalent (D5, K1 and K2) accounted for almost half (47%) of the total of PIMs detected (445). The same happened for the START criteria, with the three most prevalent (A6, E3 and E5) of the 34 criteria accounting for 48% of the total PPOs detected (302). Finally, there are also factors considered by several studies as predictors for PIMs and PPOs that assumed high prevalence in the study population and may contribute to the PIM and PPO rates, such as the number of daily medications (median of 9 [6; 11]), which are higher than those in other studies [302,419,422,423,431,434,435,437]; the CCI (median of 6 [5; 7]) is also higher than in published data [303,421,431].

Concerning to most common PIMs, the results are consistent with literature that has reported benzodiazepines [403,404,420,423,424,427,432–434], neuroleptics [423,430,433], tricyclic antidepressants, anticholinergic/antimuscarinic drugs [433], loop diuretics and proton-pump inhibitors [403,404,427,430,433] as the drug classes mainly involved. The analysis of drugs commonly associated with PPOs is also similar to several other studies that have reported vitamin D [438], vitamin D and calcium [420,422,424,428,433,434], ACEIs [423,438], antiplatelet therapy [423,428], beta-blockers, 5-alpha reductase, statins [420,423,428,433,438], laxatives, alpha-1 receptor blockers and non-tricyclic antidepressants [422] as more frequent PPOs.

Relatively to the predictors of PIMs, in our study and also in the literature, female gender has been frequently associated with PIMs [439–441]. Polypharmacy is also commonly identified as a PIM predictor, either as an intake of ≥ 4 drugs [430,432], ≥ 5 drugs [404,429], ≥ 10 drugs [303,424] or an increased number of medications [421,422,427,431,435]. The hospital

provenance of the patients was not directly tested, but living in an institutional setting was recognized as a predictor of PIMs [422], as well as a longer stay at the nursing home [442]. Among comorbidities, depression is mentioned in the literature [443] but only had a significant association with OR non-adjusted; cerebrovascular disease seemed to be a protective factor, which may be related to a higher supervision or more frequent revision of the therapeutic list of these patients [346]; and Parkinson's disease was also considered to be a protective factor, but no valid reason was found.

Regarding PPOs, they were associated with high values of CCI, in accordance with the literature because the most frequently mentioned factors are comorbidity (CCI) [421,431], the CCI values higher or equal to 2 [303,444], and also multimorbidity [422,424]. Fractures have also been cited as predictors [420] but diagnoses of Parkinson's disease and metastatic solid tumors are the main findings as protective determinants of PPOs.

Although no other predictors were found, it has been further reported in the literature a history of falls and previous hospitalizations for PIMs [421,422], and being aged ≥ 75 years [432] or ≥ 85 years [303] for PPOs.

III.4.2. Strengths and limitations

The utilization of a common online electronic health platform is an advantage, which permits access to diverse data from all healthcare units included in the sample, such as discharge summaries and several evaluations of the patient from different professionals that allow identification of major clinical data (such as diagnosis, medical history, list of drugs, periodic evaluations, dependency status) and scales for pain evaluation and risk of falls, which help to analyze criteria such as analgesic drugs and the need for calcium-vitamin D supplements. However, the inclusion of eight different healthcare units implies the analysis of eight different multidisciplinary teams that detail information in different ways and fields and, therefore, certain data were sometimes incomplete or even nonexistent; in some cases, it was possible to fill it through internal medical records, other online tools or by information from other settings where the patient was evaluated. Thus, improved access to patients' information could reduce the time to collect the necessary data to apply medication review criteria and contribute to a larger sample that could allow obtaining better CIs and would be more representative of the Portuguese population and elderly patients receiving post-acute care and long-term care.

Studies have already shown that STOPP/START criteria have good inter-rater reliability between multiple physicians practicing in different centers of Europe [413,445]; however, it can be difficult to obtain an unequivocal and unquestionable application of certain criteria. Limited length-of-stay, lack of specific medical information or even the interpretation of some criteria led to several limitations, comments, and suggestions regarding the application of STOPP/ START criteria discussed along with the study. For instance, it is difficult to understand whether the behavioral

and psychological characteristics of dementia are severe enough to justify the use of neuroleptic antipsychotics or to have 100% certainty that a sleep disorder is due to psychosis or dementia. Furthermore, it may not be easy to find alternative drugs for chronic pain treatment in cases of opioid-induced constipation or to ensure that there is no relevance of having a proton-pump inhibitor prescribed in a polymedicated patient with a history of peptic ulcer.

III.4.3. Implications for research and/or practice

Overall, STOPP/START criteriawere designed to be easy, practical, and fast to apply. Considering the results obtained herein, STOPP/START criteria proved to be a suitable tool for use in post-acute care and long-term care settings, as it has also been internationally demonstrated in other clinical settings. Ryan *et al.* [414] concluded that there is an overestimation of PIMs and an underestimation of PPOs if both criteria are used in the absence of sufficient clinical information. Therefore, the availability of detailed clinical data chronologically organized is essential, as well as drug lists that have complete information (dose, dosage, dosage forms, and administration route and frequency). Besides, the codification of diagnosis and medications by international classifications used worldwide (ATC and ICD-9-CM) would guarantee the universality of the results and would improve comparisons regardless of nationality.

III.4.4. Future perspectives

In Portugal, it is imperative to perform studies at larger scales and across all levels of healthcare response, not only to evaluate the national prevalence of PIMs and PPOs but, more importantly, to understand if the trend of existing studies remains high compared to international literature. For these could be important to incentive the pharmacists to introduce the information related to the medication in the online platform that is used by all UCCIs at a national level. In addition, alerts could be programmed to identify PIMs and PPOs, similarly to what happens with the software SENATOR®.

More intensive pharmaceutical interventions can substantially reduce the frequency of PIMs and PPOs, which were already exposed in interventional studies focusing on different healthcare settings [433,444,446–448]. Lang *et al.* [433] obtained a decrease from 77% to 19% for PIMs and 65% to 11% for PPOs. Moreover, Garcia-Gollarte *et al.* [449] achieved a PIM reduction from 67% to 44% in the intervention group.

It is also crucial to evaluate the compatibility of the application of STOPP and START criteria with the available data from electronic settings (as recently it was made in the US for nursing homes [450], and to improve databases, by modifying or adding relevant information indispensable to apply these criteria. Furthermore, it would be also essential to create a Portuguese version of STOPP/START criteria, as already done in other countries [451,452], and to adapt it to the national market, which would involve modifications in some criteria (such as the removal of

prochlorperazine in the STOPP criteria about its use with parkinsonism or the replacement of "hypnotic Z-drugs" by "zolpidem", which is the only Z-drug available in Portugal).

Despite the extensive literature on inappropriate prescribing generated over the last decade, much remains to be done regarding its implementation in clinical practice. Thus, further studies to assess the relationship between mis/over/underuse of drugs and adverse events (as hospitalizations, falls, deaths) should be performed with depth, as soon as possible, including an analysis of inherent costs.

III. 5. Conclusion

PIMs and PPOs are highly prevalent in geriatric patients and, therefore, more proactive interventions are needed to improve this scenario. The drugs most frequently identified as PIMs were those belonging to the CNS group, while PPOs were associated with drugs acting in the musculoskeletal and cardiovascular systems. The most common overuses were associated with benzodiazepines, which are predictors of an increased risk of falls, particularly when used for longer than 4 weeks. Omissions were more frequently related to the lack of vitamin D supplements, calcium-vitamin D supplements, ACEIs and antiplatelet agents. Female gender, hospital provenance and the higher number of medications prescribed were related to a higher rate of PIMs, in contrast to cerebrovascular disease and Parkinson's disease. PPOs were associated with CCI and a history of recent fractures, while Parkinson's disease and a metastatic solid tumor appeared to be protective. The fact that three specific criteria represent almost half of the total PIMs and PPOs show that targeted interventions can substantially improve the appropriateness of medication. Further national investigation is required, as well as international studies, focusing on the relationship between PIMs/PPOs and clinically relevant adverse events in order to better explore its consequences on patients' health and to realize its economic impact.

Chapter IV

Potentially inappropriate prescribing to the older patients admitted to units for integrated continuous care: application of STOPP/START criteria

Chapter IV – Potentially inappropriate prescribing to the older patients admitted to units for integrated continuous care: application of STOPP/START criteria

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IV.1. Introduction

Optimization of drug therapy in the elderly population is a well-known goal that can be accomplished through the prescription of appropriate drugs. In contrast, potentially inappropriate drugs prescribed to older people that have no clear indication based on evidence can lead to higher risks of developing adverse effects [393]. Considering the physiological characteristics and the existence of chronic conditions that are common in the oldest patients, the side effects of inappropriate prescribed drugs can be serious in this population. There are still a higher number of drugs prescribed to older people that can be problematic, such as anticholinergic, benzodiazepines, NSAIDs, antipsychotics, and antibiotics [453]. In fact, the clinical and economic impact of mis/over/underuse of drugs is not only a current issue, but also a future problem that increases with the aging of the population. Worldwide, life expectancy at birth reached 73.3 years in 2024, reflecting an increase of 8.4 years since 1995 [5]. By 2030, one in six people worldwide will be aged 60 or over. During this period, the number of people aged 60 and over will increase from 1 billion in 2020 to 1.4 billion. By 2050, the global population of people aged 60 and over is expected to double to 2.1 billion. In addition, the number of people aged 80 and over is expected to triple between 2020 and 2050, reaching 426 million [2].

The increase in population aging is usually followed by an increase in comorbidities, consequently leading to the use of more medications. A retrospective cross-sectional study conducted by Mo *et al.* [454] revealed that patients aged 80 years or older had statistically significant higher comorbidities, medical prescription, hospitalization expenses, length of stay, and mortality than those aged 65–79 years old. In addition to this, the same study also showed that the group of the oldest patients had more prescriptions of benzodiazepines, anticholinergics, megestrol, antipsychotics, theophylline, and aspirin. Therefore, it is essential to explore the use of PIMs, particularly in older age groups.

Several tools have been developed, published, and updated in the last years to study the inappropriate use of medication in older patients. One of these tools are the explicit criteria developed by Beers *et al.* [274] and their updates [289,290,455–457]. However, as almost half of the drugs included in the Beers criteria are not commercialized in most European countries, their clinical applicability has been questioned [458]. Instead, the reviewed STOPP/START criteria [409] demonstrated to cover significantly more PIMs that contribute to hospital admissions, also enabling the detection of PIMs and the identification of PPOs that may also have harmful clinical consequences [419,459]. Furthermore, it was also reported that the 2015 update (STOPP/START version 2) identified more PIMs of clinical relevance [460], and, more recently, version 3 [461] has shown improvements [462,463].

