Universidade de Lisboa

Faculdade de Farmácia

Patient Safety: Cardio and Cerebrovascular Risk of Major Adverse Events following exposure to Potentially Inappropriate Medications

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Orientadores: Prof. Doutora Filipa Alves da Costa
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Prof. Doutor Hubert G.M. Leufkens

Tese especialmente elaborada para obtenção do grau de Doutor em Farmácia, na especialidade de Farmacoepidemiologia

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2022

DECLARATION

All the research presented in this thesis was conducted under the supervision of the ***Faculty of Pharmacy, University of Lisbon***, Portugal, with the collaboration of the ***Division of Pharmacoepidemiology and Pharmacology from the Utrecht Institute for Pharmaceutical Sciences, Utrecht University***, The Netherlands, under the supervision of ***Professor Filipa Alves da Costa***, Assistant Professor at the Faculty of Pharmacy, University of Lisbon, ***Professor Ana Paula Martins***, Assistant Professor at the Faculty of Pharmacy, University of Lisbon, and ***Professor Hubert Leufkens***, Full Professor at the Division of Pharmacoepidemiology and Pharmacology from the Utrecht Institute for Pharmaceutical Sciences, Utrecht University. ***João Pedro Teixeira Aguiar***, who was awarded with a PhD grant from Fundação para a Ciência e a Tecnologia (FCT – SFRH/BD/132785/2017), participated in the conception and implementation of all studies as well as in the analysis, interpretation of data, and preparation of all themanuscripts forming the present dissertation. Full acknowledgements have been made where thework of others has been cited or used.

To

My beloved parents, Maria Adelaide and João

My brother, Bruno, and my Niece, Beatriz

My nanny, Cecília, and my aunt, Lurdes

"Most innovations are not obvious to other people at the time. You have to believe in yourself. If you've got a good idea, follow it even when others say it's not"

– Frances Arnold –

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LIST OF ABBREVIATIONS

AAP	Atypical Antipsychotic
ACS	Acute Coronary Syndrome
ADE	Adverse Drug Event
ADME	Absorption, Distribution, Metabolism and Elimination
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
aOR	Adjusted Odds Ratio
AP	Antipsychotic
ATC	Anatomical Therapeutic, Chemical
BPSD	Behavioral and Psychiatric Symptoms in Dementia
CCVAE	Cardiac and Cerebrovascular Adverse Events
CDSS	Clinical Decision Support System
CHD	Coronary Heart Disease
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX-II	Cyclooxygenase-II
CVD	Cardiovascular Disease
DRP	Drug-related Problem
EKG	Electrocardiogram
EMA	European Medicines Agency
EPS	Extrapyramidal Symptoms
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
HCP	Healthcare Professional
HF	Heart Failure
ICC	Intra-class Correlation Coefficient
ICH	International Council for Harmonization
ICSR	Individual Case Safety Report
IHD	Ischaemic Heart Disease
LTCF	Long-term Care Facility

MACCE	Major Adverse Cardiac and Cerebrovascular Events
MAI	Medication Appropriateness Index
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MSE	Metabolic Side Effects
NORGEP	The Norwegian General Practice
NORGEP-HN	The Norwegian General Practice – Nursing Home
NPCCD	National Programme for Cardio and Cerebrovascular Diseases
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds Ratio
PD	Pharmacodynamics
PFR	Patient-related feature
PICO	Population, Intervention, Comparator, and Outcome
PIM	Potentially Inappropriate Medication
PIP	Potentially Inappropriate Prescribing
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROR	Reporting Odds Ratio
RR	Relative Risk
SIHD	Stable Ischaemic Heart Disease
SMART	Sensitive, Measurable, Attainable, Relevant, and Time-bound
SmPC	Summary of Product Characteristics
TAP	Typical Antipsychotic
TCA	Tricyclic Antidepressants
UMC	Uppsala Monitoring Centre
US	United States
WHO	World Health Organization
WHO-ART	World Health Organization Adverse Reaction Terminology

ABSTRACT OF THE THESIS

Chapter 1 introduces what is known about the current challenges of medication management in the elderly, with a special focus on management of potentially inappropriate medications (PIMs) in clinical practice. Available evidence on PIMs with cardiac and cerebrovascular risk of adverse events, especially in terms of major outcomes (Major Adverse Cardiac and Cerebrovascular risk of Adverse Events – MACCE), is described. To answer to gaps in the knowledge identified during the literature review, a systematic review was conducted, described in **Chapter 2.1**, which showed that PIM-lists focus mainly on common adverse events and often poorly describe the potential consequence for MACCE occurrence. To evaluate the extent of utilisation of such medications in older individuals, we conducted a prevalence study in ambulatory care and in long-term care facilities, described in **Chapter 2.2**, where we found that 59.4% patients were taking medications with Cardiac and Cerebrovascular Adverse Events (CCVAEs) risk, including 38.8% who used drugs with MACCE risk. Fifty percent of patients with a previous history of cardiovascular diseases were taking PIMs with risk of CCVAEs, including 30.0% with risk of MACCE. We also found a high proportion of patients using antipsychotics (APs), described as PIMs in the literature. In order to establish the mechanisms that may be linked to the occurrence of these events when using APs, we conducted a case/non-case study in a global pharmacovigilance database (**Chapter 3.1**). We found that APs with high affinity for Adrenergic alfa-1, Histaminic H_1, Muscarinic M_1, and Serotoninergic 5-HT_{2A} receptors and with high-risk of metabolic side effects profile may explain the occurrence of those events. In **Chapter 4.1 and 4.2**, we have explored the knowledge of healthcare professionals (HCPs, including physicians, pharmacists, and nurses) on medication complexities among the elderly population, and the barriers experienced in managing these, particularly in managing PIMs. In this chapter, we also explored the patient-related features (PRFs) that should be considered when initiating treatment with APs in older individuals with dementia, and aspects to be focused during treatment monitoring. In **Chapter 4.1**, we found that most HCPs felt confident to manage medication complexities in elderly patients with dementia, but only a minority obtained a good score in the knowledge assessment test. The main barriers identified included structural barriers (tools unfit for practice) and process barriers (time), suggesting education per se will not necessarily lead to optimised pharmacotherapy in the elderly. Moreover, it seems that new tools, like clinical decision support systems (CDSS), are needed to facilitate the work of HCPs in daily practice, helping them to stratify the risk of adverse drug reactions (ADRs) when prescribing specific drugs. In **Chapter 4.2**, we found that, even though a high number of PRFs were rated as clinicallyrelevant, some of them were identified as frequently missing from electronic medical records. **Chapter 5** discusses all the results from the previous chapters. Overall, the conducted research

shows person-centred tools are needed to consider the heterogeneity inside this population subgroup, as the ones available nowadays are more focused on the medication itself or even on different subgroups defined by comorbidities. Moreover, for such tools to be implemented in clinical practice, they need to be embedded into the software system and resort to data linkage, so that the full potential of electronic records is gauged. To consider a more tailored approach, a stratification risk calculator along within an electronic decision-making support would be of great interest to foster safe prescribing of medications in the elderly, particularly among those with dementia.

Keywords: Polypharmacy; Potentially Inappropriate Medications; PIM-tools; Elderly; Dementia; Healthcare Professionals

RESUMO DA TESE DE DOUTORAMENTO

O **Capítulo 1** faz uma contextualização teórica sobre os atuais desafios na prescrição de medicamentos nos idosos, com foco especial nos Medicamentos Potencialmente Inadequados (PIMs – *Potentially Inappropriate Medications*). É apresentada a evidência disponível sobre PIMs com risco cardio e cerebrovascular de eventos adversos (CCVAEs – *Cardiac and Cerebrovascular Adverse Events*), com especial enfoque nos efeitos adversos *major* (*Major Adverse Cardiac and Cerebrovascular Risk of Adverse Events* – MACCE). Para responder às lacunas identificadas durante a revisão da literatura, foi realizada uma revisão sistemática, descrita no **Capítulo 2.1**, que demonstrou que as listas de PIMs disponíveis focam sobretudo eventos adversos comuns e muitas vezes pouca referência fazem a eventos considerados graves, como é o caso dos MACCE. Tendo identificado quais os PIMs com risco de MACCE, foi então altura de avaliar a prevalência desses medicamentos numa amostra de idosos, tendo-se realizado um estudo transversal nos cuidados de saúde primários e em residências séniores (**Capítulo 2.2**). Verificou-se que 59,4% dos idosos utilizavam medicamentos com risco de ocorrência de CCVAEs, sendo que 38,8% usavam medicamentos com risco de ocorrência de MACCE. Cinquenta por cento dos idosos com história prévia de doenças cardiovasculares utilizavam medicamentos com risco de CCVAEs, sendo 30,0% associado a MACCE. Também se verificou uma elevada proporção de idosos sob antipsicóticos (APs), sendo estes descritos como PIMs na literatura. Com o intuito de estudar quais os mecanismos que podem estar relacionados com a ocorrência desses eventos durante a utilização de APs, realizou-se um estudo de caso/não caso com recurso a uma base de dados de Farmacovigilância mundial (**Capítulo 3.1**). Verificou-se que os APs com alta afinidade para os recetores adrenérgicos alfa-$_1$, histamínicos H_1, muscarínicos M_1 e serotoninérgicos 5-HT_{2A} e com um perfil metabólico de alto risco podem explicar a ocorrência desses eventos. Nos **Capítulos 4.1 e 4.2**, exploramos o conhecimento dos profissionais de saúde (HCPs – *Healthcare Professionals*, incluindo médicos, farmacêuticos e enfermeiros) sobre as complexidades terapêuticas na população idosa e as barreiras enfrentadas durante a sua gestão, particularmente no caso dos PIMs. Nestes capítulos, também exploramos as possíveis características do doente (PRFs – *Patient-related features*) que devem ser consideradas ao iniciar o tratamento com APs em idosos com demência e os aspetos a serem considerados durante a monitorização do tratamento. No **Capítulo 4.1**, verificou-se que a maioria dos HPCs se sentia confiante na gestão das complexidades terapêuticas nestes doentes, mas apenas uma minoria obteve uma boa pontuação no teste de avaliação de conhecimento. As principais barreiras identificadas incluíram barreiras estruturais (ferramentas pouco práticas) e barreiras de processo (tempo), sugerindo que a educação por si só não levará necessariamente a melhorias na gestão dos PIMs. Além disso, parece que novas ferramentas, como os sistemas de apoio à decisão clínica (CDSS – *Clinical*

Decision Support Systems), são necessárias para facilitar o trabalho dos HCPs na prática clínica, ajudando-os a estratificar o risco de ocorrência de reações adversas a medicamentos (RAMs) quando prescrevem medicamentos específicos. No **Capítulo 4.2**, verificou-se que, embora um grande número de PRFs tenha sido classificado como clinicamente relevante, alguns deles foram identificados como estando frequentemente ausentes dos registos eletrónicos. O **Capítulo 5** discute todos os resultados dos capítulos anteriores. De uma forma geral, o projeto realizado demonstra que ferramentas centradas na pessoa são necessárias para considerar a heterogeneidade dentro deste subgrupo populacional, já que as disponíveis atualmente estão mais focadas na medicação ou em doenças específicas. Além disso, para que tais ferramentas sejam implementadas na prática clínica, elas necessitam de ser incorporadas nos *softwares* já disponíveis e possibilitar a integração dos dados. De forma a considerar uma abordagem mais personalizada, seria útil a conjugação de uma calculadora de estratificação de risco com um suporte eletrônico para a tomada de decisão e a promoção da prescrição de medicamentos em idosos de forma segura, principalmente entre aqueles com demência.

Palavras-chave: Polifarmácia; Medicamentos Potencialmente Inadequados; Listas de PIMs; Idoso; Demência; Profissionais de saúde

THESIS OUTLINE

This thesis is divided into five chapters. **Chapter 1** introduces the special features of the elderly population, alongside with the challenges, especially the management of PIMs, that they may introduce in the worldwide aging process. Additionally, paucity of information available on the literature linking exposure to PIMs and MACCE occurrence is also discussed. **Chapter 1** is finalized by presenting the rationale for this PhD project.

Chapter 2 is sub-divided into two sub-chapters – **Chapter 2.1** and **Chapter 2.2**. In general, this chapter explores what is already known about PIMs with risk of MACCE on the literature and on the field. In **Chapter 2.1**, a systematic review that aimed to identify and compile an extensive list of PIMs with risk of MACCE using tools addressing inappropriate prescribing (e.g., Beers criteria, START/STOPP criteria) will be presented. This list was used in **Chapter 2.2** to determine the prevalence of use of PIMs with CCVAEs, especially MACCE, by using a cross-sectional study in older adults from ambulatory setting and long-term care facilities.

Chapter 3 has only one study and intended to explore which pharmacological mechanisms may explain the association between MACCE occurrence and exposure to APs. APs were selected based on the results from **Chapter 2.1** and **Chapter 2.2**, where it was found that APs were one of the PIMs most used by older adults, and also one of PIMs with MACCE risk more reported in the tools addressing inappropriate prescribing. This chapter will present a case/non-case study to evaluate the association between receptor binding affinity and metabolic side effects profile of APs and the reporting of MACCE.

Chapter 4 is sub-divided into two chapters – **Chapter 4.1** and **Chapter 4.2**. In general, this chapter focuses on the transition of a more population-centred approach to PIMs management to a more personalized patient-centred approach. In **Chapter 4.1** a cross-sectional study is presented; this study intended to evaluate healthcare professionals' knowledge (real vs perceived knowledge) and practice (potential barriers to PIMs management in daily practice) about the optimization of pharmacotherapy in the elderly. Given that APs can be used for several indications in the elderly, in **Chapter 4.2** we have studied which patient's features could be more relevant to use when prescribing an AP to an older individual in terms of safety. We undertook a two-round Delphi survey to validate a set of indicators, i.e., patients' characteristics that may be sensitive, measurable, attainable, relevant, and time-bound (SMART) to foster a safe prescribing of APs in this population, comprising both treatment initiation and treatment monitoring. Additionally, a cross-sectional study was also undertaken to evaluate the exhaustiveness of medical records

regarding the indicators considered relevant for each of the selected drugs (haloperidol, olanzapine/risperidone, quetiapine, and aripiprazole), using a Portuguese Psychiatric Hospital.

Chapter 5 is the General Discussion, where the main findings of the studies presented in the previous chapters are discussed in light of the existing literature and celebrating on potential clinical implications and ways to improve patient safety that may be addressed by future research. Strengths and limitations and future research of the work conducted are acknowledged in this chapter.

CHAPTER 1

General Introduction

CHAPTER 1.1

The elderly and medication management: what cardiovascular challenges are we facing nowadays?

AGEING AND THE ELDERLY POPULATION

Worldwide ageing

The world is nowadays facing a demographic transition. In the beginning of the 20th century, infections and parasitic diseases were the major health treats. In the last years, the falling of fertility rates and the remarkable increase in life expectancy is accelerating population ageing.[1] Population ageing is the process by which older individuals become a proportionally larger share of the total population.[2] In 2010, an estimated 524 million people were aged 65 or older – 8.0% of the world's population.[1] This phenomenon is increasing rapidly, and it is estimated that by 2025 there will be a total of about 1.2 billion people aged 60 or older.[3] Individuals aged 80 or older are the fastest growing section of the population and are expected to reach, in 2050, 30.0% of the overall population in developed countries (**Figure 1.1.1**).[4]

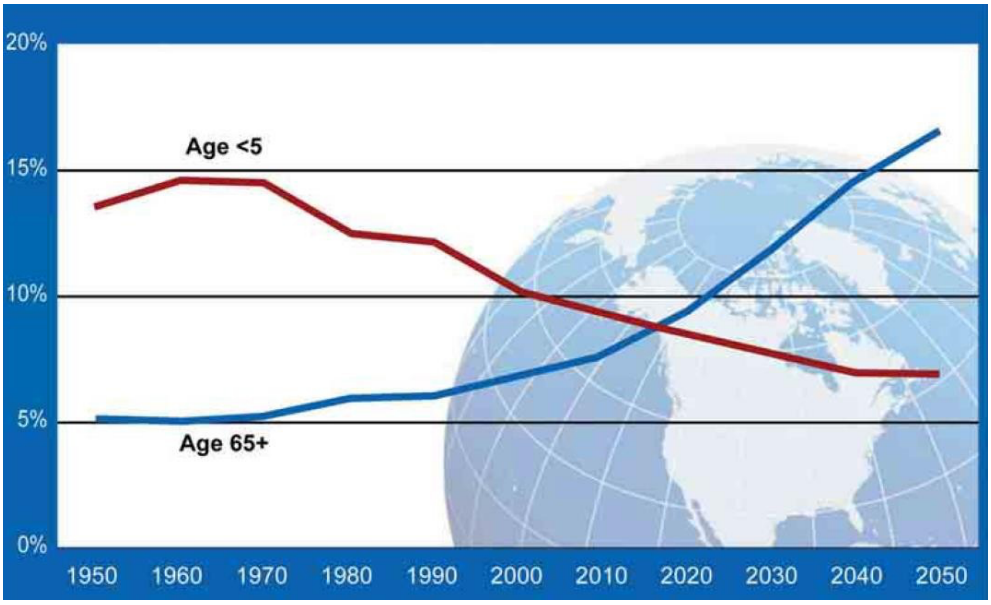

Figure 1.1.1 - Children and Older people as a percentage of Global Population: 1950-2050[1]

The elderly patient features

The elderly are conventionally defined, in developed countries, as individuals aged 65 or more. The International Conference on Harmonization considers the elderly as a special population. Inside this population, a special group is also defined: the frail elderly. Frailty is currently defined as a clinical state in which there is an increase in individual's vulnerability to developing negative health-related events (e.g., disability, hospitalizations, and death) when exposed to endogenous and exogenous stressors.[5] Nevertheless, given the ageing population, shift in the "elderly patient" term is now appearing in many studies as over 70-80 years. This implies that this population will

be even less represented in trials. In the future, experts support the idea that further evidence will be needed to ensure proper management of this new "elderly population".[6]

Ageing is characterized by a progressive decline in the functional reserve of many organs and systems, which can influence drug disposition. Therefore, absorption, distribution, metabolism, and elimination (ADME) may be compromised. Absorption in the elderly may be decreased given the increase of gastric pH (consequence of reduced parietal cell function) and the delayed gastric emptying. Decrease in the absorption surface can also compromise the bioavailability of drugs in the bloodstream. Changes in drug distribution are also important. Increased body fat, decreased lean body mass, decreased in total body water, decreased serum albumin, and increased α_1-acid glycoprotein are important physiological changes that can compromised distribution. For instance, increased body fat can increase the half-life of lipophilic drugs (e.g., morphine, benzodiazepines, antipsychotics, and amitriptyline) and decreased serum albumin can increase free fraction in plasma of highly protein-bound acidic drugs (e.g., warfarin, non-steroidal anti-inflammatory drugs – NSAIDs, and antipsychotics). Metabolism is normally decreased given the reduction in hepatic blood flow and hepatic mass. These changes may decrease first-pass metabolism and Phase I metabolism of some drugs (e.g., morphine, buprenorphine, midazolam, propranolol, nitrates, verapamil, and tricyclic antidepressants). Finally, changes in renal system can also play important role in elderly tolerance to drugs. Decreased renal blood flow and glomerular filtration rate can impair renal elimination of drugs (**Figure 1.1.2**).[5]