As polypharmacy and comorbidities have been widely reported as predictors of PIMs [303,404,429–432,442] and PPOs [303,421,422,431], respectively, a higher prevalence of PIMs and PPOs is expected to be found in older patients. Mostly due to their frailer healthcare status, these patients should be more supervised by healthcare professionals, which may contribute to

avoiding inappropriate prescriptions. Nevertheless, care must be taken at the time of applying different criteria to identify possible PIMs and PPOs. This is particularly true for the oldest and frailest patients, as both the validity and reliability of the criteria in this population can be somewhat controversial. An example of this is that contrary to STOPP criteria where the application to patients aged ≥ 65 years seems to be the only requirement, the START criteria safeguard patients at the end of life [409].

Considering the elderly population, with specific or diverse comorbidities, and living or not in an institutional setting, the literature is already extensive regarding these issues. However, most studies have included all patients in one age group without exploring potential differences in clinical characteristics and drug use among elderly people of different ages [417,431,432,464–467]. Besides that, few studies restricted a minimum age cut-off above 75 years old [420,424,459,468], or compared different age groups of the same population in order to establish conclusions about the oldest patients [424]. Nevertheless, after applying the STOPP/START criteria, Liu *et al.* [423] found that an age above 75 years old increased the risk of PIM, particularly for those aged ≥ 85 years. In addition, other studies have also found a significant association between PPOs and older age [428,465].

With this in mind, the primary objective of this study was to determine and compare the prevalence of PIMs and PPOs (overall and per individual STOPP and START criteria, respectively) among the patients aged between 75 and 84 years old, and those aged 85 years or older from UCCIs. The secondary objective was to identify potential predictors of PIMs and PPOs among the demographic and clinical features of elderly patients of both age groups hospitalized in UCCIs.

IV.2. Patients and methods

IV.2.1. Study design, setting, and participants

An observational, retrospective, multicenter study was conducted on patients hospitalized in UCCIs included in the RNCCI. Patients were randomly selected from eight UCCIs that provided post-acute and long-term care and were discharged between June 2015 and April 2016. The protocol of this study was approved by the Ethics Committee of the Faculty of Health Sciences of the University of Beira Interior (CE-FCS-2015-030). The retrospective nature of this study did not affect any healthcare aspect of the inpatients, whereby informed consent was not required. Patient data were anonymized by attributing an alphanumeric code, and data access was restricted to the first author, who was responsible for the application of STOPP/START criteria. Statistical analysis was performed exclusively with the coding used.

IV.2.2. Data sources

Patients' clinical information was accessed through an online software where data were recorded: periodic evaluations registered by physicians, nurses, and other health professionals of the multidisciplinary team, providing information on patients' clinical status, diagnosis, and prescriptions. Diagnoses were collected through ICD-9-CM [469] and others only using the information provided in the online clinical process. The therapeutic list was initially extracted from each patient's discharge letter or from clinical evaluations, being then coded according to the ATC classification system. No patient was excluded due to missing data: whenever information was not available in the selected primary source, other sources were consulted to complete missing or incomplete online information.

IV.2.3. Data collection and analysis

Demographic characteristics (age, gender, origin, length of institution stay, and discharge) and clinical features [enteral nutrition, chronic medications, daily doses, chronic conditions, CCI [227], and geriatric syndromes] of patients aged 74–85 years (the youngest group) and over 85 years (the oldest group) were compared. Among geriatric syndromes, polypharmacy, number of comorbid diseases ≥ 2, CCI ≥ 6, dependency in ADL assessed using the Barthel index, risk of falls, malnutrition/anorexia, obesity, pressure ulcers, and history of recent fractures were included.

Comorbid diseases included only those considered in the CCI (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any non-metastatic solid tumor, leukemia, malignant lymphoma, moderate or severe liver disease, metastatic solid tumor, and Acquired Immune Deficiency Syndrome). However, to determine the most common chronic conditions, other diseases were also analyzed: angina, arrhythmia, valvular disease, hypertension, Parkinson's disease, renal disease either severe or not, urinary incontinence, recurrent urinary tract infection, rheumatoid arthritis, rheumatic disease, osteoporosis, depression, constipation, benign prostatic hypertrophy, and glaucoma. The prevalence of chronic conditions and prescribed therapeutics in each subgroup was analyzed and calculated as a proportion of all patients and of each studied age group (75–84 years old and ≥85 years old).

Despite the different meanings associated with the term polypharmacy, in this study, polypharmacy was defined as the chronic use of 5 or more medications per day [202]. The CCI [227], a morbidity index that considers the number of comorbid conditions and their severity, was also calculated to investigate comorbidities in each studied group.

The prevalence of PIMs and PPOs were found through the application of the overall STOPP and START criteria, respectively, that were explored and compared in both age groups. For that,

continuous variables (the number of PIMs and PPOs identified) and categorical variables (with or without PIM and/or PPO) were considered. Also, the PIM index, which is calculated by dividing the number of PIMs by the number of prescribed medications, is another tool that can complement the analysis of PIM prevalence [470].

Demographic characteristics, clinical features (including all geriatric syndromes), and chronic conditions were also analyzed as potential predictors of PIMs and PPOs in patients aged 75–84 years and those aged ≥ 85 years.

In descriptive statistics, continuous variables were expressed as mean ± SD, as median, and as the interquartile range (P25; P75). On the other hand, categorical variables were expressed as the number of observations (absolute frequency) and percentages (relative frequency).

The Kolmogorov–Smirnov test was used to determine whether continuous variables had a normal distribution, and Student's t-test or the Mann–Whitney test was used depending on the result. In contrast, categorical variables were compared using Chi-Square or Fisher's Exact Tests. The existence of associations between PIMs or PPOs and the other variables was first tested with a bivariate logistic regression and the respective ORs were estimated. Then, to identify the determinants of PIMs and PPOs, variables with a significant association with PIMs or PPOs were tested in a multivariate analysis. ORs were adjusted for sex and for the significant variables previously found and the logistic regression analysis, with logit link function, was performed using the forward selection method based on the likelihood ratio (significance level of 5% for a variable entered and 10% for its removal) to find independent predictors associated with PIMs or PPOs. The Hosmer–Lemeshow test was performed to assess the goodness of fit, whereas the ROC curve allowed the evaluation of the model's discriminatory power and its sensitivity/specificity. Differences were considered statistically significant when $p < 0.05$ and the CI was 95%. Statistical analyses were performed using IBM SPSS Statistics version 27.

IV.3. Results

IV.3.1. Characteristics of the study population

The demographic characteristics and clinical features of patients are detailed in Table IV.1. Of the 135 patients studied, 79 were aged between 75 and 84 years old (median age of 80 [78; 82] years old), while 56 were aged ≥ 85 years old (median age of 89 [86; 91] years old). Among those aged between 75 and 84 years old, 68.4% were female, most came from the hospital (58.2%), had a median length of stay of 90 [45; 146] days, and most returned to their residence (48.1%). However, a considerable number of patients died in the UCCI or soon after emergency hospital admission (20.3%). Patients aged ≥ 85 years old were also predominantly female (66.1%), arising from either a residence (46.4%) or a hospital (41.1%), had a length of stay median of 102 [89; 173]

days, and also had a higher discharge to residence (28.6%). The youngest age group was more likely to come from the hospital (p = 0.018).

Table IV.1. Characteristics of the patients according to age groups.

	75–84 Years (n = 79)	**≥85 Years (n = 56)**	p [a]
Demographic characteristics			
Age (years)			
Mean ± SD	79.8 ± 2.8	89.4 ± 4.0	
Median (P25; P75)	80 (78; 82)	89 (86; 91)	
Gender, *n* (%)			0.780 [1]
Male	25 (31.6)	19 (33.9)	
Female	54 (68.4)	37 (66.1)	
Medical history			
Provenance/Origin, n (%)			**0.018** [2]
Hospital	46 (58.2)	23 (41.1)	**0.049** [1]
Residence	33 (41.8)	26 (46.4)	0.591 [1]
Nursing home	0 (0.0)	2 (3.6)	
Primary care	0 (0.0)	3 (5.4)	
Other	0 (0.0)	2 (3.6)	
Length of stay			0.156 [3]
Mean ± SD	146.0 ± 191.0	141.1 ± 166.9	
Median (P25; P75)	90 (45; 146)	102 (89; 173)	
Discharge to, *n* (%)			
Residence	33 (48.1)	16 (28.6)	0.342 [1]
Death	16 (20.3)	8 (14.3)	
Another RNCCI response	13 (16.5)	11 (19.6)	
Social option/response	8 (10.1)	11 (19.6)	
Nursing home	7 (8.9)	7 (12.5)	
Other or not referred	2 (2.5)	3 (5.4)	
Clinical features			
Enteral Nutrition, *n* (%)			
Yes	11 (13.9)	8 (14.3)	0.953 [1]
No	68 (86.1)	48 (85.7)	
Medication per patient			**0.029** [4]
Mean ± SD	9.3 ± 3.1	8.0 ± 3.3	
Median (P25; P75)	9 (7; 11)	8 (6; 10)	
Number of doses			**0.020** [3]
Mean ± SD	10.7 ± 3.9	9.2 ± 4.0	
Median (P25; P75)	11 (8; 13)	8 (6; 12)	
Comorbid diseases (CCI)			0.400 [3]
Mean ± SD	1.8 ± 1.2	1.6 ± 1.1	
Median (P25; P75)	2 (1; 3)	2 (1; 2)	
CCI			**0.046** [3]
Mean ± SD	5.8 ± 1.6	6.3 ± 1.5	
Median (P25; P75)	6 (5; 7)	6 (5; 7)	
Geriatric syndromes, *n* (%)			
Polypharmacy (≥5 drugs/day)			
Yes	73 (92.4)	50 (89.3)	0.553 [2]
No	6 (7.6)	6 (10.7)	
Comorbid diseases ≥ 2			
Yes	43 (54.4)	30 (53.6)	0.921 [1]
No	36 (45.6)	26 (46.4)	
CCI ≥ 6			
Yes	40 (50.6)	39 (69.6)	**0.027** [1]
No	39 (49.4)	17 (30.4)	
Dependency in ADL			
Yes	67 (84.8)	56 (100.0)	**0.001** [2]
No	12 (15.2)	0 (0.0)	
Fall Risk (medium or high)			
Yes	66 (83.5)	44 (78.6)	0.464 [1]
No	13 (16.5)	12 (21.4)	
Malnutrition/anorexia			
Yes	2 (2.5)	2 (3.6)	1.000 [2]
No	77 (97.5)	54 (96.4)	

Obesity			
Yes	17 (21.5)	1 (1.8)	**0.001** [1]
No	62 (78.5)	55 (98.2)	
Pressure ulcers at discharge			
Yes	16 (20.3)	9 (16.1)	0.538 [1]
No	63 (79.7)	47 (83.9)	
History of recent fractures			
Yes	18 (22.8)	19 (33.9)	0.153 [1]
No	61 (77.2)	37 (66.1)	

ADL, dependency in activities of daily living; CCI, Charlson Comorbidity Index; SD, Standard deviation; a Wald test; [1] Pearson Chi-Square test; [2] Fisher's Exact Test; [3] Mann–Whitney test; [4] Student t-test. All significant variables are in bold.

Considering the prevalence of patients fed through enteral nutrition and also the prevalence of comorbid diseases, no significant differences were found between patients aged 75–84 years old and ≥85 years old. Instead, patients aged ≥ 85 years old had fewer chronic medications prescribed (p = 0.029), fewer doses per day (p = 0.020), and higher CCI (p = 0.046). Concerning geriatric syndromes, patients aged ≥ 85 years old were more likely to have a CCI ≥ 6 (p = 0.027), were more dependent on ADL (p = 0.001), and were less obese (p = 0.001). No significant differences were found for the following variables: polypharmacy, two or more comorbid diseases, fall risk (medium or high), malnutrition/anorexia, the existence of pressure ulcers, or a history of recent fractures.

Table IV.2 presents all the information regarding the most common chronic conditions and most prescribed therapeutic subgroups in the studied population. The most common chronic conditions in patients aged 75–84 years old were hypertension (67.1%), diabetes mellitus (40.5%), depression (38.0%), and constipation (35.4%). At the same time, the most commonly prescribed drugs were antithrombotic agents (77.2%), drugs for acid-related disorders (68.4%), psycholeptics (65.8%), and psychoanaleptics (64.6%). In patients aged ≥ 85 years old, hypertension (71.4%), urinary incontinence (42.9%), cerebrovascular disease (33.9%), and dementia (33.9%) were the most common chronic conditions. In this age group, the most commonly prescribed drugs were drugs for acid disorders (69.6%), psycholeptics (67.9), antithrombotic agents (62.5%), and diuretics (55.4%). The youngest patients were more likely to have diabetes mellitus (p = 0.020) and depression (p = 0.041), and to take psychoanaleptics (p = 0.007), drugs for diabetes treatment (p = 0.012), and antiepileptics (p = 0.002). Older patients were more likely to have urinary incontinence (p = 0.008).

Table IV.2. Most common chronic conditions and therapeutic subgroups prescribed according to age groups.

	Total (*n* = 135)	**75–84 Years (*n* = 79)**	**≥85 Years (*n* = 56)**	***p*** [1]
Chronic conditions [a], ***n* (%)**				
Hypertension	93 (68.9)	53 (67.1)	40 (71.4)	0.592
Constipation	46 (34.1)	28 (35.4)	18 (32.1)	0.690
Cerebrovascular disease	45 (33.3)	26 (32.9)	19 (33.9)	0.902
Dementia	44 (32.6)	25 (31.6)	19 (33.9)	0.780
Diabetes mellitus	44 (32.6)	32 (40.5)	12 (21.4)	**0.020**
Depression	42 (31.1)	30 (38.0)	12 (21.4)	**0.041**
Urinary incontinence	41 (30.4)	17 (21.5)	24 (42.9)	**0.008**
Congestive heart failure	34 (25.2)	18 (22.8)	16 (28.6)	0.445
Rheumatic disease	33 (24.4)	24 (30.4)	9 (16.1)	0.057
Arrhythmia	27 (20.0)	13 (16.5)	14 (25.0)	0.221
Benign prostatic hypertrophy	25 (56.8)	14 (56.0)	11 (57.9)	0.900
Renal disease	21 (15.6)	10 (12.7)	11 (19.6)	0.270
Any non-metastatic solid tumor	18 (13.3)	13 (16.5)	5 (8.9)	0.205
Chronic pulmonary disease	17 (12.6)	8 (10.1)	9 (16.1)	0.305
Hemiplegia	12 (8.9)	8 (10.1)	4 (7.1)	0.548
Recurrent urinary tract infection	12 (8.9)	6 (7.6)	6 (10.7)	0.530
Most frequent drug prescribed (ATC_2 [b]**), *n* (%)**				
Antithrombotic agents (B01)	96 (71.1)	61 (77.2)	35 (62.5)	0.063
Drugs for acid related disorders (A02)	93 (68.9)	54 (68.4)	39 (69.7)	0.873
Psycholeptics (N05)	90 (66.7)	52 (65.8)	38 (67.9)	0.805
Psychoanaleptics (N06)	74 (54.8)	51 (64.6)	23 (41.1)	**0.007**
Diuretics (C03)	71 (52.6)	40 (50.6)	31 (55.4)	0.588
Agents acting on the renin–angiotensin system (C09)	62 (45.9)	38 (48.1)	24 (42.9)	0.546
Lipid modifying agents (C10)	54 (40.0)	36 (45.6)	18 (32.1)	0.117
Drugs for constipation (A06)	45 (33.3)	27 (34.2)	18 (32.1)	0.805
Analgesics (N02)	43 (31.9)	26 (32.9)	17 (30.4)	0.754
Drugs used in diabetes (A10)	40 (29.6)	30 (38.0)	10 (17.9)	**0.012**
Beta-blocking agents (C07)	40 (29.6)	26 (32.9)	14 (25.0)	0.321
Cardiac therapy (C01)	34 (25.2)	19 (24.1)	15 (26.8)	0.718
Antiepileptics (N03)	30 (22.2)	25 (31.6)	5 (8.9)	**0.002**
Antianemic preparations (B03)	28 (20.7)	14 (17.7)	14 (25.0)	0.304

[a] The chronic conditions reported by more than 5% of patients; ATC_2, ATC second level (therapeutic subgroup); [b] the therapeutic subgroups reported by more than 20% of patients. [1] Pearson Chi-Square. All significant variables are in bold.

IV.3.2. Potentially inappropriate medications

Table IV.3 shows the prevalence of PIM and PPO in both age groups. In patients aged 75–84 years old, the median number of PIMs was 3 [1; 4], and the prevalence of PIM was 88.6%. In patients aged ≥ 85 years old, a median of 2 [1; 3.75] PIMs were identified per patient, and the prevalence of PIM was 85.7%. Almost three-quarters of the patients in both age groups had two or more PIMs, but no significant difference was found between patients aged 75–84 years old and those aged ≥ 85 years old. The PIM index was 0.273 [0.143; 0.429] for the youngest elderly and 0.333 [0.157; 0.441] for the oldest, with no statistically significant difference.

Table IV.3. Prevalence of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria.

Criteria	75–84 Years (*n* = 79)	≥85 Years (*n* = 56)	*p*
STOPP			
Number of PIMs per patient			0.401 [1]
Mean ± SD	2.9 ± 2.2	2.5 ± 1.8	
Median (P25; P75)	3 [1; 4]	2 [1; 3.75]	
0, *n* (%)	9 (11.4)	8 (14.3)	
1, *n* (%)	14 (17.7)	8 (14.3)	
2, *n* (%)	14 (17.7)	15 (26.8)	
3, *n* (%)	17 (21.5)	11 (19.6)	
≥4, *n* (%)	25 (31.6)	14 (25.0)	
Number of patients with ≥1 PIM, n (%)	70 (88.6)	48 (85.7)	0.618 [2]
START			
Number of PPOs per patient			0.169 [1]
Mean ± SD	1.8 ± 1.4	2.1 ± 1.4	
Median (P25; P75)	2 [1; 3]	2 [1; 3]	
0, *n* (%)	16 (20.3)	8 (14.3)	
1, *n* (%)	21 (26.6)	8 (14.3)	
2, *n* (%)	18 (22.8)	21 (37.5)	
3, *n* (%)	13 (16.5)	12 (21.4)	
≥4, *n* (%)	11 (13.9)	9 (12.5)	
Number of patients with ≥1 PPO, *n* (%)	63 (79.7)	48 (85.7)	0.372 [2]
PIM Index			0.754 [1]
Mean ± SD	0.312 ± 0.229	0.317 ± 0.215	
Median (P25; P75)	0.273 [0.143; 0.429]	0.333 [0.157; 0.441]	
STOPP-PIM or START-PPO, *n* (%)	76 (96.2)	54 (96.4)	1.000 [3]
STOPP-PIM and START-PPO, *n* (%)	57 (72.2)	41 (75.0)	0.712 [2]

SD, Standard deviation; [1] Mann–Whitney; [2] Pearson Chi-Square; [3] Fisher's Exact Test.

The most common PIMs in both age groups (with their prevalence in patients aged 75–84 years old vs. ≥85 years old, respectively) were the following: benzodiazepines as drugs that predictably increase the risk of falls (54.4% vs. 51.8%); benzodiazepines for longer than four weeks (50.6% vs. 50.0%) and neuroleptics in elderly prone to falls (25.3% vs. 23.2%) (Table IV.4). However, no statistically significant differences were found among these PIMs.

In the multivariate logistic regression, a statistically significant association was found between the number of medications [OR = 1.71, 95%CI: 1.19–2.48), p = 0.004] and the diagnosis of cerebrovascular disease [OR = 0.16 (95% CI 0.03–0.91), p = 0.038] in the group aged 75–84 years old. There was also a statistically significant association with the number of medications [OR = 1.44 (95% CI 1.04–2.01), p = 0.028] and the diagnosis of chronic pulmonary disease [OR = 0.12 (95% CI 0.02–0.90), p = 0.039] for those aged ≥ 85 years old. Logistic regression information is presented in Table IV.5 (univariate level) and Table IV.6 (multivariate level).

As the number of drugs prescribed was the only predictor of PIM for both age groups, the relationship between this variable and the number of PIMs was evaluated. A statistically significant association was found for the whole population (p = 0.020), for patients aged 75–84 years old (p = 0.001), and for patients aged ≥ 85 years old (p = 0.018). Figure IV.1 shows the corresponding box-and-whisker plots, and the results of multiple comparisons performed using the Kruskal–Wallis test.

Table IV.4. Most frequent potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) (at least in 5% of the total population) and comparison between age groups.