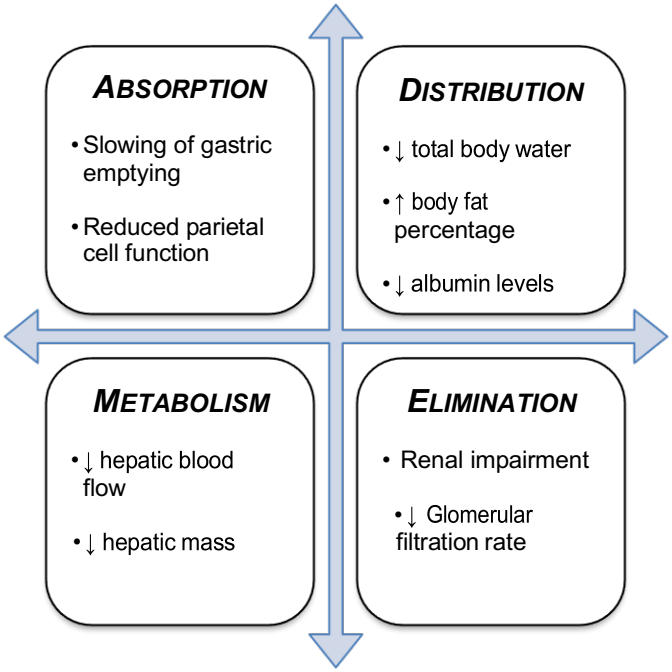

Figure 1.1.2 - Pharmacokinetic changes in the elderly

Pharmacodynamics is the study on how and which effect the drug can produce in a specific body site. Therefore, drugs exert their effects by binding as agonists, partial agonists, or antagonists to receptors within specific sites of human body. However, receptor expression, density, activity, and affinity change with age.[7] Since the effect of age on drug sensitivities varies with the drug studied and the response measured, generalizations are often difficult. The measurements of drug concentration in plasma are required to study drug sensitivity. Moreover, changes in pharmacokinetics with increasing age may increase or decrease changes in response to the drug.[8]

Multimorbidity affects 25.0% of the population and this proportion increases substantially with age. At present, 81.5% of people aged 85 or older experience multimorbidity, compared to 62.0% of those aged 65-74 years and 50% of those under 65 years old.[9] Multimorbidity is defined as the presence of two or more chronic conditions and most of the individuals aged 65 or more are at risk of experiencing this phenomenon. Multimorbidity currently poses a concern both in the clinical context, and for public health. Aside with increased number of co-morbidities, complexity of therapeutic regimens (including the number of drugs) also increases. This can lead to: a) decreased in life quality; b) decreased in self-reported health status; c) decreased in mobility and cognitive function; d) increased number of hospital admissions; e) increased mortality and health care costs.[10,11] Therefore, disease management is complicated since multiple treatments may be needed to treat different co-morbidities, and some of the drugs can interact with each other or even with underlying conditions. Thus, the elderly patient poses a challenge when it comes to multimorbidity management. Ischaemic heart disease, osteoarthritis, osteoporosis, type 2 diabetes, metabolic syndrome, chronic renal disease, Alzheimer's disease, and chronic obstructive pulmonary disease (COPD) are the most prevalent conditions among the elderly.[9]

CARDIO AND CEREBROVASCULAR DISEASES (CVD)

Epidemiology

The World Health Organization (WHO) identified cardiovascular diseases (CVD – which includes cardio and cerebrovascular diseases) as the number one cause of global mortality and approximately 80.0% of all CVD deaths are associated with heart attacks and strokes.[11,12] In 2015, an estimated 17.7 million people died from CVDs, representing 31.0% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. In Europe, CVD were responsible for 3.9 million deaths and over 1.8 million deaths in European Union (EU). This represents a total of 45.0% of all-cause mortality. Death rates of ischaemic heart disease (IHD) and stroke were higher in Central and Eastern Europe compared to Northern, Southern and Western Europe. In 2015, there were just fewer than 11.3 million new cases and more than 85 million people living with CVD.[13] In Portugal, CVD are one of the leading

causes of death[14], accounting for 29.5% of mortality in 2013.[15,16] CVDs are a group of conditions that affect the heart and the blood vessels of different parts of the body.[17]

CVD and the elder patient

Cardiovascular diseases are very common in the elder patient and are their leading cause of death. Coronary heart disease, congestive heart failure, stroke and atrial fibrillation are the most common CVDs in elderly.[6]

Coronary heart disease (CHD) is characterized by a blockage of the coronary arteries which can be caused by atherosclerosis and/or thrombotic obstruction. This condition can range from an asymptomatic event to an acute coronary syndrome (ACS) (unstable angina, acute myocardial infarction). Stable ischaemic heart disease (SIHD) refers to patients with known or suspected events who have no recent or acute changes in symptoms, which suggest no active thrombotic events underlying. CHD is the leading cause of death in the elderly: 81.0% of the deaths correspond to individuals aged 65 or more.[6]

Heart failure (HF) is a major public issue worldwide and is more common in the older individuals. At least 80.0% of this population suffers from HF and the prevalence and incidence increases with age. Contrarily to CHD, HF is the leading cause of hospitalization among elderly population.HF is defined as a progressive chronic disease where the heart is unable to pump enough blood to the body, compromising the blood and oxygen needs of different organs.[6,18]

Stroke is the second leading cause of death worldwide and the incidence increases with age. Up to 69.0% of the individuals aged 65 or older have suffered a stroke and the prevalence of this condition in individuals aged 75 or older is 34.4%. Stroke is an acute focal injury in the Central Nervous System (CNS) from a vascular cause, including ischaemic event, intracerebral haemorrhage, and subarachnoid haemorrhage. Nowadays, definition of stroke is not yet clear in clinical practice, despite its global impact.[19,20]

Atrial fibrillation (AF) is the most common arrhythmia in the elderly, and they represent 70.0% of all individuals diagnosed with AF. It affects commonly more women than men and increases the risk of stroke. AF is defined as an abnormal and irregular heart rhythm in which electrical signs are generated chaotically throughout upper chambers (atria) of the heart. This condition can be classified as paroxysmal (two episodes spontaneously terminates within 7 days), persistent (beyond 7 days), longstanding persistent (longer than 12 months) and permanent (refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means).[21]

To decrease the burden and mortality associated with CVDs, the WHO has implemented different policies, strategies, and interventions. Prevention is of major importance and combination of population-wide and individual healthcare strategies are required. Population-wide strategies would benefit not only people at high cardiovascular risk, but also prevent the transition of individuals with low-risk to higher-risk categories. Strategies to reduce the use of alcohol, comprehensive tobacco control policies and providing healthy school meals for children are examples of how to reduce the burden of CVD. At the individual level, controlling some of the risk factors can be an option to control or prevent this issue. For instance, the management of specific conditions as type 2 diabetes, hypertension, dyslipidemia, and atrial fibrillation can pose a challenge for clinicians as these risk factors can increase the odds of cardiovascular events. Lifestyle also plays an important role in the prevention of CVD. Cigarette smoking, alcohol consumption, unbalanced diet and physical inactivity are risk factors for CVD and addressing them can prevent the occurrence of CVD.[17]

In Portugal, a National Programme for Cardio and Cerebrovascular Diseases (NPCCD) has been developed and is currently considered a priority in national public health policy[17,22]. This program intends to characterize the mortality rates, incidence, and prevalence of CVD and to quantify the impact of different strategies and interventions on the control and prevention of CVD. The 2017 report of the NPCCD have concluded that:

1) there are less deaths due to CVD comparing to the previous decades;
2) between 2011 – 2015, stroke deaths were reduced by 39.0%;
3) between 2011 – 2015, hospitalizations due to heart diseases increased;
4) more drugs are used, but the overall financial burden of the National Health System is lower.[17]

PRESCRIBING FOR OLDER PATIENTS

Polypharmacy and its consequences

Aside with population ageing, often polypharmacy emerges.[2,23,24] Many definitions have been proposed but there is still controversy as they do not explicitly address the appropriateness and safety in relation to the number of medications used. In fact, polypharmacy is expected to worsen as the life span and multimorbidity pattern increases.[25]

Examining the word ***polypharmacy*** in a medical dictionary reveals that the word ***poly*** is derived from the Greek word, meaning more than one and ***pharmacy*** is derived from the Greek word *pharmacon*, meaning drug. Polypharmacy is normally defined as the use of multiple drugs or more than are medically needed (e.g., high-risk, or unnecessary medications). A recent systematic review has investigated the different definitions available in the literature, showing in their results

a large heterogeneity. The authors have divided the different definitions in two categories: numerical counts only and numerical counts for a given duration of therapy or setting. Forty six percent of the included articles have defined polypharmacy as the use of five or more medications, ranging from two or more medications to 11 or more medications. The addition of duration of therapy or healthcare-related setting has provided more specific definitions, but not any further clarity or consistency. In fact, the addition of duration of treatment has allowed the possibility to identify individuals who use chronic medications and are at high-risk of experiencing Adverse Drug Events (ADE). On the other hand, transitions of care, such as patient's admission and discharge, can also introduce and increase the risk of ADEs when coupled with polypharmacy. Polypharmacy definition has evolved over time, simply as more medications used or taken despite their clinical appropriateness. If a patient is taking too many medications, does not necessarily mean that they are inappropriate. In fact, they can be all clinically needed as well as appropriate. Therefore, polypharmacy should be seen as a starting point to identify patients with high-risk of Drug-Related Problems (DRPs), but medications should be further assessed in terms of their indication, efficacy, and safety, to foster deprescribing of inappropriate medication.[25,26]

In the US, among individuals aged 65 or older, from 1999-2000 to 2011-2012, polypharmacy increased from 24.0% to 39.0%.[27] In Europe, the prevalence of polypharmacy ranges from 33.8% to 73.3% depending on the definition used.[28] It has been reported to be between 25.0% and 35.0%.[11] Other studies have shown that, at least, 30.0% of the elderly are prescribed with five or more drugs. Polypharmacy is sometimes underestimated in different studies as they do not include medications without reimbursement or non-prescription medicines.[28]

Polypharmacy in long-term care facilities (LTCFs) is highly prevalent and presents considerable challenges to older residents, healthcare professionals and aged care providers. Polypharmacy has been defined as the use of five or more, nine or ten medications by residents of LTCFs and the prevalence varied widely, with up to 91.0%, 74.0%, and 65.0%, respectively. The prevalence varies considerably between facilities and geographical locations. The most prevalent drug classes were medications of the central nervous system (e.g., sedative/hypnotic/anxiolytic agents, antidepressant, antipsychotics), cardiovascular system (e.g., diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and lipid-lowering agents), alimentary tract and metabolism (e.g., laxative, vitamins/minerals, and antidiabetic), and blood and blood-forming organs (e.g., antithrombotic agents).[29]

In the last years, polypharmacy has become an important public health issue. Evidence from observational studies has shown that polypharmacy is normally associated with clinical consequences, including: a) increased healthcare costs; b) falls; c) ADEs; d) medication nonadherence; e) reduced functional capacity; and f) multiple geriatric syndromes.[10,25]

Potentially Inappropriate Prescribing

When a medicine enters the market, there is sufficient evidence of a favourable benefit-risk ratio. If ever through the lifecycle of the medicine, this ratio is reversed, the medicine is withdrawn from the market. However, the medicine may have a favourable risk ratio in the overall population but require special precautions in particular population subgroups. The observation of a distinct behaviour will determine for example a type I or type II change in drug approval, which in practice means that additional information must be made available to the citizens and/or clinicians to ensure a judicious use of the drug.[30]

Potentially Inappropriate Prescribing (PIP) is defined as the prescribing of medication that could introduce a significant risk of an ADR, when there is an equally or more effective alternative with lower risk available.[31] On the other hand, a Potentially Inappropriate Medication (PIM) is defined as any medication used where the risk outweighs the benefits, particularly when safer alternatives are available.[32] Both terms refer to the same issue, which is associated with different negative outcomes: a) adverse events; b) hospitalizations; c) morbidity and mortality; d) increased costs to the healthcare system.[31,32] Polypharmacy is different from inappropriate prescribing, but evidence suggests they are strongly associated.[10,25]

Aiming to respond to the resulting dangers of medication use in this vulnerable population group, inappropriate prescribing tools have emerged since the 90s. These tools were initially developed to guide prescribing and aimed to maximize efficacy and safety and minimize costs, hospitalizations, and mortality. Choosing the right medication for an elderly patient to achieve the therapeutic goals and safety, pose a difficult task for healthcare professionals. Physiological changes, pharmacokinetics/pharmacodynamics profiles in drug processing and other parameters are of extreme importance when prescribing in this specific population.

Tools developed in different countries show major differences in terms of structure and content. Traditionally, such tools may be classified as implicit, explicit, and mixed-approach tools. Implicit tools are more patient's oriented, and judgment based. They consider differences between individuals but their use in practice is more time consuming, require additional expertise in clinical pharmacy, and have low reliability. The Medication Appropriateness Index is an example of implicit criteria that aims to assess if a particular drug is appropriate for a specific patient. Explicit tools are normally drug-oriented or disease-oriented and are developed based on literature review, expert opinions, and consensus techniques. As they can be implemented with little or no clinical judgment, explicit criteria represent rigid standards of drugs that should not be used or that should be used with caution in the elderly. Different drug markets and guidelines make it hard to develop a single tool applicable and transferrable to all the globe.[33,34] Beers criteria, developed in 1991 and last updated in 2015, are one of the most used tools worldwide. In Europe,

the first explicit tool was developed in France (Laroche criteria). In 2008, Ireland has released the START/STOPP Criteria, which are nowadays widely used in different European countries. Nevertheless, these tools need to be update regularly to ensure their conclusiveness. **Table 1.1.1** summarizes the strong points and weakness of the different groups of criteria.

Table 1.1.1 – Overview of the characteristics of each group of criteria

Group of Criteria	Characteristics	Examples
Implicit Criteria	▪ Judgement-based ▪ Patient oriented ▪ Influenced by the physician's knowledge and experience ▪ Time consuming	Medication Appropriateness Index (MAI)
Explicit Criteria	▪ Developed based on literature search, expert opinion and consensus techniques ▪ Little or no clinical judgement ▪ Drug or disease oriented ▪ Higher reproducibility	Beers Criteria START/STOPP Criteria Laroche Criteria

The prevalence of polypharmacy and inappropriate prescribing (e.g., PIP or PIM) is normally estimated by applying these tools.[36-63] A systematic review has estimated an overall PIP prevalence of 22.6% (95.0% Confidence interval, CI – 0.0 to 98.0%) in Europe. The wide CI can be explained by the different drug market in each country, which makes hard to apply the tools outside the country where they were developed (e.g., Beers Criteria use in European countries). Different settings where the criteria were applied can also lead to broad values of prevalence (e.g., nursing homes usually present higher values of PIP prevalence when compared to primary care).[35] A Swedish study compared different tools to assess the PIM use prevalence and values varied between 16.0% (NORGEP criteria) to 24.0% (2012 Beers criteria).[64] A Portuguese study also compared prevalence using three tools (Beers criteria 2012 update; Beers Portuguese version dated 2008; and START/STOPP criteria), finding 85.1%, 60.3% and 75.4%, respectively.[65]

There are two main therapeutic groups represented in explicit criteria, the cardio and cerebrovascular system, and the central nervous system. A recent systematic review has identified which medications were more reported in 14 different explicit criteria developed in the last decade. Benzodiazepines, antihistamines, NSAIDs, antipsychotics and alpha-blockers are the most commonly medication described in the analyzed tools. The authors aimed to investigate

which of the drugs could be used in global criteria that could fit worldwide reality.[30] NSAIDs are one example of a pharmacological class that is widely used by older people[66] and is described in these tools, with an associated cardio and cerebrovascular risk. For example, ibuprofen has been associated with higher risk of stroke (Relative Risk – RR – 3.36; Confidential Interval – CI – 1.0 to 11.6), while etoricoxib (RR: 4.07; CI: 1.23-15.7) and diclofenac (RR: 3.98; CI: 1.48-12.7) were associated with higher risk of cardiovascular death.[67]

Several strategies have been developed and implemented to reduce inappropriate prescribing and polypharmacy. Deprescribing is defined as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.[68] This process often results as a natural consequence from medication review and educational programs directed at different HCPs. Although deprescribing presents potential value in clinical practice, studies have not been consistent in showing major improvements in patient related-health status. In fact, a systematic review has studied the impact of different interventions (e.g., structured pharmaceutical care programmes, medication review) in mortality, hospitalization, and changes in number of drugs. These strategies to reduce polypharmacy had no effect on all-cause mortality, and only few studies had a positive result in reducing of the number of hospital admissions. An overall decrease was found for the number of drugs after interventions in most of the included studies.[69]

ADVERSE DRUG EVENTS IN OLDER INDIVIDUALS

Prescription errors in the elderly may be a consequence of the pharmacologic changes, specially related to the PK/PD changes, inadequate orientations about drug change, dosage modification, and lack of information on medication safety.[21,22,70]

Sometimes, this age group is not included in clinical trials and, therefore, some safety issues cannot be generalized, calling for observational studies to supplement data available.[70] An ADR may be defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. In older people, ADRs can be sometimes difficult to recognize as they often appear in the form of unspecific symptoms (e.g., falls, fatigue, orthostatic hypotension).[2,70] ADRs are observed 2-3 times more often in the elderly and account for 5.0-17.0% of all hospital admissions.[5] A study in the United Kingdom, found that ADRs contributed to 6.5% of admissions and more than 50.0% of those were preventable.[70]

ADRs are normally classified in five groups (A-E), based on their relationship with medication. Type A ADRs are normally linked to the pharmacologic action of the medications and are,

therefore, predictable, and dosage-associated (e.g., drug-drug, drug-food, or drug-disease interactions). In type B group is the opposite, i.e., there is no relation to the pharmacological effect of the drug, or the dosage used, but the ADRs are more severe, less frequent, and unpredictable. Type C ADRs are normally associated with continuous exposure to the drug, whereas group D are linked to teratogenicity and carcinogenesis. Finally, type E appears when a drug is discontinued ("rebound effect"). Other classification systems can be used, which includes the approached proposed by Mallet and collaborators, which includes only three categories: ADRs caused by pharmacologic interactions; ADRs detected in patients who consume multiple medications and/or have multiple diseases; and the prescribing cascade phenomenon.[70]

Prescribing Cascades

Prescribing cascades are a type of problematic polypharmacy that often occurs when the side effect of a medication is interpreted as a new medical condition, resulting in a potential unnecessary drug being prescribed to treat this new condition.[6,71] This concept has been first observed in clinical practice and described in the Lancet (1995) and the British Medical Journal (BMJ, 1997) more than 20 years ago, and since then the scope expanded to include all drug prescribing that may lead to potentially unnecessary non-prescription medications or medical devices (**Figure 1.1.3**).[72]

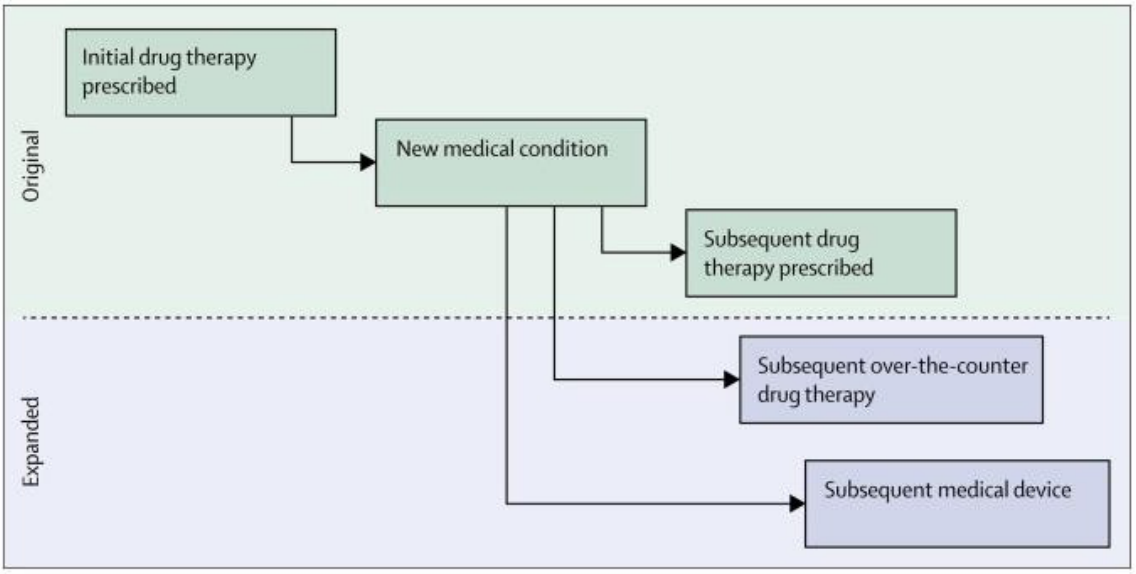

Figure 1.1.3 – The prescribing cascade definition and expanded definition[72]

Over this two past decades, some of the prescribing cascades have been described in the literature and can include the whole drug classes. NSAIDs and antihypertensive drugs are an example of drugs classes that are linked to a well-established prescribing cascade. It has been shown that the use of NSAIDs may be associated with initiation or intensification of antihypertensive

therapy.[71,73] Another established example is the use of antipsychotics and antiparkinsonian drugs, since the first ones can cause parkinsonism, which can be resolved by prescribing the second ones.[73] Even though, prescribing cascades can occur at any age, the elderly are more prone to this phenomenon since they are more likely to experience multimorbidity and polypharmacy, being up to four times more likely to experience adverse events than younger individuals.[71-73]

Prescribing cascades have been linked to drug-related adverse events, which may includesyncope, traumatic falls, invasive procedures (*e.g.,* pacemaker insertion), and drug toxicity. Functional decline and hospitalization were also examples of adverse events associated with prescribing cascades. A current study from Farrell et al (2020) showed that patients and healthcareprofessionals seem to struggle to recognize prescribing cascades and identify when they had occurred. Authors have also shown that knowledge gaps may have contributed to this challenge and led to inaction.[74]

Since prescribing cascades have been associated with adverse events and unnecessary costs, strategies to prevent, detect, and reverse this problem have been studied. A recent systematic review has identified several interventions that may help to prevent, detect, and reverse this issue in clinical practice. For example, the use of either health administrative data or social data could be useful tools to detect prescribing cascades. A study conducted in dementia patients used health administrative data to detect cholinesterase inhibitor (drug A)-anticholinergic drug (drug B) cascade, where the strategy was to identify new users of the drug A and controls and follow them over time to detect if drug B was dispensed.[71-74] In the study using social media data, the strategy was to detect tweets about adverse drug event or drug and tracing it forwards and backwards to examine other mentioned drugs or adverse events. Prevention of prescribing cascades can be made by increasing either prescriber or patient general awareness on this topic. Good prescribing practices were one of the solutions found to raise awareness on ADRs and drug safety, where polypharmacy and prescribing cascades where included. Another solution found, based on well-established prescribing cascades, was the use of lists describing the most common ones to alert healthcare professionals (e.g., physicians, pharmacists, nurses) on possible ADRs that patients may present when taking specific drugs. When a prescribing cascade is detected, it is important to know which steps should be implemented to reverse that situation. One of the examples provided was the use of deprescribing protocols, that tackle not only this phenomenon, but also problematic or inappropriate polypharmacy.[72-74]

Drug-drug and drug-disease interactions

Medications may be classified as PIMs *per se* or as interacting with other drugs (drug-drug interactions) or with specific diseases (drug-disease interactions). Either way, they are associated

with an increased risk of ADRs, functional status decline, increased use of health services, and mortality among older individuals. A cross-sectional study has evaluated the presence of drug-drug and drug-disease interactions among 3,055 community-dwelling older adults and found that 25.1% of them presented at least one drug-drug interaction. In 10.7% of those, a non-prescription medication was involved, and the most common interaction was between NSAIDs and antihypertensive drugs. Almost 16.0% presented drug-disease interactions, with 3.7% of them being associated with non-prescription drugs. The most common type of drug-disease interaction was aspirin/NSAIDs use in patients with previous history of peptic ulcer disease without gastroprotection. Each prescription medication increased the odds of having at least one type of drug interaction by 35–40% [drug–drug interaction adjusted-Odds Ratio (aOR)-1.35 (1.27–1.42); drug–disease interaction aOR-1.30 (1.21– 1.40); and both aOR-1.45 (1.34–1.57)]. A prior hospitalization increased the odds of having at least one type of drug interaction by 49–84% compared with those not hospitalized (drug–drug interaction aOR-1.49 (1.11–2.01); drug–disease interaction aOR-1.69 (1.15–2.49); and both aOR-1.84 (1.20–2.84).[75] A current systematic review has evaluated drug-drug interactions among older individuals in primary care, hospital, and nursing home settings. They found that the prevalence of PIM in primary care, nursing home and hospital were 19.1% (95% CI:15.1–23.0%), 29.7% (95% CI: 27.8–31.6%), and 44.6% (95% CI: 28.3–60.9%), respectively. Clinically significant severe risk-rated DDI averaged 28.9% (95% CI: 17.2–40.6), in a hospital setting; and were approximately 7-to-9 lower in primary care and nursing home, respectively.[76]

WHAT DO WE KNOW ALREADY ON PIMs AND CARDIAC AND CEREBROVASCULAR DISEASE?

To the authors' best knowledge, there are few studies investigating the use of PIMs among patients with cardiovascular diseases, but none of them seem to explore PIMs with potential risk for cardiac and cerebrovascular events, especially MACCE. A study conducted in the US, have included 404 older patients with cardiovascular diseases who were admitted to cardiology service with the aim of determining the frequency and factors associated with PIMs use (measured by using the 2015 update of Beers criteria). They found that 87.4% of the sample was using at least one PIM, with an average of 2.4 PIMs per patient. Heart failure, atrial fibrillation/flutter, history of falls/fractures, cerebrovascular accidents, and depression were associated with the use of more PIMs.[77] A recent Moroccan study have found that 84.0% of patients with previous history of cardiovascular diseases were receiving at least one PIM, after applying the 2015 update of Beers criteria. The most prescribed PIMs were drugs that may exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia (27.3%), NSAIDs use in patients under anticoagulants (21.2%), use of PIPs for more than 8 weeks (10.5%), and benzodiazepines

(5.7%)[78] Another study, using the same criteria, conducted in Pakistan has found that 67.4% of elderly cardiac patients were exposed to at least one PIM, being the most prescribed hydrochlorothiazide (21.5%), furosemide (17.1%), omeprazole (13.7%), and orphenadrine (6.7%).[79]

RATIONALE OF THE STUDY

Population ageing has introduced many challenges in current clinical practice. With life expectancy increasing, the elderly become an important share of the total population. Multimorbidity, polypharmacy and, consequently, inappropriate prescribing emerge as potential risk factors for increased mortality, hospitalization, and ADRs. ADRs have been associated with hospital admission and, at least, 50.0% of them are considered preventable.

The odds of MACCE occurrence as a result of exposure to PIM are considered scarce, although there is some controversy among the tools addressing inappropriate prescribing. The accurate identification of those medications (using the tools available in the literature) and the assessment of their cardio and cerebrovascular risk (using external databases), after drug exposure, are of major importance. Subsequently inclusion of this information in electronic clinical decision-support systems (CDSS) used by different healthcare professionals (e.g., physicians, pharmacists, and nurses) would have the potential to increase patient safety and decrease the cardiac and cerebrovascular associated mortality and morbidity.

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CHAPTER 1.2

Main Goals

MAIN GOALS OF THIS PhD THESIS

Since the elderly are the age group that consume more medications, the identification and management of PIMs in this population is of special importance as a safety concern. However, to the best of our knowledge, data on PIMs that could increase the risk of MACCE occurrence is still scarce. Therefore, our main goals were:

a) to identify and compile a list of PIMs that may be associated with CCVAEs, especially MACCE, and reported in tools addressing inappropriate prescribing;

b) to determine the prevalence of use of PIMs with MACCE risk among the elderly population from the outpatient setting and long-term care facilities;

c) to explore possible pharmacological mechanisms (e.g., receptor binging affinity) that may be associated with MACCE occurrence;

d) to study the knowledge and practice of different healthcare professionals about PIM management;

e) to compile and validate patient-centred indicators sensitive enough to foster safe prescribing of APs in the elderly, especially in patients with dementia; and to determine their exhaustiveness in the medical records of a Portuguese Psychiatric Hospital.

CHAPTER 2

Potentially Inappropriate Medications with risk of Cardiac and Cerebrovascular Adverse Events: what do we know?

PERSPECTIVE

The purpose of this chapter was to explore what is already known in the literature about PIMs involved in cardio and cerebrovascular adverse events, especially MACCE. To accomplish this goal, the first study explored which PIMs are known to be associated with such events and how often are they described in the literature, using a systematic review of tools addressing inappropriate prescribing. The second study evaluated the prevalence of use of such PIMs in the outpatient setting and in long-term care facilities, and which of those PIMs are more frequently found in the medical charts of the elderly patients included.

CHAPTER 2.1

Potentially Inappropriate Medications with risk of Cardiovascular Adverse Events in the elderly: a systematic review of tools addressing inappropriate prescribing

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ABSTRACT

What is known and objective: In the last decades, many lists have been developed to screen inappropriate prescribing. However, information on which potentially inappropriate medications (PIMs) could increase the cardiovascular risk in the elderly is not objectively presented. This review aimed to identify and quantify those PIMs by extracting information from published PIM-lists.

Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), a systematic review of PIM-lists was conducted. The search strategy was run in PubMed, MEDLINE, and Google Scholar (1991-09/2017). All PIMs described in those lists were extracted and stratified by their potential cardiovascular risk (including major adverse cardiovascular events – MACE). The number of times each PIM was reported on those lists was also assessed.

Results and discussion: We identified 724 papers, and 24 were retained. From those, a total of 17 PIMs to be avoided by the elderly and 21 drug-disease interactions were retrieved. The reporting of PIMs with risk of cardiovascular adverse events was 15.3%, whereas the reporting of those with MACE risk was 7.2%. PIMs most frequently described were tricyclic antidepressants (TCAs; 12/24), centrally acting anti-adrenergic agents (11/24), NSAIDs (7/24), antiarrhythmics (Class I and III; 6/24), peripherally acting antiadrenergic agents (6/24) and antithrombotic agents (5/24), peripherally acting antiadrenergic agents (6/24), and antithrombotic agents (5/24). Most frequently described PIMs with MACE risk were NSAIDs (7/24), antiarrhythmics (Class I and III; 7/24), selective calcium channel blockers with vascular effects (6/24), and antipsychotics (4/24).

What is new and conclusion: Data suggest that PIM-lists focus mainly on common adverse events and often poorly describe the potential consequence for MACE occurrence. This systematic review could help healthcare professionals in the identification and deprescribing of these medicines in older patients with high cardiovascular risk during medication review.

WHAT IS KNOWN AND OBJECTIVE

The World Health Organization (WHO) identified cardiovascular diseases (CVD – which includes cardio and cerebrovascular diseases) as one of the leading causes of premature mortality worldwide. Approximately 80.0% of all CVD deaths are associated with heart attacks and stroke.[1,2] These conditions are very common among the elderly, and their burden is expected to increase aside with population ageing.[1,3]

The elderly normally present higher rates of multimorbidity, polypharmacy, inappropriate prescribing (including potentially inappropriate medications – PIMs), and physiological changes (that affect the PK/PD of drugs).[4] Therefore, this population seem to be more prone to drug-related problems (DRPs), including to the potential occurrence of adverse drug reactions (ADRs).[5,6] According to the WHO, an ADR may be defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modifications of physiological functions.[7] In older individuals, ADRs can be sometimes difficult to recognize as they may present themselves atypically (*e.g.* falls, fatigue, and orthostatic hypotension).[8,9] A study in the United Kingdom found that ADRs contributed to 6.5% of hospital admissions and more than 50% of those were preventable.[9]

Since the 1990s, several lists have been developed to screen for PIMs. A PIM can be defined as any medication used by a patient that could introduce a significant risk of an ADR, when there is an equally or more effective alternative available with a lower risk. These PIM-lists can be classified into explicit, implicit, and mixed-approach criteria. Explicit criteria often describe drug- or disease-oriented lists resulting from literature review and expert panels.[10] Implicit criteria tend to be more person-centred and rely on clinical judgement.[11-38] Mixed approach criteria tend to combine explicit and implicit criteria, to optimize the advantages of both approaches.[39] The first PIM-list was developed in 1991, in the US, by Mark Beers (MD), and last updated in 2015 by the American Geriatric Society.[11-40] In Europe, the first list was developed in 2007 in France, and many others have been released since.[24,36] Non-steroidal anti-inflammatory drugs (NSAIDs) are one example of a pharmacological class that is widely used by older people[41] and is described in these lists. For example, ibuprofen has been associated with higher risk of stroke (relative risk – RR: 3.36; confidence interval – CI: 1.0-11.6), while etoricoxib (RR: 4.07; CI: 1.23-15.7) and diclofenac (RR: 3.98; CI: 1.48-12.7) were associated with higher risk of cardiovascular death.[42]

A recently published systematic review identified benzodiazepines, NSAIDs, antihistamines, and antipsychotics as the most reported PIMs in these lists.[43] However, information on the use of these tools to detect PIMs with cardiovascular risk (including MACE – major adverse cardiovascular events) is still unknown.

Our main goals were: (a) to identify PIMs with risk of cardiovascular adverse events from lists already published in the literature; and (b) to quantify those PIMs.

METHODS

LITERATURE SEARCH

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[44] The search strategy was developed using population, intervention, comparator, and outcome (PICO) method and all the keywords and MeSH terms selected. The final search strategy was defined as:

1. Population: Older patients; Frail elderly [MeSH term]; Geriatrics [MeSH term]; Elder; Aged [MeSH term]; Aged, 80 and over [MeSH term].

2. Intervention: Inappropriate prescribing [MeSH term]; Medical overuse [MeSH term]; Potentially Inappropriate Medication List [MeSH term]; Potentially Inappropriate Medications; Inappropriate Medications; PIM screening tools; Deprescriptions [MeSH term].

3. Outcome: Drug-related side effects and adverse reactions [MeSH term] (for full search strategy, see **Appendix 2.S1**).

This search strategy was run in PubMed, Ovid® (MEDLINE), and Google Scholar (from January 1, 1991 to September 11, 2017). This time period was selected based on the year of the first published PIM-list (Beers criteria. 1991).[31] Population, intervention, and outcome were combined as "Population" AND "Intervention" AND "Outcome". Original research articles, reviews, and systematic reviews were included. This search was supplemented with a manual search of the references of included full-text papers. The reviewers (JPA and AMB) assessed independently publications for eligibility by title and abstract content. In case of disagreement, consensus was reached between three of the authors (JPA, AMB and FAC).

ELIGIBILYY CRITERIA (INCLUSION AND EXCLUSION CRITERIA)

Original research articles, reviews, and systematic reviews describing PIM-lists were included in this study if they involved individuals aged 65 or older and objectively presented PIMs to be avoided by the elderly and drug-disease interactions with risk of cardiovascular adverse events (including MACE). All articles describing PIMs without any association with ADRs were excluded. Additionally, non-English and/or unavailable full-text articles were also excluded. Unavailable full-text articles were defined as papers that could not be accessed either electronically or by a library, even when requested, via e-mail, to the corresponding authors.

OUTCOME DEFINITIONS AND MEASURES

The primary endpoint was defined as the description, and the number of times each PIM with risk of MACE was reported in the PIM-lists. The composite endpoint, MACE, was defined as: (a) stroke (ischaemic or haemorrhagic); (b) transient ischaemic attack; (c) myocardial infraction; (d) acute decompensated heart failure; and (e) cardiovascular death.[45]

The secondary endpoint was defined as the description, and the number of times each PIM with risk of cardiovascular adverse events was reported in the PIM-lists. The cardiovascular adverse events were defined using the same nomenclature as described in the original tool.

Both endpoints were divided into two groups: PIMs to be avoided by the elderly and drug-disease interactions. The first group included drugs which should be avoided in this population because the risk of ADRs outweighs the clinical benefit, particularly when there is evidence in favour of a safer or more effective alternative therapy for the same condition. The second group included all combinations of drugs and underlying conditions that could be exacerbated by their use.

DATA EXTRACTION

For each paper, we have extracted information on nature of the criteria, year, and country where the criteria were developed, validation methods (*e.g.,* consensus technique), healthcare setting where the PIM-lists are applicable, total number of PIMs per tool, total number of PIMs with cardiovascular risk per tool, and total number of PIMs with MACE risk per tool. Additionally, the description of PIMs and ADRs were also extracted. PIMs were coded as medication classes and, when available, as individual medication using the Anatomical Therapeutic Chemical (ATC) classification system.[46]

Information was extracted independently by two authors (JPA and AMB), using a piloted checklist. In case of uncertainty, consensus was sought between three of the authors exploring and discussing discrepancies (JPA, AMB and FAC).

DATA ANALYSIS

Descriptive statistics were used to assess the total number of PIMs, total number of PIMs with risk of cardiovascular adverse events, and total number of PIMs with risk of MACE. The intra-class correlation coefficient (ICC) was used to study the reliability of the different PIM-lists in the identification of each medication class or individual drugs (each list was considered as a rater). For a 95% CI, ICC values of <0.5, between 0.5 and 0.75, between 0.75 and 0.90, and >0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[47] The analysis was undertaken using the IBM SPSS v.25.0 (IBM®, New York, US).

RESULTS

STUDY SELECTION AND CHARACTERISTICS

A total of 724 references were identified through a database search. **Figure 2.1.1** illustrates the number of included and excluded articles at each stage. In the end, 24 lists met the inclusion criteria and described 19 different lists and 5 updates (**Appendix 2.S2**). Seventy-five per cent (18/24) of the PIM-lists included were based on previously published tools.