		Total (*n* = 135)	75–84 Years (*n* = 79)	≥85 Years (*n* = 56)	*p*
STOPP Criteria	Benzodiazepines as drugs that predictably increase the risk of falls	72 (53.3)	43 (54.4)	29 (51.8)	0.762 [1]
	Benzodiazepines for ≥4 weeks	68 (50.4)	40 (50.6)	28 (50.0)	0.942 [1]
	Neuroleptics as drugs that predictably increase the risk of falls	33 (24.4)	20 (25.3)	13 (23.2)	0.779 [1]
	Tricyclic antidepressants with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention	22 (16.3)	15 (19.0)	7 (12.5)	0.315 [1]
	Anticholinergics/antimuscarinics in patients with delirium or dementia	20 (14.8)	13 (16.5)	7 (12.5)	0.524 [1]
	Any drug prescribed without an evidence-based clinical indication	13 (9.6)	6 (7.6)	7 (12.5)	0.341 [1]
	Any duplicate drug class prescription	11 (8.1)	7 (8.9)	4 (7.1)	1.000 [2]
	Benzodiazepines with acute or chronic respiratory failure	11 (8.1)	6 (7.6)	5 (8.9)	0.762 [2]
	Use of regular (as distinct from PRN) opioids without concomitant laxative	11 (8.1)	8 (10.1)	3 (5.4)	0.361 [2]
	Proton pump inhibitors for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for >8 weeks	10 (7.4)	4 (5.1)	6 (10.7)	0.318 [2]
	Drugs likely to cause constipation in patients with chronic constipation where non-constipating alternatives are available	9 (6.7)	7 (8.9)	2 (3.6)	0.305 [2]
	Hypnotic Z-drugs	9 (6.7)	5 (6.3)	4 (7.1)	1.000 [2]
	Loop diuretic for treatment of hypertension with concurrent urinary incontinence	8 (5.9)	3 (3.8)	5 (8.9)	0.276 [2]
	Initiation of tricyclic antidepressants as first-line antidepressant treatment	8 (5.9)	7 (8.9)	1 (1.8)	0.139 [2]
	Neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia unless symptoms are severe and other non-pharmacological treatments have failed	8 (5.9)	5 (6.3)	3 (5.4)	1.000 [2]
	Long-acting opioids without short-acting opioids for break-through pain	7 (5.2)	5 (6.3)	2 (3.6)	0.699 [2]
START Criteria	Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia	59 (43.7)	28 (35.4)	31 (55.4)	**0.022** [1]
	Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or Bone Mineral Density T-scores more than −2.5 in multiple sites	38 (28.1)	19 (24.1)	19 (33.9)	0.209 [1]
	Angiotensin converting enzyme inhibitor with systolic heart failure and/or documented coronary artery disease	26 (19.3)	14 (17.7)	12 (21.4)	0.590 [1]
	Antiplatelet therapy with a documented history of coronary, cerebral or peripheral vascular disease	20 (14.8)	10 (12.7)	10 (17.9)	0.402 [1]
	Appropriate beta-blocker with stable systolic heart failure	17 (12.6)	7 (8.9)	10 (17.9)	0.121 [1]
	5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary	16 (11.9)	10 (12.7)	6 (10.7)	0.731 [1]
	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years	14 (10.4)	11 (13.9)	3 (5.4)	0.108 [1]
	Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary	11 (8.1)	4 (5.1)	7(12.5)	0.200 [2]
	Laxatives in patients receiving opioids regularly	11 (8.1)	8 (10.1)	3 (5.4)	0.361 [2]
	Non-tryciclic antidepressant drug in the presence of persistent major depressive symptoms	10 (7.4)	8 (10.1)	2 (3.6)	0.194 [2]
	Regular inhaled beta-2 agonist or antimuscarinic bronchodilator for mild to moderate asthma or chronic obstructive pulmonary disease	8 (5.9)	4 (5.1)	4 (7.1)	0.718 [2]

[1] Pearson Chi-Square; [2] Fisher's Exact Test.

Table IV.5. Predictors of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria, respectively, in study sample (n = 135) for the age groups 75–84 and ≥85 years old—univariate logistic regression.

	STOPP_PIM				**START_PPO**			
	75–84 Years Old Group (*n* = 79)		**≥85 Years Old Group (*n* = 56)**		**75–84 Years Old Group (*n* = 79)**		**≥85 Years Old Group (*n* = 56)**	
	OR (95% CI)	***p*** [a]	**OR (95% CI)**	***p*** [a]	**OR (95% CI)**	***p*** [a]	**OR (95% CI)**	***p*** [a]
Demographic characteristics								
Age (years)	-	-	-	-	-	-	-	-
Gender								
Male	0.54 (0.13; 2.20)	0.386	0.25 (0.05; 1.18)	0.079	9.23 (1.15; 74.42)	0.037	0.25 (0.05; 1.18)	0.079
Female	1		1		1		1	
Medical history								
Provenance/Origin								
Hospital	1.13 (0.28; 4.58)	0.863	3.15 (0.57; 17.48)	0.189	1.11 (0.37; 3.35)	0.857	0.47 (0.10; 2.23)	0.342
Residence	1		1		1		1	
Nursing home	-	-	-	-	-	-	-	-
Primary care	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-
Length of stay	1.00 (1.00; 1.01)	0.536	1.01 (0.99; 1.02)	0.293	1.00 (1.00; 1.01)	0.252	1.00 (0.99; 1.00)	0.183
Discharge to		0.454		0.962				0.943
Residence	-	-	-	-	-	-	3.50 (0.21; 58.77)	0.384
Death	-	-	-	-	-	-	3.50 (0.15; 84.69)	0.441
Another RNCCI response	-	-	-	-	-	-	2.25 (0.13; 38.81)	0.577
Social option/response	-	-	-	-	-	-	5.00 (0.21; 117.89)	0.318
Nursing home	-	-	-	-	-	-	3.00 (0.12; 73.64)	0.501
Other or not referred	-	-	-	-	-	-	1	
Clinical features								
Enteral nutrition	0.52 (0.09; 2.89)	0.451	-	-	2.83 (0.34; 23.91)	0.339	1.20 (0.13; 11.26)	0.876

Medication per patient	1.67 (1.19; 2.33)	0.003	1.56 (1.19; 2.24)	0.014	1.14 (0.94; 1.38)	0.172	1.23 (0.94; 1.60)	0.132
Number of doses	1.37 (1.08; 1.75)	0.011	1.40 (1.04; 1.88)	0.028	1.08 (0.93; 1.26)	0.309	1.19 (0.94; 1.50)	0.145
Comorbid diseases	1.05 (0.59; 1.87)	0.879	1.00 (0.51; 1.98)	1.000	1.68 (0.98; 2.87)	0.059	2.50 (1.02; 6.14)	0.046
CCI	1.18 (0.75; 1.86)	0.473	0.86 (0.53; 1.41)	0.554	1.34 (0.92; 1.96)	0.127	1.59 (0.85; 2.97	0.145
Geriatric syndromes								
Polypharmacy (≥5 drugs/day)	11.17 (1.84; 67.90)	0.009	9.00 (1.42; 57.12)	0.020	2.11 (0.35; 12.68)	0.416	3.67 (0.55; 24.51)	0.180
Comorbid diseases ≥ 2	0.95 (0.24; 3.84)	0.943	1.18 (0.26; 5.28)	0.827	2.37 (0.77; 7.34)	0.134	4.20 (0.77; 22.99)	0.098
CCI ≥ 6	1.32 (0.33; 5.35)	0.694	0.73 (0.13; 4.07)	0.723	2.75 (0.86; 8.84)	0.090	2.69 (0.59; 12.37)	0.203
Dependency in ADL	0.67 (0.08; 5.91)	0.719	-	-	3.64 (0.97; 13.57)	0.055	-	-
Fall risk (medium or high)	1.53 (0.28; 8.37)	0.622	1.27 (0.22; 7.26)	0.791	3.13 (0.86; 11.37)	0.084	1.27 (0.22; 7.26)	0.791
Malnutrition/anorexia	-	-	0.15 (0.01; 2.66)	0.196	0.24 (0.01; 4.09)	0.325	0.15 (0.01; 2.66)	0.196
Obesity	0.96 (0.18; 5.08)	0.957	-	-	0.78 (0.22; 2.82)	0.705	-	-
Pressure ulcers at discharge	2.18 (0.25; 18.84)	0.478	1.40 (0.15; 13.00)	0.767	4.69 (0.57; 38.50)	0.150	0.51 (0.09; 3.07)	0.464
History of recent fractures	1.04 (0.20; 5.50)	0.966	1.65 (0.30; 9.06)	0.567	-	-	4.20 (0.48; 36.98)	0.196
Chronic conditions [a]								
Hypertension	1.02 (0.23; 4.46)	0.977	1.62 (0.34; 7.74)	0.548	0.91 (0.28; 2.96)	0.874	3.00 (0.65; 13.89)	0.160
Constipation	5.02 (0.60; 42.43)	0.138	1.50 (0.27; 8.29)	0.642	1.27 (0.39; 4.10)	0.695	3.84 (0.44; 33.86)	0.226
Cerebrovascular disease	0.20 (0.05; 0.88)	0.033	0.46 (0.10; 2.07)	0.308	1.10 (0.34; 3.58)	0.874	1.65 (0.30; 9.06)	0.567
Dementia	1.71 (0.33; 8.91)	0.522	4.20 (0.48; 36.98)	0.196	2.33 (0.60; 9.04)	0.223	4.20 (0.48; 36.98)	0.196
Diabetes mellitus	0.88 (0.21; 3.38)	0.798	2.08 (0.23; 18.80)	0.514	1.65 (0.51; 5.31)	0.401	2.08 (0.23; 18.80)	0.514
Depression	5.66 (0.67; 47.74)	0.111	2.08 (0.23; 18.80)	0.514	1.03 (0.33; 3.18)	0.965	-	-
Urinary incontinence	2.37 (0.28; 20.40)	0.432	6.44 (0.74; 56.43)	0.093	2.19 (0.45; 10.74)	0.335	2.54 (0.47; 13.87)	0.282
Congestive heart failure	1.04 (0.20; 5.50)	0.966	3.18 (0.36; 28.21)	0.299	2.38 (0.49; 11.65)	0.283	-	-
Rheumatic disease	0.86 (0.20; 3.76)	0.838	0.51 (0.09; 3.07)	0.464	0.67 (0.21; 2.11)	0.490	1.40 (0.15; 13.00)	0.767
Arrhythmia	-	-	0.50 (0.10; 2.41)	0.384	-	-	-	-
Benign prostatic hypertrophy	4.88 (0.43; 55.29)	0.201	0.25 (0.02; 2.84)	0.263	-	-	10.00 (0.84; 119.32)	0.069
Renal disease	-	-	1.84 (0.20; 16.76)	0.588	2.50 (0.29; 21.33)	0.402	0.69 (0.12; 4.01)	0.682
Any non-metastatic solid tumor	1.66 (0.19; 14.49)	0.649	-	-	0.82 (0.20; 3.40)	0.782	0.64 (0.06; 6.55)	0.704
Chronic obstructive pulmonary disease	-	-	0.12 (0.02; 0.62)	0.011	-	-	1.40 (0.15; 13.00)	0.767

Hemiplegia	0.89 (0.10; 8.19)	0.917	0.47 (0.04; 5.14)	0.534	1.88 (0.21; 16.45)	0.570	0.47 (0.04; 5.14)	0.534
Recurrent urinary tract infection	-	-	-	-	-	-	-	-

ADL, dependency in activities of daily living; CCI, Charlson Comorbidity Index; RNCCI, Portuguese National Network for Long-term Integrated Care; [a] Wald's test; For the binary categorical variables, we considered the category "no" as a reference.