Most of the available lists (n=11; 45.8%) were developed in Europe (one from the Netherlands, two from Germany, two from Norway, one from Austria, one from France, three from Ireland, and one from Croatia) and in the US (n=8; 33.3%). Only a few tools were developed in Asia (n=3; 12.5%) or in Oceania (n=1; 4.2%). Two lists were developed in different European countries as a collaborative study. Looking at patient groups, the lists focused mainly on individuals aged 65 or older (n=20; 79.2%). Twenty-two (91.7%) lists were developed based on explicit criteria and only 8.3% used mixed approach criteria. Evidence arose from consensus methods in the vast majority (n=23; 95.8%), mostly using Delphi technique (n=19; 79.2%). Eight (33.3%) were developed to screen for PIMs in primary care, three (12.5%) in long-term care facilities/nursing homes, and one (4.2%) in the hospital setting. Twelve tools (50.0%) did not specify the healthcare setting they were meant to be applied in. Most of the PIM-lists focused on both individual medication and medication classes (n=16; 66.7%). A quarter focused only on individual medication and 8.3%(n=2) on medication classes. A summary of studies' characteristics is detailed in **Table 2.1.1**.

PIMs WITH RISK OF CARDIOVASCULAR ADVERSE EVENTS

From the 24 papers included in this review, a total of 1389 PIMs were extracted. Of those and excluding all the ADRs not related to the cardiovascular system, a total of 302 PIMs (21.7%) were considered. Two hundred and thirty-seven (78.5%) of those were classified as PIMs to be avoided by the elderly due to cardiovascular risk and 65 (21.5%) as drug-disease interactions affecting the cardiovascular system. After removing duplicates, we retained 112 PIMs to be avoided by the elderly and 13 drug-disease interactions (**Figure 2.1.2**).

Regarding the PIMs to be avoided by the elderly, tricyclic antidepressants (TCAs – reported in 12 out of 24 tools), centrally acting antiadrenergic agents (11/24), NSAIDs (7/24), antiarrhythmics (Class I and III) (6/24), peripherally acting antiadrenergic agents (6/24), and antithrombotic agents (5/24) were the most prevalent medications classes among the lists. Within these groups, methyldopa (11/24), amitriptyline (10/24), clonidine (10/24), doxepin (8/24), clomipramine (6/24), imipramine (5/24), trimipramine (5/24), dipyridamole (5/24), and doxazosin (5/24) were the most prevalent individual medications. These PIMs were mostly

associated with orthostatic hypotension, and cardiac arrhythmias. Additionally, NSAIDs were frequently linked to hypertension and antiadrenergic drugs to bradycardia.

TCAs (7/24) and NSAIDs (6/24) were mostly associated with exacerbation of arrhythmias, postural and orthostatic hypotension, and hypertension (for full list of PIMs, see **Appendix 2.S3**). To a lower extent, psychostimulants (2/24) and antipsychotics (2/24) were associated with exacerbation of hypertension and cardiac arrhythmias.

PIMs WITH RISK OF MACE

Of the initial 1389 PIMs, we retained 38 (11.4%) PIMs with risk of MACE: 17 to be avoided by the elderly and 21 drug-disease interactions (**Figure 2.1.2**).

NSAIDs (7/24), antiarrhythmics (Class I and III) (7/24), selective calcium channel blockers with mainly vascular effect (6/24), and antipsychotics (4/24) were the most prevalent medication classes of PIMs to be avoided by the elderly among the PIM-lists. Within these groups, disopyramide (7/24), short-acting nifedipine (6/24), piroxicam (3/24), and COX-II inhibitors (2/24) were the most prevalent individual medications (**Table 2.1.2**).

Stroke and myocardial infarction were the most reported ADRs following exposure to NSAIDs, antipsychotics, and short-acting nifedipine. To a lower extent, sudden cardiac death was associated with exposure to domperidone (>30 mg/d) and heart failure with disopyramide.

NSAIDs (10/24), selective calcium channel blockers with cardiac effects (9/24), antiarrhythmics (Class I and III) (7/24), blood glucose-lowering drugs (7/24), and formulations with a high content of salt (5/24) were the most prevalent medication classes associated with exacerbation of heart failure. Within each group, thiazolidinediones (6/24), verapamil (4/24), diltiazem (4/24), and COX-II inhibitors (3/24) were the most frequently described individual medications.

The establishment of casual relationships between exposure to medication and MACE has been progressive. Disopyramide was the first individual medication reported as inducing heart failure in Beers criteria arising in 1997. Later, in 2003, Fick and collaborators also included NSAIDs as a medication class that can potentially induce heart failure. After 2007, other medications have been described as linked to myocardial infarction and stroke, namely selective calcium channel blockers with mainly vascular effects (2007), NSAIDs (2008), oestrogens (2008), and antipsychotics (2012) (**Table 2.1.3**).

RELIABILITY OF THE DIFFERENT TOOLS

The ICC was 0.234 (95% CI: 0.121-0.784) which represents a low relative agreement between the analysed lists for classifying PIMs.

DISCUSSION

Cardiovascular diseases are among the leading causes of death worldwide and are an important cause of morbidity in the elderly. As a result of inappropriate prescribing, this population is more prone to DRPs, including ADRs. However, experience tells us that the clinical relevance of outcomes has a major importance on the prescribing pattern and possibly successful future interventions to change it.

Therefore, it is crucial to identify PIMs with risk of cardiovascular adverse events in the PIM-lists already available. In this review, a total of 129 PIMs to be avoided by the elderly and 34 drug-disease interactions were found. Risk of MACE was associated with 38 PIMs and 21 drug-disease interactions.

Several drug classes were identified as having an associated cardiovascular risk. The most frequently described were TCAs, centrally acting antiadrenergic agents, NSAIDs, antiarrhythmics (Class I and III), antithrombotic agents, and antipsychotics. For instance, TCAs have been described as PIMs since 1991, when the first Beers criteria list was released. However, only in 1997, their potential to exacerbate postural hypotension and heart failure was first reported.[14] Since then, TCAs have been associated with cardiac arrhythmias, and orthostatic hypotension. Literature search has enabled the identification of several studies where cardiovascular complications of TCAs were reported not only in patients with CVD, but also in individuals with no prior history of those conditions. On the other hand, MACE was described to a lower extent. TCAs were associated with exacerbation of heart failure in 8% of the lists. Ventricular tachycardia or sudden cardiac deaths were also described.[48] Cardiovascular risk of NSAIDs was also widely described in our study. This medication class was initially reported in the PIM-lists as being associated with gastrointestinal (GI) bleeding or with central nervous system (CNS) side effects (particularly indomethacin). In 2003, concerns about their effect on hypertension and heart failure were first described.[12] Some lists refer also other ADRs, like myocardial infarction (especially with COX-II inhibitors).[25,27,32,49] A study conducted by Bally and collaborators found that the risk of myocardial infarction after exposure to celecoxib in real-world patients was similar to the risk associated with traditional NSAIDs (*e.g.* ibuprofen and naproxen). The risk was also reported to be higher in the first month of treatment and with higher doses.[50] In heart failure, the current use of any NSAID (defined as the use in the preceding 14 days) was associated with a 19% increased risk of hospital admission (odds ratio [OR]: 1.19; 95%CI: 1.17-1.22).[51]

Safety concerns have also arisen with the use of antipsychotics. Looking at the different lists, this drug class was first described in the Beers criteria (1991) as associated with extrapyramidal effects and recommended to be avoided in non-psychiatric patients.[31] In 1997, McLeod and colleagues

described that typical antipsychotic exacerbate hypotension in individuals with the history of postural hypotension. In 2010, Holt and colleagues described that clozapine, an atypical antipsychotic, could be associated with risk of myocarditis.[19] More recently, the 2015 Beers criteria update mentions antipsychotics as associated with stroke in people with dementia.[32] Wu and collaborators (2013) suggested that the stroke risk with antipsychotic use is dose-related and possibly appears only in the first 28 days of antipsychotic use.[52,53] A WHO VigiBase study has supported that dose-related cardiac events need to be monitored, based on ADR reports of QT-prolongation and torsades de pointes after exposure to intravenous haloperidol.[54]

Minor events were more frequently described than major adverse events (15.3% vs 7.2%, respectively), leading to a low reporting rate of MACE. This aspect is of major importance as it suggests that clinicians may have some reluctance to change theirs prescribing patterns unless the outcome is clinically significant. Conversely, it supports there is an effective risk management strategy implemented as most medicines with a significant risk have been withdrawn (e.g., rofecoxib).

It is undeniable that these PIM-lists can give good insights on which medications healthcare professionals should be alerted to during medication review. However, few updates of these lists are available, which may sometimes lack new pharmacovigilance signals arising as important safety concerns for the elderly. A good example is the absence of some antiplatelet/anticoagulants, which are also linked to the occurrence of haemorrhagic stroke. Therefore, updates of these lists should be done periodically to include new PIMs and eventually new ADRs for the PIMs already available.

Additionally, a low reliability between the different tools was found. It was expected to find a higher relative agreement as some of the tools are generated from previous criteria. This result may be explained by the differences between drug markets and/or prescribing patterns in different countries. It seems also plausible to assume that the low agreement may also result from the methods leading to the development of these lists, undoubtedly considered as having little robustness.

To the authors' best knowledge, this review adds valuable information as it focuses on PIMs with risk of MACE, which had not yet been explored. Knowing that the elderly population is very heterogeneous, results may be used to generate a more specific PIM-list or algorithms to target real inappropriate prescribing in patients with high cardiovascular risk. Moreover, omission of relevant drugs should also be addressed as a potential way to increase cardiovascular morbid-mortality in the elder patient.

There are some limitations that should be acknowledged. The literature search was restricted to English papers, and therefore, criteria published in other languages were missed. Conscious that some search terms could also be missed, the authors performed a manual search in an effort to refine the search strategy. Access to other databases, such as EMBASE, which is paid, was not possible, and therefore, criteria published in those were also missed.

WHAT IS NEW AND CONCLUSION

This study suggests a low reporting rate of PIMs with risk of MACE in the PIM-lists. However, data also suggest that special attention should be given to some events, as they can be the trigger for MACE (e.g., cardiac arrhythmias and QT-prolongation). This review could help healthcare professionals in the identification and deprescribing of PIMs known to be associated with MACE in patients with high cardiovascular risk during medication review.

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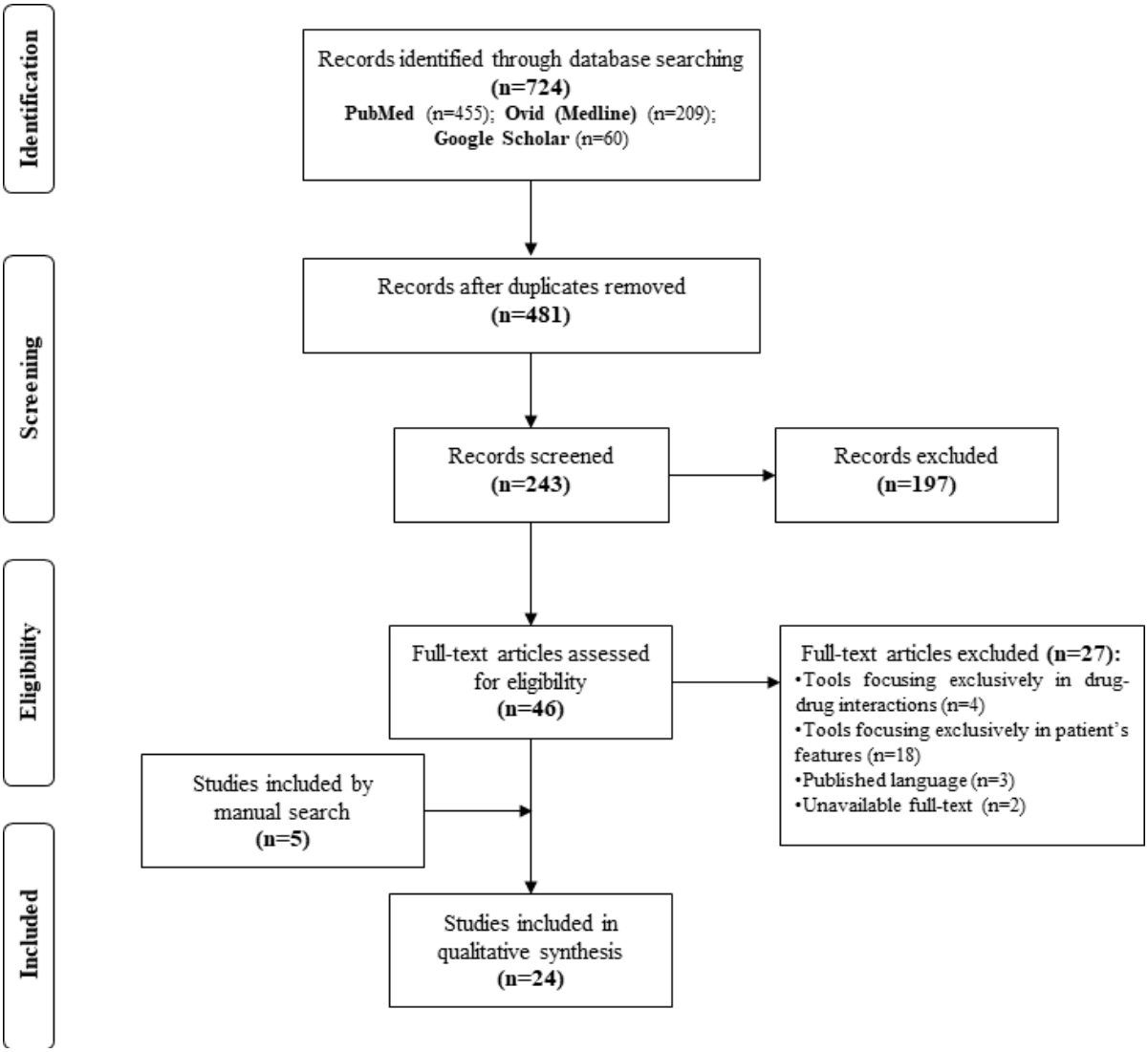

Figure 2.1.1 – Flowchart of study selection

Table 2.1.1 – Overview of the characteristics of the inappropriate prescribing tools included in this study

Publication, Year	Country	Nature of criteria	Validation methods	n of PIMs (%)*		
				Total	CVAEs risk	MACE risk
Beers, 1991 [34]	United States	Explicit	Delphi technique (2 rounds by written survey)	30	3 (10.0)	0 (0.0)
Beers, 1997 [14]	United States	Explicit	Delphi technique (2 rounds by written survey)	63	6 (9.5)	3 (4.8)
McLeod, 1997 [17]	Canada	Explicit	Delphi technique (2 rounds by mail survey)	68	4 (5.9)	3 (4.4)
Sloane, 2002 [24]	United States	Explicit	Update of the Beers Criteria (1997)	32	1 (3.1)	1 (3.1)
Fick, 2003 [15]	United States	Explicit	Delphi technique (3 rounds)	66	11 (16.7)	3 (4.5)
Lindblad, 2006 [40]	United States	Explicit	Modified Delphi panel (2 rounds)	28	4 (14.3)	1 (3.6)
Raebel, 2007 [38]	United States	Explicit	No consensus technique was used	11	2 (18.2)	0 (0.0)
Laroche, 2007 [39]	France	Explicit	Delphi technique (2 rounds)	25	4 (16.0)	3 (12.0)
Basger, 2008 [32]	Australia	Mixed approach	Without any validation process	48	0 (0.0)	11 (22.9)
Gallagher, 2008 [27]	Ireland	Explicit	Delphi technique (2 rounds by mail survey)	61	2 (3.3)	1 (1.6)
Winit-Watjana, 2008 [30]	Thailand	Explicit	Delphi process (three rounds)	65	5 (7.7)	3 (4.6)
Maanen, 2009 [21]	The Netherlands	Mixed approach	Validation of the tool using the case histories of ten geriatric patients admitted to the geriatric outpatient clinic	13	1 (7.7)	6 (46.2)
Rognstad, 2009 [19]	Norway	Explicit	Delphi process (three rounds)	21	6 (28.6)	0 (0.0)
Kim, 2010 [37]	Korea	Explicit	Delphi technique (2 rounds)	57	8 (14.0)	9 (15.8)
Holt, 2010 [22]	Germany	Explicit	Modified Delphi process (two rounds)	83	10 (12.0)	1 (1.2)
Mann, 2012 [33]	Austria	Explicit	Modified Delphi panel process (2 rounds)	73	22 (30.1)	1 (1.4)
Matanović, 2012 [18]	Croatia	Explicit	No validation using consensus techniques	104	9 (8.7)	6 (5.8)
Chang, 2012 [36]	Taiwan	Explicit	Delphi technique (2 rounds)	36	3 (8.3)	2 (5.6)
Beers, 2012 [26]	United States	Explicit	Modified Delphi technique	53	15 (28.3)	11 (20.8)
Bermingham, 2014 [25]	Ireland	Explicit	Modified Delphi technique (2 rounds)	11	0 (0.0)	11 (100.0)
Renom-Guiteras, 2015 [52]	7 European countries	Explicit	Delphi panel process (2 rounds)	282	80 (28.4)	8 (2.8)
Nyborg, 2015 [20]	Norway	Explicit	Delphi technique (3 rounds)	11	2 (18.2)	0 (0.0)
O'Mahony, 2015 [28]	13 European countries	Explicit	Delphi technique (2 rounds)	80	2 (2.5)	5 (6.25)
Beers, 2015 [43]	United States	Explicit	Modified Delphi technique	68	13 (19.1)	11 (16.2)
			TOTAL	**1389**	**213 (15.3)**	**100 (7.2)**

Abbreviations: CVAEs – Cardiovascular Adverse Events; MACE – Major Adverse Cardiovascular Events.

* Include PIMs to be avoided by the elderly and drug-disease interaction

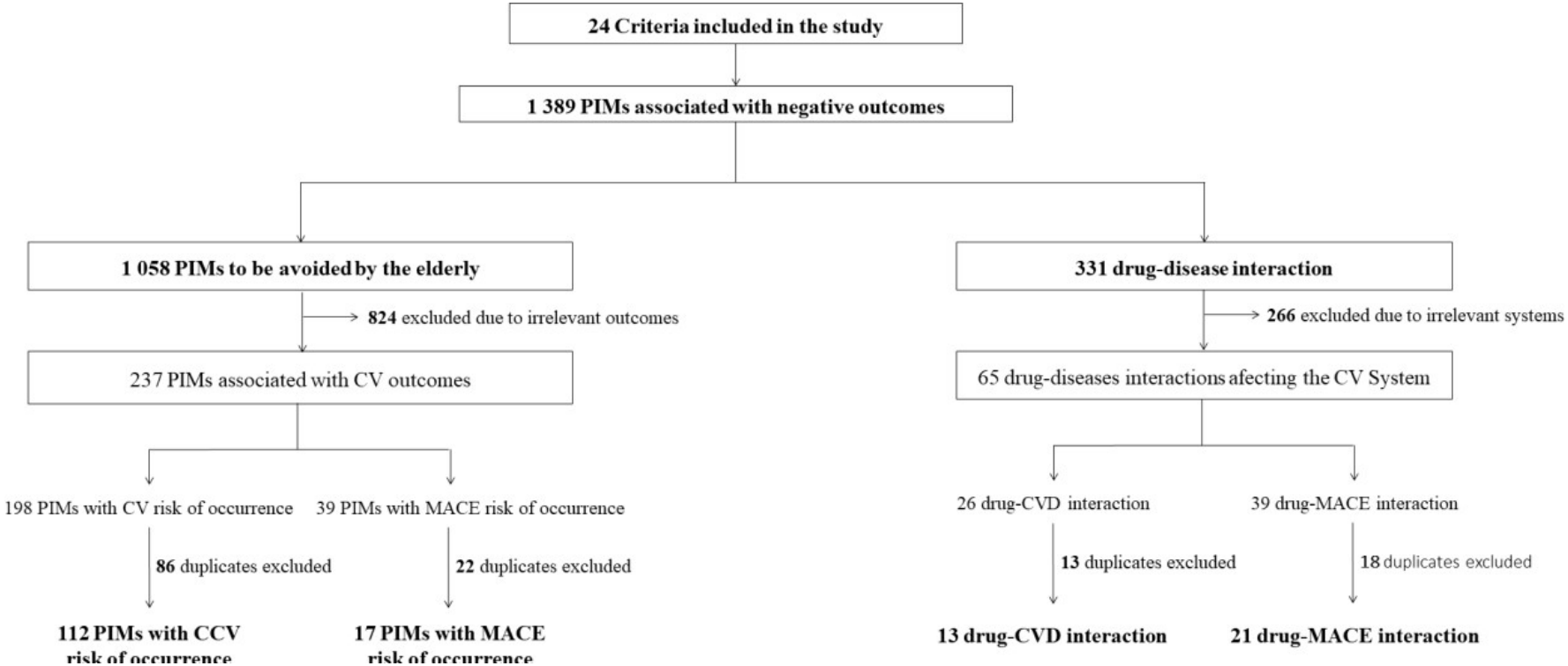

Figure 2.1.2 – Flowchart of PIMs selection

Table 2.1.2 – Description and prevalence of PIMs with risk of MACE among the 24 PIM-lists

Drug-classes	ADRs or exacerbation of underlying conditions	Prevalence among the lists	References
PIMs to be avoided by the elderly			
***NSAIDs* [M01A]**	May induce heart failure, myocardial infarction, and stroke	**29.2 (7/24)**	15, 27, 30, 21, 37, 18, 36
COX-II Inhibitors [M01AH]		8.3 (2/24)	30, 43
Naproxen (long-term use) [M01AE02]	May induce myocardial infarction and stroke	8.3 (2/24)	37, 18
Piroxicam (long-term use) [M01AC01]	May induce heart failure	12.5 (3/24)	37, 18, 36
Oxaprozin (long-term use) [M01AE12]	May induce heart failure	4.2 (1/24)	37
	May induce heart failure		
Amphetamines	May induce myocardial infarction	**4.2 (1/24)**	15
***Urologicals* [G04B]**		**4.2 (1/24)**	43
Sildenafil [G04BE03]	May induce heart failure	4.2 (1/24)	43
Tadalafil [G04BE08]	May induce heart failure	4.2 (1/24)	43
***Antipsychotics* [N05A]**	May induce stroke	**16.7 (4/24)**	52, 28, 43, 26
Pimozide [N05AG02]	May induce stroke	4.2 (1/24)	52
***Propulsives* [A03F]**		**4.2 (1/24)**	52
Domperidone (> 30mg/d) [A03FA03]	May cause sudden cardiac death	4.2 (1/24)	52
***Hormones and related agents* [L02A]**		**4.2 (1/24)**	30
Estrogens [L02AA]	May induce stroke	4.2 (1/24)	30
***Selective calcium channel blockers with mainly vascular effects* [C08C]**		**25.0 (6/24)**	39, 22, 18, 26, 52, 28
Nicardipine [C08CA04]	May induce myocardial infarction and stroke	8.3 (2/24)	52, 39
Short acting nifedipine [C08CA05]	May induce myocardial infarction and stroke	25.0 (6/24)	39, 22, 18, 26, 52, 28
Long acting nifedipine [C08CA05]	May induce myocardial infarction and stroke	4.2 (1/24)	52
***Antidepressants* [N06A]**		**4.2 (1/24)**	52
Venlafaxine [N06AX16]	May induce stroke	4.2 (1/24)	52
***Antiarrhythmics (Class I and III)* [C01B]**		**29.2 (7/24)**	14, 24, 15, 39, 26, 52, 28
Disopyramide [C01BA03]	May induce heart failure	29.2 (7/24)	14, 24, 15, 39, 26, 52, 28
Drug-disease interaction			
***NSAIDs* [M01A]**	May exacerbate heart failure	**41.7 (10/24)**	17, 32, 21, 37, 18, 36, 26, 25, 28, 43
COX-II Inhibitors [M01AH]	May exacerbate heart failure	12.5 (3/24)	
***Antiarrhythmics (Class I and III)* [C01B]**	May exacerbate heart failure	**29.2 (7/24)**	14, 32, 37, 18, 26, 28, 33
Disopyramide [C01BA03]	May exacerbate heart failure	12.5 (3/24)	14, 37, 18
Dronedarone [C01BD07]	May exacerbate heart failure	12.5 (3/24)	26, 28, 33
***Beta-blocking agents* [C07A]**	May exacerbate heart failure	**12.5 (3/24)**	17, 32, 37
Sotalol [C07AA07]	May exacerbate heart failure	4.2 (1/24)	32

Table 2.1.2 – (Continued)

Selective calcium channel blockers with direct cardiac effects **[C08D]**	May exacerbate heart failure	**37.5 (9/24)**	17, 40, 32, 21, 37, 18, 26, 25, 28
Verapamil [C08DA01]	May exacerbate heart failure	16.7 (4/24)	32, 21, 26, 28
Diltiazem [C08DB01]	May exacerbate heart failure	16.7 (4/24)	32, 21, 26, 28
Selective calcium channel blockers with mainly vascular effects **[C08C]**		**8.3 (2/24)**	32, 21
Short acting nifedipine [C08CA05]	May exacerbate heart failure	8.3 (2/24)	32, 21
Antiepileptics **[N03A]**		**8.3 (1/24)**	25
Carbamazepine [N03AF01]	May exacerbate heart failure	4.2 (1/24)	25
Pregabalin [N03AX16]	May exacerbate heart failure	4.2 (1/24)	25
Antithrombotic agents **[B01A]**		**8.3 (2/24)**	26, 28
Cilostazol [B01AC23]	May exacerbate heart failure	8.3 (2/24)	26, 28
Corticosteroids for systemic use **[H02A]**	May exacerbate heart failure	**8.3 (2/24)**	25, 32
Decongestants and antiallergies **[S01G]**	May exacerbate heart failure	**4.2 (1/24)**	25
Formulations with high-content of salt	May exacerbate heart failure	**20.8 (5/24)**	14, 32, 37, 18, 25
Antimycotics for systemic use **[J02A]**		**4.2 (1/24)**	25
Itraconazol [J02AC02]	May exacerbate heart failure	4.2 (1/24)	25
Blood glucose lowering drugs (excluding insulins) **[A10B]**		**29.2 (6/24)**	32, 21, 26, 25, 28, 43
Metformin [A10BA02]	May exacerbate heart failure	4.2 (1/24)	25
Thiazolidinediones [A10BG]	May exacerbate heart failure	29.2 (6/24)	32, 21, 26, 25, 28, 43
Antidepressants **[N06A]**		**8.3 (2/24)**	32, 37
Tricyclic antidepressants	May exacerbate heart failure	8.3 (2/24)	32, 37

Table 2.1.3 – Chronologic overview of PIMs with risk of MACE in the PIM-lists

Drug-classes	Beers, 1991 [34]	Beers, 1997 [14]	McLeod, 1997 [17]	Sloane, 2002 [24]	Fick, 2003 [15]	Lindblad, 2006 [40]	Raebel, 2007 [38]	Laroche, 2007 [39]	Basger, 2008 [32]	Gallagher, 2008 [27]	WW, 2008 [30]	Maanen, 2009 [21]	Rongstad, 2009 [19]	Kim, 2010 [37]	Holt, 2010 [22]	Mann, 2012 [33]	Matanović, 2012 [18]	Chang, 2012 [36]	Beers, 2012 [26]	Bermingham, 2014 [25]	RG, 2015 [52]	Nyborg, 2015 [20]	Beers, 2015 [28]	O' Mahony, 2015 [43]
PIMs to be avoided by the elderly																								
***NSAIDs* [M01A]**					√					√	√						√							√
COX-II Inhibitors [M01AH]											√													√
Naproxen (long-term use) [M01AE02]														√			√							
Piroxicam (long-term use) [M01AC01]														√			√	√						
Oxaprozin (long-term use) [M01AE12]														√										
Amphetamines					√																			
***Urologicals* [G04B]**																								√
Sildenafil [G04BE03]																								√
Tadalafil [G04BE08]																								√
***Antipsychotics* [N05A]**																			√				√	√
Pimozide [N05AG02]																					√			
***Propulsives* [A03F]**																								
Domperidone (> 30mg/d) [A03FA03]																					√			
***Hormones and related agents* [L02A]**																								
Estrogens [L02AA]											√													
***Selective calcium channel blockers with mainly vascular effects* [C08C]**																								
Nicardipine [C08CA04]								√													√			
Short acting nifedipine [C08CA05]								√							√		√		√		√		√	
Long acting nifedipine [C08CA05]																					√			
***Antidepressants* [N06A]**																								
Venlafaxine [N06AX16]																					√			
***Antiarrhythmics (Class I and III)* [C01B]**																								
Disopyramide [C01BA03]		√		√	√			√											√		√		√	

Table 2.1.3 – (Continued)

Drug-disease interaction																				
***NSAIDs* [M01A]**		√		√		√		√		√			√		√	√			√	
COX-II Inhibitors [M01AH]													√		√	√			√	
***Antiarrhythmics (Class I and III)* [C01B]**						√														
Disopyramide [C01BA03]	√							√			√									
Dronedarone [C01BD07]										√			√						√	
***Beta-blocking agents* [C07A]**		√						√												
Sotalol [C07AA07]						√														
***Selective calcium channel blockers with direct cardiac effects* [C08D]**		√		√				√			√					√				
Verapamil [C08DA01]						√		√					√						√	
Diltiazem [C08DB01]						√		√					√						√	
***Selective calcium channel blockers with mainly vascular effects* [C08C]**																				
Short acting nifedipine [C08CA05]						√		√												
***Antiepileptics* [N03A]**																				
Carbamazepine [N03AF01]						√														
Pregabalin [N03AX16]																√				
***Antithrombotic agents* [B01A]**																				
Cilostazol [B01AC23]													√						√	
***Corticosteroids for systemic use* [H02A]**						√										√				
***Decongestants and antiallergies* [S01G]**																√				
Formulations with high-content of salt	√					√		√			√					√				
***Antimycotics for systemic use* [J02A]**																				
Itraconazol [J02AC02]																√				
***Blood glucose lowering drugs (excluding insulins)* [A10B]**																				
Metformin [A10BA02]																√				
Thiazolidinediones [A10BG]						√		√					√			√	√		√	√
***Antidepressants* [N06A]**																				
Tricyclic antidepressants						√					√									

Legend: WW - Winit-Watjana; RG - Renom-Guiteras

APPENDICES

SUPPLEMENTARY MATERIAL

Appendix 2.S1 – Strict description of the searches

Strict description of the search used in Ovid® (MEDLINE) database is available in **Table 1**.

Table 1 – Strict description of the search used in Ovid® (MEDLINE)

Number	Searches	Results
1	Inappropriate Prescribing/	2014
2	Medical Overuse/	591
3	Potentially Inappropriate Medication List/	130
4	inappropriate medications.mp.	585
5	Deprescriptions/	108
6	PIM screening tools.mp.	1
7	exp Aged/	2859782
8	older patients.mp.	32222
9	elderly.mp.	227828
10	elder.mp.	8562
11	drug-related side effects and adverse reactions.mp. [mp= title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	28506
12	1 or 2 or 3 or 4 or 5 or 6	3061
13	7 or 8 or 9 or 10	2930366
14	11 and 12 and 13	209
15	limit 14 to (humans and last 26 years)	209

For PubMed database:

((“inappropriate prescribing”[MeSH Terms] OR (“inappropriate”[All Fields] AND “prescribing”[All Fields]) OR “inappropriate prescribing”[All Fields]) OR (“medical overuse”[MeSH Terms] OR (“medical”[All Fields] AND “overuse”[All Fields]) OR “medical overuse”[All Fields]) OR (“potentially inappropriate medication list”[MeSH Terms] OR (“potentially”[All Fields] AND “inappropriate”[All Fields] AND “medication”[All Fields] AND “list”[All Fields]) OR “potentially inappropriate medication list”[All Fields]) OR (“potentially inappropriate medication list”[MeSH Terms] OR (“potentially”[All Fields] AND “inappropriate”[All Fields] AND “medication”[All Fields] AND “list”[All Fields]) OR “potentially inappropriate medication list”[All Fields] OR (“potentially”[All Fields] AND “inappropriate”[All Fields] AND “medication”[All Fields]) OR “potentially inappropriate medication”[All Fields]) OR (inappropriate[All Fields] AND (“pharmaceutical preparations”[MeSH Terms] OR (“pharmaceutical”[All Fields] AND “preparations”[All Fields]) OR “pharmaceutical preparations”[All Fields] OR “medications”[All Fields])) OR (PIM[All

Fields] AND tools[All Fields]) OR (“deprescriptions”[MeSH Terms] OR “deprescriptions”[All Fields])) AND ((older[All Fields] AND (“patients”[MeSH Terms] OR “patients”[All Fields])) OR (“frail elderly”[MeSH Terms] OR (“frail”[All Fields] AND “elderly”[All Fields]) OR “frail elderly”[All Fields]) OR (“geriatrics”[MeSH Terms] OR “geriatrics”[All Fields]) OR (“sambucus”[MeSH Terms] OR “sambucus”[All Fields] OR “elder”[All Fields]) OR (“aged”[MeSH Terms] OR “aged”[All Fields]) OR (“aged, 80 and over”[MeSH Terms] OR “80 and over aged”[All Fields] OR “aged, 80 and over”[All Fields])) AND (“drug-related side effects and adverse reactions”[MeSH Terms] OR (“drug-related”[All Fields] AND “side”[All Fields] AND “effects”[All Fields] AND “adverse”[All Fields] AND “reactions”[All Fields]) OR “drug-related side effects and adverse reactions”[All Fields] OR (“drug”[All Fields] AND “related”[All Fields] AND “side”[All Fields] AND “effects”[All Fields] AND “adverse”[All Fields] AND “reactions”[All Fields]) OR “drug related side effects and adverse reactions”[All Fields]).

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Appendix 2.S3 – Full list of PIMs with risk of cardiovascular adverse reactions

Drug-classes	ADRs or Exacerbation of Underlying conditions	Prevalence among the lists (%)	References
PIMs to be avoided by the elderly			
NSAIDs [M01A]	May have cardiovascular contraindications and cause hypertension, with long-term use and full doses	**25.0 (7/24)**	17, 15, 37, 22, 33, 18, 52
Aceclofenac [M01AB16]		4.2 (1/24)	52
Acemetacin [M01AB11]		4.2 (1/24)	33
Celecoxib [M01AH01]		4.2 (1/24)	33
Dexketoprofen [M01AE17]		4.2 (1/24)	52
Diclofenac [M01AB05]		4.2 (1/24)	33
Etoricoxib [M01AH05]		4.2 (1/24)	22
Flurbiprofen [M01AE09]		4.2 (1/24)	52
Ibuprofen [M01AE01]		4.2 (1/24)	33
Indometacin [M01AB01]		4.2 (1/24)	33
Ketoprofen [M01AE03]		4.2 (1/24)	33
Lornoxicam [M01AC05]		4.2 (1/24)	52
Mefenamic acid [M01AG01]		4.2 (1/24)	52
Meloxicam [M01AC06]		4.2 (1/24)	33
Nabumetone [M01AX01]		4.2 (1/24)	52
Naproxen [M01AE02]		12.5 (3/24)	37, 33, 18
Oxaprozin [M01AE12]		4.2 (1/24)	37
Piroxicam [M01AC01]		12.5 (3/24)	37, 33, 18
Antidepressants [N06A]	May cause heart block, postural and orthostatic hypotension, cardiac arrhythmias and cardiotoxicity	**50 (12/24)**	24, 38, 39, 30, 19, 22, 33, 18, 26, 52, 20,
Amitriptyline [N06AA09]		41.7 (10/24)	43
Amoxapin [N06AA17]		8.3 (2/24)	24, 38, 39, 30, 19, 22, 33, 18, 26, 52
Clomipramine [N06AA04]		25.0 (6/24)	39, 52
Desipramine [N06AA01]		4.2 (1/24)	39, 30, 22, 33, 26, 52
Doxepin [N06AA12]		33.3 (8/24)	52
Dosulepin [N06AA16]		8.3 (2/24)	38, 39, 30, 19, 22, 33, 26, 52
Imipramine [N06AA02]		20.8 (5/24)	39, 52
Maprotiline [N06AA21]		20.8 (5/24)	39, 30, 22, 26, 52
Nortriptyline [N06AA10]		4.2 (1/24)	39, 22, 33, 18, 52
Reboxetine [N06AX18]		4.2 (1/24)	52
Tranylcypromine [N06AF04]		4.2 (1/24)	52
Trimipramine [N06AA06]		20.8 (5/24)	52
			39, 30, 22, 26, 52
Androgens [G03B]	May cause cardiac problems	**4.2 (1/24)**	28
Methyltestosterone [G03BA02]		4.2 (1/24)	28
Testosterone [G03BA03]		4.2 (1/24)	28
Antiadrenergic agents (centrally acting) [C02A]	May cause bradycardia and orthostatic hypotension	**45.8 (11/24)**	14, 15, 39, 30, 37, 22, 18, 36, 26, 52, 28
Clonidine [C02AC01]		41.7 (10/24)	15, 39, 30, 37, 22, 18, 36, 26, 52, 28
Guanabenz		8.3 (2/24)	26, 28
Guanfacine [C02AC02]		16.7 (4/24)	39, 26, 52, 28