Table IV.6. Predictors of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) according to Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria in study sample (n = 135) for the age groups 75–84 and ≥85 years old — multivariate logistic regression.

STOPP_PIM	**75-84 Years Old Group (*n* = 79) [1]**		**≥85 Years old Group (*n* = 56) [2]**	
	Adjusted OR (95% CI)	***p*** [a]	**Adjusted OR (95% CI)**	***p*** [a]
Number of medications	1.71 (1.19–2.48)	0.004	1.44 (1.04–2.01)	0.028
Cerebrovascular disease	0.16 (0.03–0.91)	0.038	-	-
Chronic obstructive pulmonary disease	-	-	0.12 (0.02–0.90)	0.039
START_PPO	**75-84 Years Old Group (*n* = 79) [1]**		**≥85 Years old Group (*n* = 56) [2]**	
	Adjusted OR (95% CI)	***p*** [a]	**Adjusted OR (95% CI)**	***p*** [a]
Gender				
Male	14.41 (1.55; 134.47)	0.019	-	-
Female	1			
Fall risk (medium or high)	5.72 (1.21; 27.05)	0.028	-	-
Comorbid diseases	-	-	2.50 (1.02; 6.14)	0.046

CI, confidence interval; OR, odd ratio; a Wald's test; For the binary categorical variables, we con-sidered the category "no" as a reference; The ORs were adjusted for sex and for the significant variables in Table IV.5 and we used a forward variable selection method based on the likelihood ratio (significance level at 5% for a variable entering and 10% for its removal). 1 Cox&Snell r^2: 0.197; Nagelkerke r^2: 0.388; Hosmer and Lemeshow: p = 0.205; Area under ROC curve: 0.840; Sensitivity = 81.4% and Specificity = 77.8% for the cut-off probability 0.861. 2 Cox&Snell r^2: 0.208; Nagelkerke r^2: 0.372; Hosmer and Lemeshow: p = 0.254; Area under ROC curve: 0.789; Sensitivity = 66.7% and Specificity = 75.0% for the cut-off probability 0.884. 3 Cox&Snell r^2: 0.145; Nagelkerke r^2: 0.229; Hosmer and Lemeshow: p = 0.689; Area under ROC curve: 0.724; Sensitivity = 38.1%; Specificity = 93.7% for the cut-off probability 0.835 4 Cox&Snell r^2: 0.085; Nagelkerke r^2: 0.152; Hosmer and Lemeshow: p = 0.942; Area under ROC curve: 0.724; Sensitivity = 58.3% and Specificity = 75.00% for the cut-off probability 0.872.

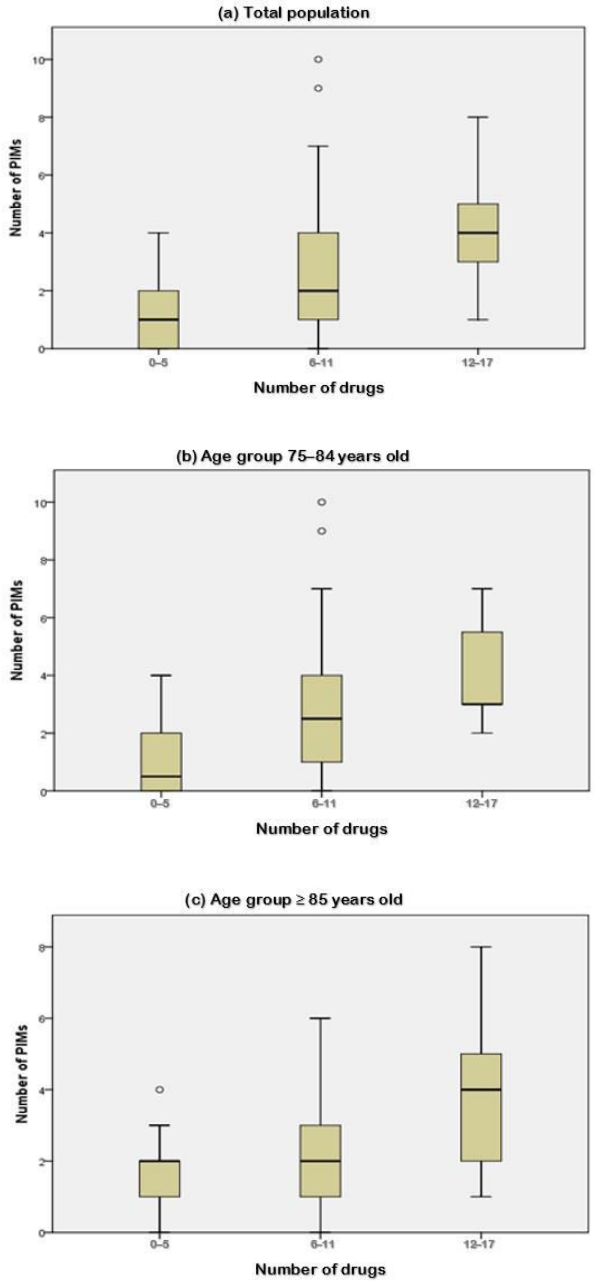

Figure IV.1. Relationship between the number of potentially inappropriate medications (PIMs) and the number of drugs, according to age groups. Box-and-whisker plots showing the relationship between the number of PIMs and the number of drugs prescribed in (a) all population, (b) patients aged 75–84 years old, and (c) patients aged ≥ 85 years old.

IV.3.3. Potentially prescribing omissions

A median of 2 [1; 3] PPOs was found in patients aged between 75 and 84 years old. Almost half had more than one PPO, and the prevalence of PPO was 79.7%. The oldest old had a median of 2 [1; 3] PPOs, almost 75% had at least 2 PPOs, and the prevalence of PPO was 85.7%. No significant differences were found between both age groups (Table IV.3).

The most common PPOs and their respective prevalence among patients aged between 75 and 84 years old and among patients with ≥85 years old were the following: vitamin D supplements in the oldest that are housebound, experiencing falls, or with osteopenia (35.4% vs. 55.4%); vitamin D–calcium supplement in patients with osteoporosis and/or previous fragility fracture(s) (24.1% vs. 33.9%); and ACEIs with systolic heart failure and/or documented coronary artery disease (17.7% vs. 21.4%) (Table IV.4). The oldest age group with a history of falls showed higher potential omission of vitamin D supplements (p = 0.022) than those aged between 75–84 years old.

In the age group between 75 and 84 years old, a statistically significant association was found between the male gender [OR = 14.41 (95% CI 1.55–134.47), p = 0.019] and the fall risk [OR = 5.72 (95% CI 1.21–27.05), p = 0.028]. However, in the oldest group, only the number of comorbidities [OR = 2.50 (95% CI 1.02–6.14), p = 0.046] demonstrated to be a predictor of PPO (Table IV.6).

IV.4. Discussion

IV.4.1. Main findings

Patients aged ≥ 85 years old were less likely to come from a hospital, had fewer daily medications, and had fewer oral doses, but had a higher CCI, were more likely to have a CCI ≥ 6, were more dependent on ADL, and were less obese than those aged between 75 and 84 years old.

Regarding comorbidities, hypertension was the most common chronic condition present in both age groups. In patients aged 75–84 years old, diabetes mellitus, depression, and constipation followed hypertension as existent comorbidities. In the oldest group, the other conditions that were more prevalent were urinary incontinence, cerebrovascular disease, and dementia. Antithrombotic agents, drugs for gastric acid-related disorders, and psycholeptics were the therapeutic subgroups more commonly prescribed in both age groups, although with a distinct hierarchy. Drugs used for the treatment of hypertension were not in the top three, probably because of the different clinical approaches that can be chosen (e.g., diuretics, agents acting on the renin–angiotensin system, beta-blocking agents, and cardiac insufficiency therapy). Psycholeptics had a high prevalence in both age groups, even though they are a therapeutic subgroup directly related to PIM in the elderly, once they predictably increased the risk of falls. In addition, drugs for gastric acid-related disorders are also commonly prescribed, despite fewer patients having a history of peptic ulcer. However, this may be related to the use of drugs that can be harmful to the gastrointestinal system, such as antithrombotic agents, corticosteroids, and NSAIDs.

PIM and PPO were ubiquitous in the youngest studied group (88.6% and 79.7%, respectively) and also in the oldest group (85.7% for both). Still, no statistically significant differences were found. This may be related to the additional concern that most physicians may have at the time of

prescribing PIM drugs to older patients, which may lower the PIM prevalence in the oldest studied population. Nevertheless, the PIM index was higher among the oldest, which may mean that patients aged 75–84 years old may have received more appropriate prescriptions [470]. Concerning PPO, there were also no statistically significant differences in the youngest group, in contrast to the higher prevalence of PPO found in the oldest group, which may be related to the higher CCI.

The most common PIMs were the same in both age groups (benzodiazepines as drugs that predictably increase the risk of falls, benzodiazepines for ≥ 4 weeks, and neuroleptics as drugs that predictably increase the risk of falls). The same trend was observed for PPOs between the two age groups studied here (vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia; vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s), and ACEIs with systolic heart failure and/or documented coronary artery disease). Thus, assuming that an intervention was carried out that resulted in the elimination of the three most common PIMs and PPOs, it is possible that this reevaluation would reduce their prevalence of PIMs and PPOs in the youngest group up to 74.7% and 62.0%, respectively, and in the oldest group up to 64.3% in both cases. In this way, PIMs and PPOs would be absent in 13.9% of patients aged between 75 and 84 years old (against 3.8%) and in 10.7% of patients aged ≥ 85 years old (against 3.6%).

The number of medications was a predictor of the existence of PIM in both age groups. At the same time, this variable was also found to be associated with prevalence of cerebrovascular disease in patients aged 75–84 years old and with the prevalence of chronic pulmonary disease in those aged ≥ 85 years old. Considering the total population studied, and both the youngest and the oldest groups, the total number of medications had a significant relationship with the number of PIMs found. For PPO, male gender and fall risk were predictors in the youngest group, whereas the number of comorbidities was significantly associated with PPO in the oldest group.

IV.4.2. Comparing with existing literature

National data are scarce and do not compare different age groups. However, the available data show a high prevalence of PIM values (75.4% in nursing homes [417], 74.0% in hospitalized patients [471]), and of PPO values (68.1% in a stroke unit [436]). However, from an international perspective, the reported prevalence of medication misuse, overuse, and underuse is very different for both PIMs and PPOs, ranging from 15% to 81% for PIMs [302,303,397,403,404,419–423,426,427,429–435,467] and from 23% to 74% for PPOs [302,303,420–423,428,429,431–435]. This diversity is probably not only the result of different healthcare practices, but also to different types of target population (oldest or frailest) in different situations (admission or discharge, with acute or chronic conditions) and in different healthcare settings (primary care, nursing home, hospital).