Methyldopa [C02AB]		45.8 (11/24)	14, 15, 39, 30, 37, 22, 18, 36, 26, 52, 28
Moxonidine [C02AC05]		12.5 (3/24)	39, 52, 28
Reserpine [C02AA02]		12.5 (3/24)	14, 15, 52
Rilmenidine [C02AC06]		8.3 (2/24)	39, 52
Antiadrenergic agents (peripherally acting) [C02C]	May cause hypotension and cardiac and cerebrovascular disease	**25.0 (6/24)**	39, 37, 18, 26, 52, 28
Doxazosin [C02CA04]		20.8 (5/24)	37, 18, 26, 52, 28
Guanethidine [C02CC02]		4.2 (1/24)	52
Prazosin [C02CA01]		16.7 (4/24)	39, 26, 52, 28
Urapidil [C02CA06]		8.3 (2/24)	39, 52
Antiarrhythmics (Class I and III) [C01B]	May cause QT-prolongation and arrhythmias	**25.0 (6/24)**	15, 37, 33, 26, 52, 18
Amiodarone [C01BD01]		16.7 (4/24)	15, 37, 52, 18
Dronedarone [C01BD07]		12.5 (3/24)	33, 26, 52
Flecainide [C01BC04]		4.2 (1/24)	33
Propafenone [C01BC03]		4.2 (1/24)	33
Anticholinergic agents [N04A]	May cause orthostatic hypotension	**4.2 (1/24)**	52
Benzatropine [N04AC01]		4.2 (1/24)	52
Biperiden [N04AA02]		4.2 (1/24)	52
Orphenadrine [N04AB02]		4.2 (1/24)	52
Trihexyphenidyl [N04AA01]		4.2 (1/24)	52
Tropatepin [N04AA12]		4.2 (1/24)	52
Antiepileptics [N03A]	May cause bradycardia	**4.2 (1/24)**	52
Carbamazepine [N03AF01]		4.2 (1/24)	52
Antihistamines for systemic use [R06A]	May cause QT-prolongation	**8.3 (2/24)**	52, 33
Chlorpheniramine [R06AB02]		8.3 (2/24)	52, 33
Clemastine [R06AA04]		4.2 (1/24)	52
Dimetindene [R06AB03]		4.2 (1/24)	52
Doxylamine [R06AA09]		4.2 (1/24)	52
Triprolidine [R06AX07]		4.2 (1/24)	52
Antipsychotics [N05A]	May cause QT-prolongation and hypotension. Clozapine can also increase the risk of myocarditis.	**8.3 (2/24)**	22, 52
Clozapine [N05AH02]		4.2 (1/24)	22
Chlorpromazine [N05AA01]		4.2 (1/24)	52
Flupentixol [N05AF01]		4.2 (1/24)	52
Prochlorperazine [N05AB04]		4.2 (1/24)	52
Sertindole [N05AE03]		4.2 (1/24)	52
Trifluoperazine [N05AB [06]		4.2 (1/24)	52
Ziprasidone [N05AE04]		4.2 (1/24)	52
Zuclopenthixol [N05AF05]		4.2 (1/24)	52
Antithrombotic agents [B01A]	May cause orthostatic hypotension	**20.8 (5/24)**	14, 39, 37, 26, 52
Dipyridamole [B01AC07]		20.8 (5/24)	14, 39, 37, 26, 52
Anxiolytics [N05B]	May cause QT- prolongation	**4.2 (1/24)**	52
Hydroxyzine [N05BB01]		4.2 (1/24)	52
Agents acting on arteriolar smooth muscle [C02D]	May cause orthostatic hypotension	**4.2 (1/24)**	52
Hydralazine [C02DB02]		4.2 (1/24)	52
Beta blocking agents [C07A]	May cause cardiac arrhythmias	**8.3 (2/24)**	33, 19
Sotalol [C07AA07]		8.3 (2/24)	33, 19

Capillary stabilizing agents [C05C]	May cause orthostatic hypotension	**4.2 (1/24)**	52
Hidrosmin [C05CA05]		4.2 (1/24)	52
Cardiac glycosides [C01A]	May cause heart block	**8.3 (2/24)**	28, 33
Digoxin [C01AA05]		8.3 (2/24)	28, 33
Dopaminergic agents [N04B]	May cause orthostatic hypotension. Cabergoline and Pergolide may also cause cardiac valve fibrosis	**8.3 (2/24)**	33, 52
Cabergoline [N04BC06]		4.2 (1/24)	33
Pergolide [N04BC02]		4.2 (1/24)	33
Piribedil [N04BC08]		4.2 (1/24)	52
Pramipexole [N04BC05]		4.2 (1/24)	52
Ropinirole [N04BC04]		4.2 (1/24)	52
Rotigotine [N04BC09]		4.2 (1/24)	52
Selegiline [N04BD01]		4.2 (1/24)	
Drugs affecting bone structure and mineralization [M05B]	May cause venous thromboembolism	**4.2 (1/24)**	52
Strontium ranelate [M05BX03]		4.2 (1/24)	52
Drugs used in benign prostatic hypertrophy [G04C]	May cause hypotension. There is also an increased risk of cardiac and cerebrovascular disease	**4.2 (1/24)**	52
Terazosin [G04CA03]		4.2 (1/24)	52
Hypnotics and sedatives [N05C]	May cause cardiopulmonary death and hypotension	**4.2 (1/24)**	52
Clometiazole [N05CM02]		4.2 (1/24)	52
Propiomazine [N05CM06]		4.2 (1/24)	52
Muscle relaxants (centrally acting) [M03B]	May cause orthostatic hypotension	**4.2 (1/24)**	52
Baclofen [M03BX01]		4.2 (1/24)	52
Carisoprodol [M03BA02]		4.2 (1/24)	52
Cyclobenzaprine [M03BX08]		4.2 (1/24)	52
Methocarbamol [M03BA03]		4.2 (1/24)	52
Tetrazepam [M03BX07]		4.2 (1/24)	52
Tizanidine [M03BX02]		4.2 (1/24)	
Natural products	May cause orthostatic hypotension	**4.2 (1/24)**	52
Escin		4.2 (1/24)	52
Gingko Biloba		4.2 (1/24)	52
Other analgesics and antipyretics [N02B]	May cause hypertension	**4.2 (1/24)**	33
Acetylsalicylic acid [N02BA01]		4.2 (1/24)	33
Other cardiac preparations [C01E]	May cause cardiac arrhythmias	**4.2 (1/24)**	52
Ivabradine [C01EB17]		4.2 (1/24)	52
Other systemic drugs for obstructive airway diseases [R03D]	May cause cardiac arrhythmias	**8.3 (2/24)**	19, 52
Theophylline [R03DA04]		8.3 (2/24)	19, 52
Peripheral vasodilators [C04A]	May cause orthostatic hypotension	**8.3 (2/24)**	52, 27
Buflomedil [C04AX20]		4.2 (1/24)	52
Cyclandelate [C04AX01]		4.2 (1/24)	52
Dihydroergocristine [C04AE04]		4.2 (1/24)	52
Dihydroergotoxine		4.2 (1/24)	52
Moxisylyte [C04AX10]		4.2 (1/24)	52
Naftidrofuryl [C04AX21]		4.2 (1/24)	52
Nicergoline [C04AE02]		4.2 (1/24)	52
Pentoxifylline [C04AD03]		4.2 (1/24)	52

Vinburnine [C04AX17]		4.2 (1/24)	52
Vincamine [C04AX07]		4.2 (1/24)	52
Psychostimulants [N06B]	May cause orthostatic hypotension	**4.2 (1/24)**	52
Piracetam [N06BX03]		4.2 (1/24)	52
Quinolones antibacterials [J01M]	May cause cardiac arrhythmias	**4.2 (1/24)**	52
Ofloxacin [J01MA01]		4.2 (1/24)	52
Selective calcium channel blockers with direct cardiac effects [C08D]	May cause bradycardia	**4.2 (1/24)**	52
Diltiazem [C08DB01]		4.2 (1/24)	52
Verapamil [C08DA01]		4.2 (1/24)	52
Selective calcium channel blockers with mainly vascular effects [C08C]		**20.8 (5/24)**	15, 39, 30, 37, 18
Nifedipine [C08CA05]	May cause severe hypotension	20.8 (5/24)	15, 39, 30, 37, 18
Thyroid preparations [H03A]	May cause cardiac arrhythmias	**4.2 (1/24)**	30
Levothyroxine [H03AA01]		4.2 (1/24)	30
Urologicals [G04B]	May cause QT-prolongation	**4.2 (1/24)**	52
Oxybutynin (short acting) [G04BD04]		4.2 (1/24)	52
Oxybutynin (long acting) [G04BD04]		4.2 (1/24)	52
Solifenacin [G04BD08]		4.2 (1/24)	52
Tolterodine (short acting) [G04BD07]		4.2 (1/24)	52
Tolterodine (long acting) [G04BD07]		4.2 (1/24)	52
Psychostimulants [N06B]	May cause hypertension	4.2 (1/24)	15
Amphetamine [N06BA01]		4.2 (1/24)	15
Drug-disease interactions			
NSAIDs [M01A]	May exacerbate hypertension	**25.0 (6/24)**	17, 32, 37, 18, 43, 27
Antidepressants [N06A]	May exacerbate heart block, cardiac arrhythmias and postural hypotension	**29.2 (7/24)**	17, 40, 32, 21, 37, 18, 43
Tricyclic Antidepressants		29.2 (7/24)	17, 40, 32, 21, 37, 18, 43
Psychostimulants [N06B]	May exacerbate hypertension	**8.3 (2/24)**	14, 37
Amphetamine [N06BA01]		8.3 (2/24)	14, 37
Selective calcium channel blockers with direct cardiac effects [C08D]	May exacerbate heart block	**4.2 (1/24)**	32
Verapamil [C08DA01]		4.2 (1/24)	32
Antipsychotics [N05A]	May exacerbate postural hypotension and cardiac arrhythmias	**8.3 (2/24)**	40, 37
Chlorpromazine [N05AA01]		4.2 (1/24)	37
Thioridazine [N05AC02]		4.2 (1/24)	40
Cardiac glycosides [C01A]	May exacerbate heart block	**4.2 (1/24)**	40
Digoxin [C01AA05]		4.2 (1/24)	40
Nasal decongestants for systemic use [R01B]	May exacerbate hypertension	**4.2 (1/24)**	18
Pseudoephedrine [R01BA02]		4.2 (1/24)	18

CHAPTER 2.2

Identification of potentially inappropriate medications with risk of major adverse cardiac and cerebrovascular events among elderly patients in ambulatory setting and long-term care facilities

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ABSTRACT

Purpose: Cardiovascular diseases (CVDs) are extremely common among the elderly, but information on the use of potentially inappropriate medications (PIMs) with cardiovascular risk is scarce. We aimed to determine the prevalence of PIMs with risk of cardiac and cerebrovascular adverse events (CCVAEs), including major adverse cardiac and cerebrovascular events (MACCE).

Patients and methods: A cross-sectional study was performed using a convenience sample from four long-term care facilities and one community pharmacy in Portugal. Patients were included if they were aged 65 or older and presented at least one type of medication in their medical and pharmacotherapeutic records from 2015 until December 2017. The main outcome was defined as the presence of PIMs with risk of MACCE and was assessed by applying a PIM-MACCE list that was developed from a previous study. All medications included in this list were assessed for their availability in Portugal.

Results: A total of 680 patients were included. Of those, 428 (63%) were female with a mean age of 78±8.1 years. Four-hundred and four (59.4%) patients were taking medications associated with CCVAEs risk (mean=1.7±1.0 drugs/patient), including 264 patients (38.8%) who used drugs with MACCE risk (mean=1.4±0.8 drugs/patient). Fifty percent of patients with a previous history of CVD (n=521) were taking PIMs with risk of CCVAEs, including 30.0% with risk of MACCE.

Conclusion: Our findings show that 50% of patients with previous history of CVD were taking drugs with risk of CCVAEs, and 30% with risk of MACCE. More tailored tools for the management of drug therapy in elderly patients with CVD are of major importance in clinical practice.

INTRODUCTION

The elderly are usually fragile and more susceptible to drug-related problems as a result of multimorbidity, polypharmacy, and physiological changes that affect the pharmacokinetics and pharmacodynamics of drugs.[1] Therefore, this population is more prone to using medications that can be considered inappropriate.

A potentially inappropriate medication (PIM) is any medication used by a patient that could introduce a significant risk of an adverse drug reaction (ADR), in particular when there is an equally or more effective alternative with lower risk available. In the elderly, ADRs can sometimes be difficult to recognize as they often present with unspecific symptoms (*e.g.* falls, fatigue, and orthostatic hypotension). ADRs are observed 2-3 times more often in the elderly and account for 5-17% of all hospital admissions.[2] A systematic review has found a mean prevalence of ADRs in the elderly of 11% (95%CI: 5.1-16.8%) and a prevalence of ADRs leading to hospitalization of 10% (95%CI: 7.2-12.8%). These authors have also shown that increased comorbid complexity and increased number of medications were significantly associated with an increased risk of ADRs.[3] It is estimated that 30-60% could be prevented.[2] A recent study has shown that 45.1% (95%CI: 33.1-57.2%) of the ADRs leading to hospitalization were preventable.[4] In the USA and Canada, the prevalence ranged between 14 and 37%;[5] in Europe, the prevalence ranged between 23 and 43%.[6] Differences found between both continents could be explained by different drug markets, different prescribing patterns, and most importantly, by the tool used to measure prevalence.[7]

Several tools have been developed to guide prescribing, to maximize the efficacy and safety of therapy, and to minimize the consequences of using PIMs, including costs, hospitalizations, and mortality.8 The Beers criteria (Mark Beers, MD) was the first tool, developed in 1991, and last updated in 2019 by the American Geriatric Society.[9,10] Since then, a considerable number of tools have been developed, describing not only PIMs, but also drug–drug and drug– disease interactions.3 Most of these tools are based on explicit criteria, i.e., are normally more drug- or disease-oriented and are developed based on literature review, expert opinions, and consensus techniques.[3]

Cardiovascular diseases ([CVDs] which also include cerebrovascular diseases) such as hypertension, coronary heart disease, congestive heart failure, stroke, and atrial fibrillation are prevalent among the elderly.[11] They represent one of the leading causes of death worldwide, with 17.7 million deaths registered in 2015 (31.0% of all-cause mortality).[12,13] In Europe, 3.9 million people (45.0% of all-cause mortality) have died from CVDs in 2016.[13]

Few studies have identified PIMs in patients with CVD. A study conducted in a cardiology service showed that 20% of hospitalized patients were previously exposed to a PIM in the ambulatory setting.[14] However, information on PIMs associated with risk of cardiovascular adverse events, especially with major adverse cardiac and cerebrovascular events (MACCE) for elderly is still scarce. Some of these medications can increase the risk of cardiovascular events or even exacerbate underlying conditions. Our previous systematic review showed that there is a restricted number of PIMs described addressing their association with the risk of cardiovascular adverse events.[20] Some pharmacotherapeutic groups have been established to be associated with cardiovascular events such as nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, selective calcium channel blockers, and dopaminergic agents. Unfortunately, the prevalence of those PIMs in elderly patients is still unknown.

The primary objective of this study was to assess the prevalence of PIMs with risk of MACCE in the elderly. We then specifically aimed to study the prevalence of PIMs with risk of cardiac and cerebrovascular adverse events (CCVAEs) and to study the presence of these PIMs in patients with previous history of CVD.

MATERIALS AND METHODS

STUDY DESIGN

A descriptive cross-sectional study was conducted, where a convenience sample (based on geographic criteria) of citizens living in long-term care facilities (LTCFs) in the region of Lisboa e Vale do Tejo and the region of Alentejo and independently in their own home (ambulatory) in the region of Lisboa e Vale do Tejo, Portugal were invited to participate. Citizens' information (including drug use) was collected from two LTCFs in the region of Lisboa e Vale do Tejo and two LTCFs in the other region of Alentejo. While, for individuals who live independently in their own home, citizens' information was collected from their community pharmacy.

POPULATION AND SAMPLE

The study population (n=904) consisted of 224 residents and 680 patients from the community pharmacy and the LTCF, respectively. In the LTCF, residents were eligible if they were aged 65 or older and living in the facility until 2017. In the community pharmacy, the study population was calculated based on the minimum legal number of inhabitants per pharmacy (3,500 inhabitants) and on the percentage of elderly living in the district of Cascais in 2016 (19.6%). Moreover, individuals were included if they were aged 65 or older and had their medication history available in the pharmacy database in 2017. We excluded patients if their records were out of date, i.e., if there were no sales in 2017.

OUTCOMES' DEFINITION AND MEASUREMENT

Our previous study focused on a systematic review of24 PIM-lists, where PIMs associated with CCVAEs and MACCE were identified (**Table 2.S1** shows the full list of those PIMs). As the primary outcome, the presence of PIMs with risk of MACCE was defined as PIMs with risk of causing stroke, transient ischemic attack, myocardial infarction, heart failure, and cardiovascular death. A secondary outcome was defined as the presence of PIMs with risk of CCVAEs including the risk of hypertension, orthostatic or postural hypotension, bradycardia, QT prolongation, and cardiac arrhythmias.

DATA EXTRACTION

Data were extracted for sociodemographics (age and sex), clinical features (number of comorbidities, previous history of CVD, and the presence of dementia), and drug-related characteristics (number of medications and presence of polypharmacy). The previous history of CVD and the presence of dementia were defined according to medication used to treat CVD and dementia, respectively, as a proxy. Polypharmacy was defined as taking five or more medications.15 Information on comorbidities was validated by one member of the research team (JPA) and then confirmed by a physician (LHC). For the records with medical diagnosis, the validation process was performed by comparing the available medical diagnoses with the medication used. When information was insufficient to reach a consensus, data were considered missing.

ETHICS AND CONFIDENTIALITY

The use of patients' medical and pharmacotherapeutic records was authorized by the clinical directors of all participating institutions. To ensure anonymity, alphanumeric codes were used to identify the patients. All research was conducted following the principles of the Helsinki Declaration. Ethics approval was obtained from Comissão de Ética para a Investigação nas Áreas de Saúde Humana e Bem-Estar da Universidade de Évora (document 14017).

DATA ANALYSIS

The total number of PIMs, total number of patients using PIMs, and total number of patients using PIMs with previous history of CVD were assessed. The most commonly described PIMs were analyzed and coded by pharmacotherapeutic groups, using the WHO ATC classification system.15 Statistical analysis was performed using IBM SPSS v.24.0. Descriptive statistics were used, where numerical variables were expressed using central tendency and dispersion measures (either as mean and SDs, whichever was applicable) and categorical variables as absolute and relative frequencies. Bivariate statistics were used to compare both settings regarding differences

in sociodemographic, clinical, and pharmacotherapeutic features. Chi-squared test and Student's t-test for independent samples were used, whichever was applicable considering a 95% CI. For numerical variables, normal distribution was also assessed.

The prevalence of PIMs with the risk of CCVAE or MACCE occurrence was calculated using the following formula:

$$\text{Prevalence of PIMs} = \frac{\text{Elder patients presenting one or more PIMs with CV risk}}{\text{Total number of older individuals}}$$

RESULTS

PATIENTS' CHARACTERISTICS

From the initial 904 elderly patients, 63 were excluded from the LTCF sample and 161 from the community pharmacy sample due to missing data or records which were out of date. The final sample consisted of 680 patients, in which most of them were female (n=428; 62.9%) with a mean age of 78.4±8.1 years (range: 65; 101). Patients had a mean of 3.7±1.8 comorbidities, approximately 77.0% (n=521) presented with a history of CVD, and 10.7% (n=73) also presented with dementia. The total number of medications prescribed was 5,112, with a mean number of medications taken per patient of 7.5±4.2. **Table 2.2.1** describes the sample's sociodemographic and clinical features and details the differences by settings. In LTCF, patients were older than in the ambulatory setting (85.4±6.5 vs 76.7±7.5; p<0.0001). Patients in LTCFs were also more associated with a higher number of comorbidities (4.7 vs 3.5 comorbidities/patient; p<0.0001) and medications used (10.4 vs 6.8 medications/patient; p<0.0001) compared to ambulatory care.

PIM WITH RISK OF CCVAE

After applying the PIM-list specific for CCVAEs, a total of 682 PIMs were identified from the overall sample. Most of the patients (55.2%) took one PIM with a mean number of 1.7±1.0 PIMs used per patient. The prevalence of PIMs with risk of CCVAEs was 59.4% (n=404) and 47.4% (n=322) of patients had a previous history of CVD.

The prevalence of these PIMs among the elderly in LTCFs was substantially higher when compared to the ambulatory setting (78.1% vs 54.7%; p<0.0001). A similar proportion was observed for patients with a previous history of CVD (63.5% in LTCFs vs 46.6% in ambulatory setting; p<0.0001). These patients were also more prone to using two PIMs when compared to patients from ambulatory setting (33.6% in LTCFs vs 19.1% in ambulatory setting; P=0.001). **Table 2.2.2** summarizes all previously described data.

In the overall sample, the pharmacotherapeutic groups most commonly found associated with cardiovascular risk of adverse events were: non-steroidal anti-inflammatory drugs ([NSAIDs] n=199; 29.7%); antipsychotics (n=118; 17.6%); thyroid preparations, i.e., levothyroxine (n=70; 10.4%); and antidepressants (n=57; 8.5%). Other drug classes were also found to a lower extent: peripheral vasodilators, e.g., nicergoline and pentoxifylline (n=33; 4.9%), natural products, e.g., gingko biloba (n=25; 3.7%), antiarrhythmics, e.g., amiodarone, flecainide, and propafenone (n=19; 2.8%); and cardiac glycosides, e.g., digoxin (n=18; 2.7%). **Table 2.2.3** describes all the pharmacotherapeutic groups with risk of CCVAEs found in the overall sample.

NSAIDs were mostly used by patients recruited from the community pharmacy (12.7% in LTCFs vs 36.2% in ambulatory setting), as well as thyroid preparations (8.8% in LTCFs vs 11.1% in ambulatory setting). Conversely, antipsychotics (38.7% vs 9.9% in ambulatory setting), dopaminergic agents (3.3% vs 0.6% in ambulatory setting), and cardiac glycosides (6.6% vs 1.2% in ambulatory setting) were more frequently found in patients from LTCFs.

PIM WITH RISK OF MACCE

From the 682 PIMs identified, more than a half (n=378) were associated with risk of MACCE. A mean number of 1.4±0.8 PIMs were used per patient, with the majority of them using between one and two PIMs (92.4%). In the overall sample, the prevalence of PIMs with risk of MACCE was 38.8% (n=264), and 29.7% (n=202) of patients also had a previous history of CVD (**Table 2.2.2**).

The prevalence of these PIMs among the elderly was substantially higher in LTCFs compared to the ambulatory setting (51.8% vs 35.5%, respectively; $p<0.0001$). A similar proportion was observed for patients with a previous history of CVD (40.1% in LTCFs vs 27.1% in ambulatory setting; P=0.003).

NSAIDs (n=199; 53.1%) and antipsychotics (n=118; 31.5%) were the most prevalent drug classes in the overall sample. However, antipsychotics were mostly used by patients in LTCFs, and NSAIDs by patients from the ambulatory setting. To a lower extent, antidepressants (e.g., venlafaxine), selective calcium channel blockers with mainly vascular effects (e.g., nifedipine) were also identified. The individual drugs most commonly found in each group were: quetiapine (n=48; 40.7%); ibuprofen (n=46; 23.1%); diclofenac (n=43; 21.6%); melperone (n=19; 16.1%); cyamemazine (n=13; 11.0%); etoricoxib (n=20; 10.0%); and naproxen (n=20; 10.0%). **Table 2.2.4** summarizes all the PIMs with risk of MACCE identified in the overall sample and by setting.

No differences were found in the distribution of pharmacotherapeutic groups. In patients with previous history of CVD, 91.7% (LTCFs =22/ambulatory =24) were using nifedipine, 81.0%

(17/21) venlafaxine, 77.0% (10/13) estrogen, 76.7% (69/90) antipsychotics, and 76.1% (118/155) NSAIDs.

One of the subpopulations where antipsychotics should be avoided is the demented elderly patient. From the 73 demented patients, more than half (n=39; 53.4%) were taking antipsychotics.This value was even higher if we only restricted the analysis to LTCFs: 88% (22/25). Conversely,a lower proportion of patients in primary care used antipsychotics (n=17; 35.4%). In addition, thetype of antipsychotics selected also seemed to be influenced by setting, where second-generation antipsychotics were more widely found in the ambulatory setting, whilst first-generation antipsychotics were most common in LTCFs.

DISCUSSION

This study enabled the possibility of assessing the prevalence of PIMs with risk of CCVAEs and MACCE in an elderly Portuguese sample and, to the best of our knowledge this is the first study focusing on this topic in Europe. Inappropriate prescribing is more likely to occur in the elderly since this subpopulation is generally using more medications to treat several chronic conditions. In this study, patients presented an average of 3.7±1.8 comorbidities and were taking on average 7.5±4.2 medications. The majority of these patients were taking PIMs with CCVAE risk (59.4%) and almost half of them were associated with MACCE risk. It is well-known that CVDs are frequently found in the elderly and are an important cause of morbidity and mortality in these patients. Thus, in patients with a previous history of CVD, the prevalence of PIM use was also high. A previous study focusing on the identification and quantification of PIMs with MACCE risk, using tools addressing inappropriate prescribing, was used to assess the prevalence of these medications in our sample. This list was driven by a previous systematic review that included 24 of the tools currently available (e.g., Beers criteria, START/STOPP criteria, and Zhan criteria). Different studies, in different health care settings, have also investigated the prevalence of PIMs, but did not focus on a specific negative outcome. In Portugal, da Costa et al (2016) used different criteria to assess the prevalence of PIMs in elderly residents in nursing homes. They found that using Beers criteria, Beers criteria adapted to Portugal and START/STOPP criteria, the prevalence of PIMs was 85.1%, 60.3%, and 75.4%, respectively. These patients had an average age of 84.7±6.35 years and a mean of 4.1±2.14 comorbidities.[16] Another study, conducted by Nyborg et al (2017), showed that the prevalence of PIMs in Norwegian elderly was 43.8%, using the Norwegian General Practice Nursing Home (NORGEP-HN) criteria.[17] In the outpatient setting, in the USA, the prevalence of PIMs was 23.3% and 16.2% using the Beers criteria and Zhan criteria, respectively.[18]

The elderly tend to present with multiple chronic conditions, which increases the odds of using multiple medications. Many patients in this study had a previous history of CVDs and 10% also presented with dementia. The most commonly prescribed pharmacotherapeutic groups were NSAIDs and antipsychotics. NSAIDs are known to be associated with exacerbation of heart failure and to cause major cardiac events like stroke and myocardial infarction. Among NSAIDs, selective cyclooxygenase-2 (COX-II) inhibitors (e.g., etoricoxib and celecoxib) are associated with an increased risk of myocardial infarction.[19] In this study, 15.5% of patients took selective COX-II inhibitors. The 2015 Beers criteria alert for the potentially inappropriate prescribing of antipsychotics in patients with dementia. This pharmacotherapeutic group is known to be associated with an increased risk of stroke.[10] Even though not many demented patients were found in our sample, almost 77.0% of them were taking antipsychotics. These medications were commonly used in patients in LTCFs, where more frail elderly patients can be found, and are normally used in combination with other high-risk medications for cardiovascular events, such as dopaminergic agents or antidepressants.

We assume patients in LTCFs seem to have a higher risk of MACCE occurrence because of a higher prevalence of PIMs' use, in addition, a higher prevalence of medications with higher odds of drug–drug and drug–disease interactions was found. Additionally, these elderly patients have more comorbidities and use more medications increasing the cardiovascular risk for future events. These findings suggest that more attention should be paid to tertiary care to optimize medication, by reducing the use of these drugs.

The high prevalence of PIMs with the risk of CCVAEs and MACCE may suggest that interventions targeted at medication misuse need to be further developed and implemented into practice. However, we should keep in mind that the existing criteria, in most cases, do not explicitly assess patient-related indicators (e.g., weight, cardiac disturbances, and patients with high cardiovascular risk score) or drug-related indicators (e.g., route of administration, dosage, and frequency of exposure). A good example is levothyroxine. This drug does not have an alternative suggested in the lists and sometimes is considered as potentially inappropriate, given the risk for cardiac arrhythmias. This is surely a drawback in practice if we consider the likelihood of a clinician basing his decisions on such lists. Perhaps more complex and tailored indicators should be developed to target high-risk patients where the PIMs identified are indeed potentially inappropriate for that specific individual. A possible example of an intervention could be the familiarization or even the inclusion of these last indicators in an information and technology strategy to foster de-prescribing during the medication review process, where full clinical and laboratory details would be embedded in the software.

LIMITATIONS

This study has some limitations. First, to assess drug use in the ambulatory setting, we reported community pharmacy data which limited our ability to extract accurate information on patients' comorbidities, and consequently the capacity to judge drug–disease interactions. Second, the number of comorbidities, the previous history of CVD, and the presence of dementia were based on the analysis of the pharmacotherapeutic regimen of each patient available in the community pharmacy and LTCF. We therefore believe that comorbidities are more likely to be underreported and some misclassification bias could also be present. However, to minimize this bias, we have assessed comorbidities as a group (history of CVD or dementia), instead of using individual diagnoses from both settings. Third, we had incomplete information on all drug-related variables in both settings, which did not allow for the extraction of the frequency of exposure. Finally, although we had a good sample size, the results should only be generalized to elderly patients included in those regions (restricted to both settings) and not nationwide.

CONCLUSION

More than half of the elderly included in our sample were using PIMs with risk of CCVAEs, and approximately 40% of those were associated with risk of MACCE. About half of patients with a previous history of CVD took PIMs. The most commonly used PIMs with risk of MACCE were NSAIDs and antipsychotics, which accounted for almost half of the total drugs assessed in this sample. Future interventions and more tailored tools for the management of drug therapy in elderly patients with CVD are of major importance.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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Table 2.2.1 - Sociodemographic and clinical features of the Portuguese elderly sample

Characteristic	Total (n=680)	LTCFs (n=137)	Ambulatory setting (n=543)	*p*- value
Age – n (%), years				
65 – 74	**251 (36.9)**	9 (6.6)	242 (44.6)	
75 – 84	**255 (37.5)**	46 (33.6)	209 (38.5)	<0.0001*
≥ 85	**173 (25.4)**	81 (59.1)	92 (16.9)	
Age – Mean ± SD, years	**78.4±8.1**	85.4±6.5	76.7±7.5	<0.0001*
Male gender – n (%)	**252 (37.1)**	41 (29.9)	211 (38.9)	0.053
Comorbidities – Mean ± SD	**3.7±1.8**	4.7±2.3	3.5±1.6	<0.0001*
Comorbidities – n (%)				
1 – 3	**321 (47.2)**	46 (33.6)	275 (50.6)	
4	**176 (25.9)**	30 (21.9)	146 (26.9)	
5	**86 (12.6)**	16 (11.7)	70 (12.9)	
6	**46 (6.8)**	12 (8.8)	34 (6.3)	<0.0001*
7	**18 (2.6)**	12 (8.8)	6 (1,1)	
8	**18 (2.6)**	9 (6.6)	9 (1.7)	
≥ 9	**15 (2.2)**	12 (8.8)	3 (0.6)	
Previous history of CVD – n (%)	**521 (76.6)**	110 (80.3)	411 (75.7)	0.256
Dementia – n (%)	**73 (10.7)**	25 (18.2)	48 (8.8)	0.001*
Polypharmacy – n (%)	**509 (74.9)**	135 (98.5)	373 (68.7)	<0.0001*
Number of medications – Mean ± SD	**7.5±4.2**	10.4±3.9	6.8±4.0	<0.0001*
Number of medications – n (%)				
1 – 5	**240 (35.3)**	8 (5.8)	232 (42.7)	
6 – 7	**133 (19.6)**	22 (16.0)	111 (20.4)	
8 – 9	**112 (16.5)**	35 (25.5)	77 (14.2)	<0.0001*
10 – 11	**87 (12.8)**	27 (19.7)	60 (11.0)	
12 – 13	**52 (7.6)**	24 (17.5)	28 (5.2)	
14 – 15	**23 (3.4)**	8 (5.8)	15 (2.8)	
≥ 16	**33 (4.9)**	13 (9.5)	20 (3.7)	

Abbreviation: SD – Standard Deviation
*statistically significant ($p < 0.05$)

Table 2.2.2 – Number of patients using PIMs associated with risk of CCVAE or MACCE

Type of PIMs	Total	Long-term care facilities	Ambulatory setting	*p*-value
PIMs with risk of CCVAE				
Total number of PIMs – n (%)	**682 (13.3)**	185 (12.9)	497 (13.5)	-
Mean number of PIMs/patient – Mean±SD	**1.7±1.0**	1.7±0.9	1.7±1.0	0.409
1 PIM – n (%)	**223 (55.2)**	54 (50.5)	169 (56.9)	
2 PIM	**113 (28.0)**	36 (33.6)	77 (25.9)	
3 PIM	**49 (12.1)**	12 (11.2)	37 (12.5)	0.409
4 PIM	**12 (3.0)**	3 (2.8)	9 (3.0)	
≥ 5 PIMs	**7 (1.7)**	2 (1.9)	5 (1.7)	
Total number of patients with PIMs – n (%)	**404 (59.4)**	107 (78.1)	297 (54.7)	<0.0001*
Total number of patients with PIMs and previous history of CVD – n (%)	**322 (47.4)**	87 (63.5)	253 (46.6)	<0.0001*
PIMs with risk of MACCE				
Total number of PIMs – n (%)	**378 (7.4)**	100 (7.0)	278 (7.6)	-
Mean number of PIMs – Mean±SD	**1.4±0.8**	1.4±0.8	1.4±0.8	0.336
1 PIM – n (%)	**182 (68.9)**	53 (74.6)	129 (66.8)	
2 PIM	**62 (23.5)**	11 (15.5)	51 (26.4)	
3 PIM	**11 (4.2)**	4 (5.6)	7 (3.6)	0.336
4 PIM	**6 (2.3)**	2 (2.8)	4 (2.1)	
≥ 5 PIMs	**3 (1.1)**	1 (1.4)	2 (1.0)	
Total number of patients with PIMs – n (%)	**264 (38.8)**	71 (51.8)	193 (35.5)	<0.0001*
Total number of patients with PIMs and previous history of CVD – n (%)	**202 (29.7)**	55 (40.1)	147 (27.1)	0.003*

Abbreviation: CCVAE – Cardiac and Cerebrovascular Adverse Event; CVD – Cardiovascular Diseases; MACCE – Major Adverse Cardiac and Cerebrovascular Events; PIMs – Potentially Inappropriate Medications; SD – Standard Deviation
*statically significant ($p < 0.05$)

Table 2.2.3 - Most commonly prescribed pharmacotherapeutic groups associated with risk of CCVAE in both settings

Pharmacotherapeutic groups with risk of CCVAE – n (%)	ATC Code	Total	Long-term care facilities	Ambulatory setting
Antiadrenergic agents (centrally acting)	C02A	**12 (1.8)**	0 (0.0)	12 (2.5)
Antiarrhythmics (Class I and III)	C01B	**19 (2.8)**	5 (2.8)	14 (2.9)
Antidepressants	N06A	**57 (8.5)**	19 (10.5)	38 (7.8)
Antipsychotics	N05A	**118 (17.6)**	70 (38.7)	48 (9.9)
Anxiolytics	N05B	**13 (1.9)**	5 (2.8)	8 (1.6)
Beta blocking agents	C07A	**5 (0.7)**	0 (0.0)	5 (1.0)
Capillary stabilizing agents	C05C	**8 (1.2)**	2 (1.1)	6 (1.2)
Cardiac glycosides	C01A	**18 (2.7)**	12 (6.6)	6 (1.2)
Dopaminergic agents	N04B	**9 (1.3)**	6 (3.3)	3 (0.6)
Drugs affecting bone structure and mineralization	M05B	**4 (0.6)**	1 (0.6)	3 (0.6)
Hormones and related agents	L02A	**13 (1.9)**	0 (0.0)	13 (2.7)
Muscle relaxants (centrally acting)	M03B	**13 (1.9)**	3 (1.7)	10 (2.1)
Natural products	-	**25 (3.7)**	6 (3.3)	19 (3.9)
Non-Steroids Anti-Inflammatory Drugs	M01A	**199 (29.7)**	23 (12.7)	176 (36.2)
Other cardiac preparations	C01E	**4 (0.6)**	1 (0.6)	3 (0.6)
Other systemic drugs for obstructive airway diseases	R03D	**7 (1.0)**	0 (0.0)	7 (1.4)
Peripheral vasodilators	C04A	**33 (4.9)**	8 (4.4)	25 (5.1)
Psychostimulants	N06B	**6 (0.9)**	1 (0.6)	5 (1.0)
Selective calcium channel blockers with direct cardiac effects	C08D	**9 (1.3)**	0 (0.0)	9 (1.9)
Selective calcium channel blockers with mainly vascular effects	C08C	**24 (3.6)**	3 (1.7)	21 (4.3)
Thyroid preparations	H03A	**70 (10.4)**	16 (8.8)	54 (11.1)
Urologicals	G04B	**4 (0.6)**	0 (0.0)	4 (0.8)

Abbreviation: CCVAE – Cardiac and Cerebrovascular Adverse Events

Table 2.2.4 - Most commonly prescribed PIMs associated with risk of MACCE in both settings

PIMs associated with risk of MACCE – n (%)	Total	Long-term care facilities	Ambulatory setting
Antidepressants	**21 (5.6)**	**2 (2.0)**	**19 (6.9)**
Venlafaxine	21 (100.0)	2 (100.0)	19 (100.0)
Antipsychotics	**118 (31.5)**	**70 (71.4)**	**47 (17.2)**
Amisulpride	7 (5.9)	0 (0.0)	7 (14.9)
Aripiprazole	2 (1.7)	0 (0.0)	2 (4.4)
Cyamemazine	13 (11.0)	11 (15.7)	2 (4.4)
Chlorpromazine	2 (1.7)	2 (2.9)	0 (0.0)
Clozapine	7 (5.9)	3 (4.3)	4 (8.5)
Fluphenazine	1 (0.8)	1 (1.4)	0 (0.0)
Haloperidol	5 (4.2)	5 (7.1)	0 (0.0)
Levomepromazine	1 (0.8)	0 (0.0)	1 (2.2)
Melperone	19 (16.1)	17 (24.3)	2 (4.4)
Olanzapine	6 (5.0%)	4 (5.7)	2 (4.4)
Paliperidone	1 (0.8)	0 (0.0)	1 (2.2)
Quetiapine	48 (40.7)	26 (37.1)	22 (46.8)
Risperidone	5 (4.2)	0 (0.0)	5 (10.6)
Tiapride	1 (0.8)	1 (1.4)	0 (0.0)
Hormones and related agents	**13 (3.5)**	**0 (0.0)**	**13 (4.7)**

Table 2.2.4 – (Continued)