Regarding the comparison of studies that grouped by age, San-José *et al.* [424] also compared patients aged 75–84 years old with patients aged ≥ 85 years old who were admitted to the hospital. In this study, the obtained prevalence of PIM and PPO was, respectively, of 60.5% and 49.6% in the youngest group, against 63.4% and 53.7% in the oldest group. Although these are the lowest results, they could be much closer to our results by reassessing the six criteria (three PIMs and three PPOs most prevalent) mentioned above. In fact, this study is undoubtedly one of the studies focusing on the oldest patients with the highest prevalence of PIM and PPO. In the elderly aged ≥ 80 years old, Dalleur *et al.* [468] found a prevalence of 59% for PIM and 41% for PPO, and Wauters *et al.* [459] revealed misuse of 67% and underuse of 56%. They also pointed out that PIMs and PPOs coexisted in 40% of the cases and were absent in 17% of patients, a better result than that found in our study (72.2% and 3.8% for the youngest group; 75.0% and 3.6% for the oldest group). However, the lowest prevalence was found in primary care patients, who had lower levels of polypharmacy (61% and 58%, respectively) compared to both age groups of inpatients included in San-José *et al.* [424] (90.6% and 93.4%, respectively) and our study (92.4% and 89.3%, respectively).

Intriguingly, some studies of the oldest elderly presented a higher prevalence of PIM than PPO [424,459,468]. This contrasts with the results of our study, which found a higher prevalence of PPOs in the youngest group compared with the oldest group, where PPOs had a prevalence 6% greater than PIMs. Moreover, the only statistical difference found between the age groups was in the most common PPO (vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia), showing that the oldest group was more likely to have a prescription omission of vitamin D supplement than the youngest group. These findings may be due to a greater reluctance to add prescriptions for older patients who are already heavily medicated.

Regarding the most common PIMs and PPOs, the results obtained were not surprising. In fact, the literature often mentions benzodiazepines and neuroleptics as the chemical subgroups involved in the most common PIMs [403,404,420,423,424,427,430,432–434], as well as vitamin D supplements, combined or not with calcium, as the drugs that more contribute to PPOs [420,422,424,428,433,434,438].

In the literature, polypharmacy may be one of the most frequently mentioned factors as a predictor of PIMs. However, the number of prescribed medications has also been identified in previous studies as a potential factor contributing to PIMs [421,422,427,431,435], being a common predictor of PIM in both age groups. Still, the negative association of cerebrovascular disease in the youngest-old and chronic pulmonary disease in the oldest-old requires further investigation.

Concerning PPO, the oldest group had the number of comorbidities as a predictor. However, the comparison with the literature is more difficult to establish as the authors tested different variables related to different comorbidities. Nevertheless, several studies found predictors of PPO

associated with comorbidity, either CCI [421,431], CCI ≥ 2 [303,444], or multimorbidity [422,424]. For the youngest group, the male gender was more likely to have PPOs, which has also been reported in other studies [429], but it is not consistent in the literature [428].

IV.4.3. Strenghts and limitations

The multicenter character of this study is a strength, as patients from eight different UCCIs of post-acute and long-term care were included. However, the small sample size may be the main limitation of the present study, preventing the generalization of the results obtained. Furthermore, being an observational study, it does not allow for the exploration of possible improvements that could be achieved through reviewing patients' therapy and analyzing the potential outcomes obtained with this intervention.

Data were mainly collected using an online tool used by each UCCI, which contributed to the homogeneity of the information obtained. However, it could only be complemented when other sources were available.

The selection of a subset of STOPP and START indicators, rather than the total, was a valid strategy to avoid analyzing potentially incomplete information. Despite further difficulties in comparisons between studies, this practice has also been successfully applied in other published studies [429,430,441].

All referred diagnoses (coded by ICD-9-CM or not) were analyzed to gather all patients' comorbidities, but a time reference was not always available. In addition, for the counting of comorbid diseases, only those included in the CCI were considered, which does not allow the achievement of the total number of conditions for each patient. This finding could justify the highest prevalence of PIM in the oldest-old, as this is probably the age group with a higher number of chronic conditions.

IV.4.4. Implication for research and/or practice

Our study also alerts to the high prevalence of PIMs and PPOs in an older population, encouraging the periodic review of patients' therapeutic lists, with a special focus on the most common PIM and PPO and their prevalence. When the initial holistic analysis of the patient's health status and history is made by the physician, screening at admission would probably be an appropriate strategy. However, it is also important to recognize that the STOPP/START criteria should be used as part of an overall approach in which the physician's judgment is paramount and can never be overridden.

Despite being a study with a small sample, this may be the only Portuguese study that focuses on the oldest age group, highlighting the need for further investigation. Generally, national data exist

but are scarce [417,436,471]. The recent adaptation of the STOPP/START criteria to a Portuguese version [472,473] may be an important step towards the simplification of the application of the criteria and the enrichment of national research.

IV.4.5. Future perspectives

STOPP/START and other explicit criteria have been increasingly used but more has to be done. Thus, it is essential to explore the clinical relevance of using screening tools to detect possible inappropriate drugs, performing prospective long-term studies to assess either the decrease in mis/over and underuse of medication that can be achieved with closer supervision, but also the relationship between inappropriate prescribing and negative outcomes.

The clinical usefulness of the STOPP/START criteria has been proven. Gallagher *et al.* [446] showed that their use significantly improved medication appropriateness in 400 hospitalized patients. Later, O'Connor *et al.* [474] revealed a significant reduction in the incidence of ADRs incidence and costs related to medication in the intervention group. Furthermore, Hill-Taylor *et al.* [410] reviewed randomized controlled studies and concluded that the STOPP/START criteria could effectively improve the quality of prescribing and clinical, humanistic, and economic outcomes.

Therefore, it is essential to improve these criteria to guarantee that the screening is quick and reliable in the quotidian practice. First, it would be crucial to describe the ICD-9 and ATC classifications for conditions and drugs, and which criterion may be included, similarly to what was already done for the first version of the criteria [475]. This will allow not only to facilitate their application in real practice, but also to become more uniform to be used among authors. Then, computerizing the clinical processes of all patients using those codes for their diagnosis and a therapeutic list would make the screening much more straightforward. It would be ideal to create software or an online tool that would allow the addition of patient information with an automatic screening of PIMs and PPOs would be ideal. Preferably, it would offer fields for selection or completion with codes (ICD-9-CM and ATC) and clinical information requested by some criteria, such as estimated GFR, analytical data (serum K+, Na+, Ca2+), and blood pressure levels. Recent trials of STOPP/START criteria software show feasibility, but direct interaction between physicians and trained personnel is still needed to clarify specific STOPP/START recommendations for individual multi-morbid older patients [476].

The use of STOPP/START criteria may have some limitations with the existing large administrative databases. On the one hand, it should be preceded by appropriate validation [477]. On the other hand, it would only be possible to use subsets of the criteria, as some necessary information is likely to be missing. Despite that, the opportunities for large-scale research could be numerous and of paramount importance, as it could allow the investigation of the relationship between misuse, overuse, and underuse of medication with ADEs (e.g., hospitalization and death)

and their inherent costs. Bjerre *et al.* [464] have shown how this could be done, an example that must be replicated in other settings.

In summary, as future challenges, involving the pharmacist in decision making would be an important step, as in many institutions, the pharmacist does not play an active or critical role in prescribing. In addition, it would be important for professionals to have software available to support prescribing and generate important alerts that could anticipate the prescription of inappropriate drugs or alert patients to conditions that require assessment of the relevance of introducing as unprescribed drug. Finally, and most importantly, it would be possible to start by publicizing this tool and even creating multidisciplinary working groups (with physicians and pharmacists) that could in an initial phase, analyze selected patients in real time and, if it is not possible to carry out a complete screening immediately, select patients who have predictors and/or characteristics that make them more susceptible to inappropriate medication (e.g., those who are more heavily medicated, older, or have a greater number of comorbidities).

IV.5. Conclusions

The results of this study highlight the overall high prevalence of PIM and PPO in patients aged 75 years and older. The most common PIMs and PPOs were the same in both age groups. Still, the oldest-old (aged ≥ 85 years old) were significantly more likely to have PPO more frequently (vitamin D supplements in older people who are housebound or experiencing falls or with osteopenia). For the youngest- and oldest-old, the number of prescribed medications predicted the existence of PIM. Predictors of PPO were male gender, fall risk for the youngest old, and the number of comorbidities for the oldest-old. Analysis of the results could help plan a strategy focusing on specific targets, such as the most common PIM/PPO and patients with more medications and comorbidities. The STOPP/START criteria are a valuable tool for use in practice, but further research is needed to explore the association between inappropriate prescribing and ADEs as well as their costs.

Chapter V

General Discussion

Chapter V – General discussion

The work behind this doctoral thesis had several objectives, and it is essential to reflect on and analyze the various results described in the previous chapters. Therefore, the main aim of this general discussion is to synthesize the findings of the various studies, integrating them into a comprehensive, critical, and global analysis, to respond to the objectives initially proposed and improve the general understanding of this subject.

In line with European and global trends, Portugal has experienced a significant population aging, making the management of these patients and health systems more challenging. This necessarily requires a review and correlation of various concepts, such as chronic diseases, geriatric syndromes, polypharmacy, DRPs and inappropriate prescribing.

The truth is that, after an initial phase of intensive research into these various concepts, it was clear that it was important to deepen our knowledge of inappropriate prescribing in the Portuguese population, since international studies have shown some alarming results and it was important to understand what was happening in Portugal. To this purpose, the STOPP/START tool was chosen.

In addition, regarding the choice of target population, we decided to explore a solution implemented in Portugal less than 20 years ago: the Portuguese RNCCI. This network spans the private, public, and nonprofit sectors to deliver long-term, comprehensive, and coordinated services, offering continuous care in an integrated manner to people who are in a situation of dependency. It is a care solution that covers from convalescence to long-term care, in UCCIs, and also includes ECCIs, at home.

Therefore, while on the one hand this work was an opportunity to raise awareness of the RNCCI, on the other hand, the profile of the patients seems to be interesting for analyzing inappropriate prescribing, for various reasons: although they are not exclusively elderly, the prevalence of patients over 65 is significant; they are not in an acute care situation, but they are hospitalized; they are patients with probable conditions that cause dependence; and they are patients who potentially have chronic diseases and consequently are probably polymedicated.

Before analyzing the prescriptions, it was important to understand the RNCCI population. Thus, eight UCCI (coded A to H) were included, covering the three types of internment: 8.3% were admitted to UC (intended for stays of less than 30 days), 33.3% to UMDR (30-90 days), and 58.4% to ULDM (over 90 days). This proportion was very close to the national reality [378]. The studied population had a mean age of 78.4 ± 12.3 years, with 89.4% being over 65 years old. This percentage is similar to that reported at the time (84.5%) [378] and is closer to the most recently published data (83.4%) [478]. The female gender was predominant in our study, accounting for 59.4% of participants, which is in line with the national trend at that time (55.7%) [378], and more recently (55.4%) [478].

Published national reports include a variety of information. However, with regard to patient characterization, only demographic data and certain indicators were presented. The absence of information on clinical characteristics, such as medication or pathologies, is one reason why this thesis is important.

When categorized by anatomical and therapeutic classifications (see Table II.1 and Table II.4), the most commonly prescribed drugs fell into the following groups: drugs for the nervous system (including psycholeptics and psychoanaleptics), drugs for the digestive tract and metabolism (especially those for acid-related disorders), drugs for the cardiovascular system (such as diuretics, agents acting on the renin-angiotensin system, and lipid-modifying agents), and drugs for the blood and blood-forming organs (especially antithrombotic agents). These findings are consistent with those of other studies conducted in nursing homes and long-term care facilities, which also reported a high use of drugs targeting the nervous, digestive/metabolic, and cardiovascular systems [368,379]. Other medications commonly reported in the literature included NSAIDs [345,348,353,356,380] and antibiotics [380–382]; however, these were not prevalent in our study. This may be due to the fact that our data were collected at the time of patient discharge, a time when individuals are generally clinically stable. Another important point to note is that, according to previous research, several commonly prescribed therapeutic classes identified in our study have been associated with an increased risk of ADRs. These classes include cardiovascular agents [356,380,383,384], antidiabetics [356,357,380,383], analgesics [383], psycholeptics [356,380], diuretics [345,356,381], antithrombotics [351,353], and psychotropic drugs [351].

Comorbidities were initially investigated using the encoded diagnoses, based on ICD-9-CM codes, presented on the GestCare CCI platform, and only those that affected at least 5% of the total study population were reported. The most common comorbidities observed in our study (hypertension, heart failure, diabetes, osteoarthritis and related conditions) are consistent with those frequently reported in the literature: hypertension [385–387], heart failure [346,384,385], diabetes [346,384], and renal and rheumatic diseases [346].

However, this analysis alone seemed insufficient for an overall understanding of the patient's comorbidities. Therefore, the available medical records were examined, and the CCI was calculated, which showed a median value of 5 (see Table II.1).

The high number of comorbidities and CCI enabled us to anticipate the prescription of a high number of medications. This was confirmed, with CCI identified as a predictor of polypharmacy (defined as taking five or more medications). This is probably related to the fact that patients with more severe or numerous comorbid conditions often require more complex pharmacological treatments to manage their diseases.

Indeed, patients had a median of eight prescribed medications, and polypharmacy was identified in approximately 90% of cases (see Table II.1). There was significant variation in the prevalence

rates, which were 66.7% in UC patients, 93.3% in UMDR patients and 90.5% in ULDM patients. These results are slightly higher than those reported for older adults in residential care (67.4%), older outpatients (70%) [388], and nursing home residents (74%) [369], but they are comparable to rates observed in long-term care homes (91%) [389], hospital patients (87.5%) [390], older patients discharged from hospital (85.9%) [391], and even older patients with urgent ADR-related hospital admissions (86%) [392].

The literature reports a significant variability in the prevalence of polypharmacy across different care settings [379,389], a trend that is also evident in our findings. A comparison between Facilities E and H revealed a significant association between polypharmacy status and the facility of admission. This suggests that UCCIs themselves may predict polypharmacy and excessive medication use.

These findings emphasize the importance of regular monitoring and periodic prescription reviews in mitigating the risks associated with polypharmacy. The involvement of healthcare professionals in medication reconciliation could be crucial in promoting more appropriate medication use, and preventing or reducing polypharmacy. They also highlight the need for healthcare professionals to closely monitor patients with a higher burden of comorbidities.

In light of the previous results, it was important to establish whether high polypharmacy rates, comorbidities, or other factors were associated with inappropriate prescribing. Thus, the next step was to identify potentially inappropriate prescribing, PIMs and PPOs, by applying the STOPP and START criteria to patients aged over 65. The prevalence of PIMs and PPOs was similar among inpatients, at 85.1% and 81.4%, respectively.

In the Portuguese context, the application of the STOPP/START criteria remains limited. Nevertheless, some national studies have identified similar issues. For instance, Borges *et al.* [436] found PPOs in 68% of 91 elderly patients admitted to a stroke unit, and Moraes *et al.* [437] identified PIMs and PPOs in 74% and 29% of 100 hospitalized older adults, respectively. Furthermore, Costa *et al.* [417] documented PIMs in 75% of 161 elderly nursing home residents and PPOs in 43%.

Considering the international landscape, the prevalence of PIMs and PPOs in our study was generally higher than that reported in the literature. However, several factors could affect the reliability of direct comparisons. Gallagher *et al.* [303] reported PIM and PPO prevalence rates of 51.3% and 59.4%, respectively, across six European hospitals. Nevertheless, the results varied significantly between sites, with PIM and PPO prevalence reaching 77.3% and 72.7% in Geneva and Perugia, respectively. Furthermore, some studies used only a subset of the STOPP/START criteria [427,429,430], which could lead to underestimation [430] and make comparisons between studies difficult. Similarly, the prevalence of PPOs in our cohort (81.4%) was higher than that reported in other studies, which ranged from 34% to 65% [303,420–424,428]. These discrepancies may be partially explained by the care setting, as PIM and PPO rates vary

considerably across different healthcare environments. For instance, PIM prevalence has been reported to range from 15% to 46% among community-dwelling older adults [397,425,429], 21%-38% in primary care [302,403,404,430–432], and 48%-79% in nursing homes [433–435]. Similar patterns were observed for PPOs, with prevalence rates of 30% in community-dwelling [429], 23%-51% in primary care [302,431,432], and 42-74% in nursing homes [433–435].

In addition to the prevalence of PIMs and PPOs, it is interesting to note that there was an average of 2.8 PIMs and 1.9 PPOs per patient. This is noteworthy given that a recent study of acute care hospital patients reported an average of 3.55 PIMs and 0.72 PPOs per patient [418]. Despite the lower PIM count per patient, the overall prevalence of PIMs in our study (85.1%) exceeded the commonly reported rates of 35–77% in patients aged 65 and over [303,419–425,427,479].

Therefore, it is important to analyze the most common PIMs and PPOs. In our study, PIMs were most frequently associated with CNS drugs, particularly benzodiazepines, as drugs that predictable increase in the risk of falls and when used for longer than 4 weeks. PPOs, on the other hand, were frequently linked to omissions in the prescription of musculoskeletal and cardiovascular medications. The most frequent omissions included vitamin D supplements, calcium and vitamin D combinations, ACEIs, and antiplatelet agents.

The PIMs most frequently identified in our study were consistent with previous research findings. Benzodiazepines were among the most common drugs, as has been widely reported in the literature [403,404,420,423,424,427,432–434]. Other frequently implicated drug classes include neuroleptics [423,430,433], tricyclic antidepressants, anticholinergic/antimuscarinic agents [433], loop diuretics, and proton pump inhibitors [403,404,427,430,433].

Similarly, our analysis of the most common PPOs is consistent with the existing literature. These often involve vitamin D [438], vitamin D and calcium [420,422,424,428,433,434], ACEIs [423,438], antiplatelet therapy [423,428], beta-blockers, 5-alpha reductase, statins [420,423,428,433,438], laxatives, alpha-1 receptor blockers, and non-tricyclic antidepressants [422].

Narrowing the analysis to the three most frequent PIMs (D5, K1, and K2) and PPOs (A6, E3, and E5) would reduce the prevalence in our study to 69% for PIMs and 60% for PPOs. Notably, the top three STOPP criteria accounted for almost half (47%) of all PIMs detected (445 cases), whereas the top three START criteria contributed a similar proportion — 48% of all PPOs (302 cases) out of a total of 34 possible START criteria.

Then, it was important to establish whether there were any predictors of PIM or PPO that could act as early warnings. Female gender, hospital origin, and a higher number of prescribed medications were significantly associated with an increased risk of PIMs. Conversely, patients diagnosed with cerebrovascular disease or Parkinson's disease were less likely to receive PIMs. A higher CCI and a recent history of fractures were associated with an increased risk of PPOs, while

a diagnosis of Parkinson's disease or metastatic solid tumors appeared to offer protection against them.

Regarding the predictors of PIMs, our findings reinforce those in the literature, which consistently associate female gender with a higher risk of PIMs [439–441]. Polypharmacy also emerged as a key predictor, whether defined as the use of ≥4 [430,432], ≥5 [404,429], or ≥10 [303,424] or a higher overall number of medications [421,422,427,431,435]. Although the hospital provenance of patients was not directly tested, living in an institutional setting was recognized as a predictor of PIMs [422], as well as a longer stay in a nursing home [442].

Depression has been cited as a risk factor for PIMs among comorbidities [443]; however, in our study, its significance was limited to unadjusted analyses. Interestingly, cerebrovascular disease appeared to offer protection against PIMs, potentially because of closer medical supervision and regular medication reviews [346]. Parkinson's disease has also been associated with a lower risk of PIMs, although a clear explanation has yet to be established.

Concerning PPOs, they were associated with high CCI values, which is in accordance with previous studies, since the most frequently mentioned factors were comorbidity [421,431], a CCI value equal to or higher than 2 [303,444], and multimorbidity [422,424]. Fractures have also been identified as predictors of PPOs [420]. Conversely, our study identified Parkinson's disease and metastatic solid tumors as protective factors for PPOs.

Although no additional significant predictors were identified, the literature has highlighted other potential factors. For PIMs, these included a history of falls and prior hospitalizations [421,422]. For PPOs, the relevant factor was advanced age, specifically, being aged 75 years or over [432] or 85 years or over [303].

Taking these results into account, certain characteristics of our study population may have influenced the high rates of PIMs and PPOs. Specifically, the median number of daily medications taken was nine [6; 11], which is higher than that in many previous studies [302,419,422,423,431,434,435,437]. Similarly, the median CCI in our sample was 6 [5–7], which exceeds the values reported in other studies [303,421,431]. These factors are recognized predictors of inappropriate prescribing and may help explain the elevated prevalence of PIMs and PPOs.

In addition, the literature has already reported that polypharmacy, underuse, and misuse are highly prevalent in the oldest adults [459], and that advanced age is associated with PPOs [303,432].

Besides, given that an aging population may be more dependent and have more comorbidities, there could be more prescribed medications. Based on previous results, we might expect a higher prevalence of PIMs and PPOs in the older population. Thus, our final objective was to determine

and compare the prevalence of PIMs and PPOs, as well as their respective predictors, in patients aged 75–84 years and those aged ≥ 85 years old admitted to the RNCCI.

Comparing both age groups, patients aged ≥ 85 years old were less likely to came from a hospital and were prescribed fewer daily oral doses of medication. However, they had a higher CCI, were more frequently classified as having a CCI of at least 6 and showed greater dependency in ADLs. They also had lower rates of obesity than the 75–84 age group.

Hypertension was the most prevalent chronic condition in both age groups. Among patients aged 75–84 years old, diabetes mellitus, depression, and constipation were also commonly observed. In contrast, urinary incontinence, cerebrovascular disease, and dementia were more prevalent among patients aged ≥ 85 years old. The most prescribed therapeutic subgroups in both age groups were antithrombotic agents, medications for acid-related gastrointestinal disorders, and psycholeptics; however, the order of prevalence differed between the two groups. Drugs for hypertension were not among the top three, likely due to the variety of clinical options available (e.g. diuretics, renin–angiotensin system agents, beta-blockers, and heart failure medications).

Psycholeptics were commonly prescribed to both age groups, despite their association with an increased risk of falls and classification as PIM for elderly patients. Similarly, medications for acid-related disorders were frequently prescribed, even though many patients did not have a history of peptic ulcers, likely due to the concurrent use of medications that increase the risk of gastrointestinal problems, such as antithrombotics, corticosteroids, or NSAIDs.

PIMs and PPOs were highly prevalent in both age groups, at 88.6% and 79.7%, respectively, for the 75–84 age group, and at 85.7% for both in the ≥85 age group. No statistically significant differences were found between the two groups. The slightly lower PIM prevalence in the oldest group may reflect physicians' increased caution when prescribing to this age group. However, the PIM index was higher in the older group, suggesting that patients aged 75–84 years may have received more appropriate prescriptions. Regarding PPOs, no significant difference was observed in the youngest-old group, but their prevalence was higher among the oldest-old patients, possibly due to their greater burden of comorbidities.

The three most common PIMs in both age groups were benzodiazepines that increase the risk of falls, long-term benzodiazepine use (≥4 weeks), and neuroleptics associated with an increased risk of falls. A similar pattern was observed for PPOs: vitamin D supplementation for housebound patients or experience falls or have osteopenia; vitamin D and calcium for patients with osteoporosis or prior fractures; and ACEIs for patients with systolic heart failure or coronary artery disease. These results are consistent with those of previous studies.

Implementing an intervention to address and eliminate the three most prevalent PIMs and PPOs would significantly reduce their prevalence in the future. PIMs and PPOs could drop to 74.7% and 62.0%, respectively, in the 75–84 age group, and to 64.3% for both in the ≥85 age group.

Consequently, the proportion of patients without PIMs or PPOs would increase from 3.8% to 13.9% in the youngest-old group and from 3.6% to 10.7% in the oldest-old group.

Regarding studies that compare age groups, San-José *et al.* [424] examined hospitalized patients aged 75–84 and those aged ≥85 years old. They found PIM and PPO prevalence rates of 60.5% and 49.6% respectively in the youngest-old group and 63.4% and 53.7%, respectively, in the older group. Although these are the lowest results, they could be much closer to ours by reassessing the six criteria mentioned above (three PIMs and the three most prevalent PPOs). Among individuals aged 80 and over, Dalleur *et al.* [468] reported a PIM prevalence of 59% and a PPO prevalence of 41%, whereas Wauters *et al.* [459] found a PIM prevalence of 67% and a PPO prevalence of 56%. They also noted that PIMs and PPOs coexisted in 40% of patients, with the conditions being absent in only 17% of cases. This is a better outcome than that observed in our study. In our study, coexistence was found in 72.2% of patients in the youngest-old group and 75.0% in the older group. Only 3.8% and 3.6% of patients in these groups were free from inappropriate prescribing, respectively. Lower prevalence rates are typically observed in primary care settings, probably due to reduced polypharmacy reported (61% [468] and 58% [459]) compared to both age groups of hospitalized patients (90.6% and 93.4%) [424] and in our own findings (reported at 92.4% and 89.3%). Interestingly, some international studies involving very elderly patients reported a higher prevalence of PIMs than PPOs [424,459,468], which contrasts with our findings. In our study, PPOs were more prevalent than PIMs in the youngest-old group, while in the oldest-old group, PPOs exceeded PIMs by 6%. The only statistically significant age-related difference concerned the most common PPO, which was vitamin D supplementation for housebound patients or those with falls or osteopenia. This was more frequently omitted in the older group. This could reflect prescribers' reluctance to prescribe additional medications to older adults who are already taking a lot of medication.

The number of medications was a predictor of the existence of PIM, considering the total population and within both age groups. This followed the same trend as the literature already reported in the previous point. Additionally, PIM was also associated with cerebrovascular disease in the 75–84 age group and chronic pulmonary disease in the ≥85 age group, which warrant further investigation. For PPOs, male gender and fall risk were predictors in the youngest-old group. The association between the male gender and PPO was supported by some studies [429], but not by all [428]. In contrast, in the older group, the number of comorbid conditions was significantly associated with PPOs, which is consistent with prior findings also already reported. This may help explain why, surprisingly, underuse rather than misuse was strongly associated with mortality and hospitalization in patients aged over 80 years old [459].

Chapter VI

Conclusions and future perspectives

Chapter VI – Conclusions and future perspectives

Our study adds to the limited knowledge available on the demographic and clinical characteristics, medication use patterns, prevalence and predictors of polypharmacy, and prevalence and predictors of potentially inappropriate prescribing within the RNCCI.

In brief, the main key findings derived from the retrospective study conducted throughout this thesis are summarised below:

- Firstly, the analysis of the total population of 180 patients from eight UCCIs belonging to the RNCCI revealed that: patients had a mean age of 78.4 ± 12.3 years (ranging from 23 to 102 years), 59% were female, and had a median of eight prescribed medications; around 90% of these patients met the criteria for polypharmacy, which is defined as the use of five or more drugs; the most prescribed drug classes were those belonging to the nervous system, the alimentary tract and metabolism, the cardiovascular system, and the blood and blood-forming organs; and the polypharmacy status was significantly associated with the unit of internment (facility) and with the CCI;
- Then, the STOPP/START criteria were applied only to the 161 patients aged 65 years or over, revealing that: PIM and PPO are very common, with a prevalence of 85.1% and 81.4%, respectively; the most prevalent PIMs involved the CNS and psychotropic drugs, with benzodiazepines being the most identified, as drugs that increase the risk of falls and because they have been used for more than 4 weeks; PPOs more common were related to treatments affecting the musculoskeletal and cardiovascular systems, being associated with vitamin D supplements, calcium–vitamin D combinations, ACEIs and antiplatelet agents; PIM was significantly associated with female gender, hospital origin, and a greater number of prescribed medications; in contrast to cerebrovascular disease and Parkinson's disease; PPOs were significantly associated with a higher CCI and a recent history of fractures, whereas Parkinson's disease and metastatic solid tumours appeared to have a protective effect; and the three PIM and PPO criteria most identified accounted for almost half of all inappropriate medications and prescribing omissions;
- Finally, and focusing only on the 135 patients aged 75 or over, it were created two age groups (75-84 years and ≥85 years), and it was found that: the oldest-old patients (≥85 years) were less likely to come from a hospital, had fewer daily medications and a lower number of oral doses, but they presented a higher CCI, were more dependent on ADLs, and were less obese than those aged 75–84 years; there is a high prevalence of PIMs and PPOs in both age groups; the more common PIMs and PPOs were the same in both age groups; the oldest-old patients were significantly more likely to experience PPOs, particularly the omission of vitamin D supplements in those who are housebound, have a history of falls, or suffer from osteopenia; the PIM index was not significantly different

between age groups but was higher in the oldest-old group; in both age groups, a higher number of prescribed medications was associated with an increased likelihood of PIMs; and regarding PPOs, male gender and fall risk were predictors to the patients aged 75–84 years, while the number of comorbidities was a predictor to the oldest-old patients (≥85 years).

The initial warning was the high global prevalence of polypharmacy. Identifying predictors offered valuable insights for clinical practice. On the one hand, the fact that the facility itself can influence the number of drugs prescribed reinforces the idea that therapeutic regimens can be improved. Conversely, identifying the CCI as a predictor of polypharmacy may encourage its use, leading to greater attention being paid to patients with higher scores. Subsequently, the high incidence of PIM and PPO was another important finding. Identifying predictors of PIM alerts us to the fact that female, patients who have been discharged from hospital and/or have been prescribed a greater number of drugs are at greater risk and can therefore be identified earlier for specific interventions. Of these predictors, the number of prescribed drugs is potentially modifiable, so the unnecessary or harmful ones could be desprescribed. In addition to prevalence, it was important to understand that a higher CCI and a recent history of fractures are predictors of PPO. These factors are not modifiable, but they could facilitate screening patients at greater risk. As expected, high prevalence rates were observed in both age groups for PIM and PPO, but they were not statistically different. Nevertheless, it is important to note that the three most frequent criteria contributed to almost half of the overall prevalence, and that the most frequent PIM and PPO were the same in both the overall population and in each of the two age groups. This finding is another ally for improving therapeutic regimens. Patients prescribed benzodiazepines and neuroleptics should undergo an initial PIM screening. Furthermore, practitioners should be especially cautious of PPO in patients with systolic heart failure, coronary artery disease, osteoporosis, a history of fragility fractures, or who are housebound, experience falls, or have osteopenia.

These findings emphasise the importance of regular monitoring and periodic prescription reviews in mitigating the risks associated with polypharmacy and promoting more appropriate medication use. These insights can guide the creation of targeted strategies to address the most common PIMs and PPOs, particularly in patients with polypharmacy and multiple comorbidities. This highlights the need for healthcare professionals, especially within multidisciplinary teams, to closely monitor patients with a higher burden of comorbidities. Their involvement in medication reconciliation could be crucial in preventing or reducing polypharmacy.

Thus, despite the contribution of this thesis, there is still a lot of work to be done in the field of inappropriate prescribing:

- To apply the STOPP/START criteria on a larger scale, covering more patients;
- To consider other target populations, namely community-dewling, nursing homes and patients admitted to central or peripheral hospitals;

- To investigate the most common adverse effects associated with PIMs;
- To understand the main consequences associated with PPOs;
- To carry out prospective studies with intervention, in order to understand the impact of identifying PIM and PPO in clinical practice, analyzing the relevance of each one's suggestions based on the STOPP/START criteria and taking into account each individual patient;
- To study the economic impact of the identified PIMs and PPOs, either directly by not administering the drug involved in each PIM, or by preventing or not causing a particular drug-related problem;
- To develop or improve existing software, in order to facilitate, standardize and optimize the application of the STOPP/START criteria, both at the beginning of the prescription and in the routine medication review.

Therefore, there is an undeniable need for more research into the impact of specific interventions by healthcare professionals on medication use. The aim of this research is to improve the overall results of drug therapy and achieve health gains.

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