Estrogen	13 (100.0)	0 (0.0)	13 (100.0)
Non-Steroids Anti-Inflammatory Drugs	**199 (53.1)**	**23 (23.5)**	**175 (63.9)**
Aceclofenac	10 (5.0)	4 (17.4)	6 (3.4)
Acemetacin	1 (0.5)	1 (4.3)	0 (0.0)
Aspirin (500 mg)	7 (3.5)	0 (0.0)	7 (4.0)
Celecoxib	11 (5.5)	8 (34.8)	3 (1.7)
Diclofenac	43 (21.6)	3 (13.0)	40 (22.9)
Etodolac	5 (2.5)	1 (4.3)	4 (2.4)
Etoricoxib	20 (10.0)	1 (4.3)	19 (10.9)
Flurbiprofen	15 (7.5)	0 (0.0)	15 (8.6)
Ibuprofen	46 (23.1)	3 (13.0)	43 (24.6)
Indometacin	2 (1.0)	0 (0.0)	2 (1.2)
Mefenamic acid	1 (0.5)	0 (0.0)	1 (0.6)
Naproxen	20 (10.0)	2 (8.6)	18 (10.3)
Nimesulide	16 (8.0)	0 (0.0)	16 (9.1)
Piroxicam	2 (1.0)	0 (0.0)	2 (1.2)
Selective CCB with mainly vascular effects	**24 (6.4)**	**3 (3.1)**	**21 (7.7)**
Nifedipine	24 (100.0)	3 (100.0)	21 (100.0)

Abbreviation: MACCE – Major Adverse Cardiac and Cerebrovascular Events; PIMs – Potentially Inappropriate Medication

APPENDICES

SUPPLEMENTARY MATERIAL

Table 2.S1 – Potentially Inappropriate Medications with risk of cardiovascular adverse events in the elderly

Adverse Drug Reactions (ADRs)	PIMs (Medication classes or individual drugs)
Major Adverse Cardiac and Cerebrovascular Events (MACCE)	
Stroke	**NSAIDs [M01A]** COX-II Inhibitors [M01AH] **Antipsychotics [N05A]** Pimozide [N05AG02] **Hormones and related agents [L02A]** Estrogens [L02AA] **Selective calcium channel blockers with mainly vascular effects [C08C]** Nicardipine [C08CA04] Short acting nifedipine [C08CA05] Long acting nifedipine [C08CA05] **Antidepressants [N06A]** Venlafaxine [N06AX16]
Myocardial Infarction	**NSAIDs [M01A]** COX-II Inhibitors [M01AH] **Amphetamines** **Selective calcium channel blockers with mainly vascular effects [C08C]** Nicardipine [C08CA04] Short acting nifedipine [C08CA05] Long acting nifedipine [C08CA05]
Sudden Cardiac Death	**Propulsives [A03F]** Domperidone (> 30mg/d) [A03FA03]
Heart Failure	**NSAIDs [M01A]** COX-II Inhibitors [M01AH] Naproxen (long-term use) [M01AE02] Piroxicam (long-term use) [M01AC0] Oxaprozin (long-term use) [M01AE12] **Urologicals [G04B]** Sildenafil [G04BE03] Tadalafil [G04BE08] **Antiarrhythmics (Class I and III) [C01B]** Disopyramide [C01BA03]
Cardiac and Cerebrovascular Adverse Events (CCVAEs)	
Hypertension	**NSAIDs [M01A]** Aceclofenac [M01AB16] Acemetacin [M01AB11] Celecoxib [M01AH01] Dexketoprofen [M01AE17] Diclofenac [M01AB05] Etoricoxib [M01AH05] Flurbiprofen [M01AE09] Ibuprofen [M01AE01] Indometacin [M01AB01] Ketoprofen [M01AE03] Lornoxicam [M01AC05] Mefenamic acid [M01AG01]

Table S1 – (Continued)

	Meloxicam [M01AC06]
	Nabumetone [M01AX01]
	Naproxen [M01AE02]
	Oxaprozin [M01AE12]
	Piroxicam [M01AC01]
	Other analgesics and antipyretics [N02B]
	Acetylsalicylic acid [N02BA01]
	Psychostimulants [N06B]
	Amphetamine [N06BA01]
	Antidepressants [N06A]
Heart block	Amitriptyline [N06AA09]
	Amoxapin [N06AA17]
	Clomipramine [N06AA04]
	Desipramine [N06AA01]
	Doxepin [N06AA12]
	Dosulepin [N06AA16]
	Imipramine [N06AA02]
	Maprotiline [N06AA21]
	Nortriptyline [N06AA10]
	Reboxetine [N06AX18]
	Tranylcypromine [N06AF04]
	Trimipramine [N06AA06]
	Cardiac glycosides [C01A]
	Digoxin [C01AA05]
	Antidepressants [N06A]
	Amitriptyline [N06AA09]
	Amoxapin [N06AA17]
	Clomipramine [N06AA04]
	Desipramine [N06AA01]
	Doxepin [N06AA12]
	Dosulepin [N06AA16]
	Imipramine [N06AA02]
	Maprotiline [N06AA21]
	Nortriptyline [N06AA10]
	Reboxetine [N06AX18]
	Tranylcypromine [N06AF04]
	Trimipramine [N06AA06]
	Antiadrenergic agents (centrally acting) [C02A]
	Clonidine [C02AC01]
	Guanabenz
Postural and orthostatic hypotension	Guanfacine [C02AC02]
	Methyldopa [C02AB]
	Moxonidine [C02AC05]
	Reserpine [C02AA02]
	Rilmenidine [C02AC06]
	Antiadrenergic agents (peripherally acting) [C02C]
	Doxazosin [C02CA04]
	Guanethidine [C02CC02]
	Prazosin [C02CA01]
	Urapidil [C02CA06]
	Anticholinergic agents [N04A]
	Benzatropine [N04AC01]
	Biperiden [N04AA02]
	Orphenadrine [N04AB02]
	Trihexyphenidyl [N04AA01]

Table S1 – (Continued)

Tropatepin [N04AA12]
Antipsychotics [N05A]
Clozapine [N05AH02]
Chlorpromazine [N05AA01]
Flupentixol [N05AF01]
Prochlorperazine [N05AB04]
Sertindole [N05AE03]
Trifluoperazine [N05AB [06]
Ziprasidone [N05AE04]
Zuclopenthixol [N05AF05]
Antithrombotic agents [B01A]
Dipyridamole [B01AC07]
Agents acting on arteriolar smooth muscle [C02D]
Hydralazine [C02DB02]
Capillary stabilizing agents [C05C]
Hidrosmin [C05CA05]
Dopaminergic agents [N04B]
Cabergoline [N04BC06]
Pergolide [N04BC02]
Piribedil [N04BC08]
Pramipexole [N04BC05]
Ropinirole [N04BC04]
Rotigotine [N04BC09]
Selegiline [N04BD01]
Drugs used in benign prostatic hypertrophy [G04C]
Terazosin [G04CA03]
Hypnotics and sedatives [N05C]
Clometiazole [N05CM02]
Propiomazine [N05CM06]
Muscle relaxants (centrally acting) [M03B]
Baclofen [M03BX01]
Carisoprodol [M03BA02]
Cyclobenzaprine [M03BX08]
Methocarbamol [M03BA03]
Tetrazepam [M03BX07]
Tizanidine [M03BX02]
Natural products
Escin
Peripheral vasodilators [C04A]
Buflomedil [C04AX20]
Cyclandelate [C04AX01]
Dihydroergocristine [C04AE04]
Dihydroergotoxine
Moxisylyte [C04AX10]
Naftidrofuryl [C04AX21]
Nicergoline [C04AE02]
Pentoxifylline [C04AD03]
Vinburnine [C04AX17]
Vincamine [C04AX07]
Psychostimulants [N06B]
Piracetam [N06BX03]
Selective calcium channel blockers with mainly vascular effects [C08C]
Nifedipine [C08CA05]

Table S1 – (Continued)

	Antidepressants [N06A]
	Amitriptyline [N06AA09]
	Amoxapin [N06AA17]
	Clomipramine [N06AA04]
	Desipramine [N06AA01]
	Doxepin [N06AA12]
	Dosulepin [N06AA16]
	Imipramine [N06AA02]
	Maprotiline [N06AA21]
	Nortriptyline [N06AA10]
	Reboxetine [N06AX18]
	Tranylcypromine [N06AF04]
	Trimipramine [N06AA06]
	Antiarrhythmics (Class I and III) [C01B]
Cardiac Arrhythmias	Amiodarone [C01BD01]
	Dronedarone [C01BD07]
	Flecainide [C01BC04]
	Propafenone [C01BC03]
	Beta blocking agents [C07A]
	Sotalol [C07AA07]
	Other cardiac preparations [C01E]
	Ivabradine [C01EB17]
	Other systemic drugs for obstructive airway diseases [R03D]
	Theophylline [R03DA04]
	Quinolones antibacterials [J01M]
	Ofloxacin [J01MA01]
	Thyroid preparations [H03A]
	Levothyroxine [H03AA01]
	Antiadrenergic agents (centrally acting) [C02A]
	Clonidine [C02AC01]
	Guanabenz
	Guanfacine [C02AC02]
	Methyldopa [C02AB]
	Moxonidine [C02AC05]
	Reserpine [C02AA02]
Bradycardia	Rilmenidine [C02AC06]
	Antiepileptics [N03A]
	Carbamazepine [N03AF01]
	Selective calcium channel blockers with direct cardiac effects [C08D]
	Diltiazem [C08DB01]
	Verapamil [C08DA01]
	Antiarrhythmics (Class I and III) [C01B]
	Amiodarone [C01BD01]
	Dronedarone [C01BD07]
	Flecainide [C01BC04]
	Propafenone [C01BC03]
	Antihistamines for systemic use [R06A]
QT-prolongation	Chlorpheniramine [R06AB02]
	Clemastine [R06AA04]
	Dimetindene [R06AB03]
	Doxylamine [R06AA09]
	Triprolidine [R06AX07]
	Antipsychotics [N05A]
	Clozapine [N05AH02]

Table S1 – (Continued)	
	Chlorpromazine [N05AA01]
	Flupentixol [N05AF01]
	Prochlorperazine [N05AB04]
	Sertindole [N05AE03]
	Trifluoperazine [N05AB [06]
	Ziprasidone [N05AE04]
	Zuclopenthixol [N05AF05]
	Anxiolytics [N05B]
	Hydroxyzine [N05BB01]
	Urologicals [G04B]
	Oxybutynin (short acting) [G04BD04]
	Oxybutynin (long acting) [G04BD04]
	Solifenacin [G04BD08]
	Tolterodine (short acting) [G04BD07]
	Tolterodine (long acting) [G04BD07]

Abbreviation: NSAIDs – Non-steroidal anti-inflammatory drugs

CHAPTER 3

Antipsychotics as relevant PIM with risk of cardiac and cerebrovascular adverse events

PERSPECTIVE

The purpose of this chapter was to elucidate whether a more pharmacologic perspective (e.g., different binding affinities to distinct receptors and metabolic side effects profile) could explain the occurrence of MACCE while using APs. APs were selected based on the results retained from previous chapter, where we found that this drug class was one of the PIMs with MACCE risk more reported in the different tools, and with a higher prevalence of use among older individuals from ambulatory setting and long-term care facilities. This chapter will present a study conducted in a global pharmacovigilance database to explore a possible association between receptor binding affinities and metabolic side effects profile and reporting of MACCE in Individual Case Safety Reports.

CHAPTER 3.1

The association between receptor binding affinity and metabolic side effect profile of antipsychotic and major cardio- and cerebrovascular events: A case/non-case study using VigiBase

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ABSTRACT

Antipsychotics (APs) have been associated with major adverse cardio- and cerebrovascular events (MACCE), but the underlying mechanisms are unclear. Our aim was to elucidate the association between APs, stratified for receptor affinity and metabolic side effects (MSE), in the reporting of MACCE. A case/non-case study was conducted using data from the WHO global Individual Case Safety Report (ICSR) database, VigiBase, among all reports associated with an AP. Cases were ICSRs of MACCE, while non-cases were all other adverse drug reactions (ADRs). APs were classified by AP group, the degree of receptor affinity for adrenergic, dopaminergic, muscarinic, histaminic, and serotoninergic receptors and by MSE profile. The strength of the association was estimated with logistic regression and expressed as crude and adjusted reporting odds ratios (ROR adj.) with corresponding 95% confidence intervals (95%CIs). We identified 4987 reports of MACCE and 328,907 reports of other ADRs. Atypical APs (ROR adj. 2.46; 95%CI 2.20–2.74) were significantly associated with the reporting of MACCE compared to typical ones. APs with high affinity for Adrenergic alfa-1 (ROR adj. 2.98; 95%CI 1.93–4.59), Histaminic H_1 (ROR adj. 2.31; 95%CI 1.98–2.68), Muscarinic M_1 (ROR adj. 1.87; 95%CI 1.74–2.01), and Serotoninergic 5-HT_{2A} (ROR adj. 3.19; 95%CI 2.07–4.92) were associated with a higher risk of reporting of MACCE compared to low affinity. APs with higher-risk of MSE were associated with higher risk of reporting of MACCE (ROR adj. 1.88; 95%CI 1.73–2.05) compared to the lower-risk. APs with high affinity for Adrenergic alfa-1, Histaminic H_1 , Muscarinic M_1 , and Serotoninergic 5-HT_{2A} receptors and with high-risk of MSE may explain the occurrence of those events.

INTRODUCTION

The use of antipsychotics (APs) has increased in the last years worldwide. This drug class is often divided into two groups: (a) typical antipsychotics (TAPs); (b) and atypical antipsychotics (AAPs). TAPs, including for example haloperidol and fluphenazine, are available since the 1950s and have been widely used for decades in the treatment of certain psychiatric disorders. AAPs, introduced since the 1990s, have proven to be more effective in the treatment of negative psychotic symptoms and with lower risk of causing extrapyramidal effects.[1,2] However, APs use has been linked to several important adverse events, such as metabolic (e.g. weight gain, hypercholesterolemia, and diabetes), cerebro/cardiovascular events, and even sudden death.[3-5] APs are multi-target drugs, i.e. they are able to bind to different receptors in the human body, which may explain their adverse events profile. TAPs have been linked mostly to extrapyramidal effects, given their antagonism to dopaminergic receptors, whereas AAPs seem to be mostly associated with metabolic and cerebro/cardiovascular events, given their antagonism for adrenergic, serotoninergic, and histaminergic receptors.[2] Since 2004, results from clinical trials have shown that olanzapine and risperidone are associated with stroke in the elderly, which resulted in the implementation of several risk minimization strategies by the regulatory bodies (FDA –Food and Drug Administration, and EMA – European Medicines Agency) in 2008.[6,7] Since then, several epidemiological studies have investigated this association.[8] A recent systematic review identified nine observational studies and estimated that the odds of myocardial infarction (MI) occurrence was 1.88-fold higher (95% Confidence Interval–CI, 1.39–2.54) in antipsychotic users compared to non-users.[9] Another systematic review identified ten studies and estimated a significant increase in the risk of cerebrovascular accident with TAPs [Odds Ratio (OR)=1.49 (95%CI, 1.24–1.77)] but not with AAPs [OR=1.31 (95%CI, 0.74–2.30)].[10] Several mechanisms have been proposed to explain antipsychotic-induced MACCE. Metabolic syndrome, which is linked to weigh gain, increase of glucose, and triglycerides levels, seems to increase the risk of cardiovascular adverse events.[11] A cohort study has reported that antipsychotics that have been linked with a higher risk of metabolic side effects (e.g. clozapine and olanzapine) were associated with increased risk of MACCE [Relative Risk (RR)=2.82 (95%CI, 1.57–5.05)].[8] The different receptor affinity can also be an explanatory pathway. In preclinical studies, dopaminergic D_3 receptor located in the heart and peripheral vascular system may be related to atherosclerosis formation. Some serotoninergic receptors (*e.g.*, 5-HT_{2A}) seem to be activated by antipsychotics at sites of coronary atherosclerosis.[9] A recent case-crossover study has demonstrated a positive association between stroke risk and high M_1 muscarinic [AOR=1.47 (95%CI, 1.28–1.69)] and α_2 adrenergic [AOR=1.84 (95%CI, 1.64–2.07)] affinity.[11] Despite the association between AP use and MACCE, the underlying pharmacological

mechanisms remain unclear. Our main goal was to elucidate the association between antipsychotics, stratified for receptor affinity and MSE profile, in the reporting of MACCE.

EXPERIMENTAL PROCEDURE

SETTING

The World Health Organization (WHO) global Individual Case Safety Report (ICSR) database, VigiBase, is part of the WHO International Drug Monitoring Programme, which started in 1968, with the aim of identifying possible pharmacovigilance signals as soon as possible. Since 1978, the Uppsala Monitoring Centre (UMC) is responsible for maintaining and developing the VigiBase system, which includes the International Conference on Harmonization (ICH) guideline E2B compatible Individual Case Safety Reports database, the WHO Drug Dictionaries (WHO-DD and -DDE), the medical terminologies WHO Adverse Reaction Terminology (WHO-ART), the International Classification of Diseases (ICD), and the Medical Dictionary for Regulatory Activities (MedDRA).[12,13] The UMC collects all the cases of suspected ADRs spontaneously reported by healthcare professionals, lawyers, manufacturers or patients via the national pharmacovigilance centers. VigiBase contains more than 17 million ICSR collected in over 110 countries. From each ICSR sociodemographic data (*e.g.*, age, gender, seriousness of ADR), ADR-related data (e.g. descriptive term using MedDRA, date of onset of the reaction, and outcome), and suspected drug (e.g. drug name, drug start and stop dates, time to onset, dose, and indication) can be extracted. This database has been used for data mining studies as well as to investigate drug specific ADRs.[12]

STUDY DESIGN

A case/non-case study design in the WHO global ICSR database, VigiBase, including all reports associated with an AP as suspected drug between 1968 and October 2017 was undertaken. Cases were ICSRs of MACCE, while non-cases were all ICSRs containing other ADRs. As a composite endpoint, MACCE included cerebrovascular events (stroke and transient ischemic attack), MI, and cardiovascular death[14-16] and was defined using MedDRA Preferred Terms (**Supplementary material –Table 3.S1**). Reports with missing values on age and gender were excluded.

DEFINITION OF EXPOSURE

APs were identified using the WHO Anatomical Therapeutic Chemical (ATC) classification (ATC codes N05A, excluding N05AN01–lithium) and divided into two groups: TAPs and AAPs. The first group included 55 drugs, whereas the second one included 37 drugs. APs were classified by different receptor binding affinity and MSE profile. The degree of receptor affinity was studied for adrenergic (alfa-1 and alfa-2), dopamine (D_1, D_2, D_3 and D_4), histamine (H_1), muscarinic (M_1,

M_2, M_3, M_4 and M_5) and serotonin (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7) receptors. The binding affinities of each receptor were defined using the constant of affinity (K_a) and retrieved from Psychoactive Drug Screening Program funded by the National Institute of Mental Health (http://pdsp.med.unc.edu). Receptor affinity was categorized in three groups: low affinity (>1,000 nM), intermediate affinity (10–1000 nM), and high affinity (<10 nM).[17] These ranges were depicted in a gradient colour, with distinction of (partial) agonist and antagonist. Data were only available for 30 drugs out of the 92 initially identified (**Supplementary material –Table 3.S2**). MSE profiles were studied using data from previous literature, where APs were divided according to their risk of causing weight gain and increased levels of glucose and lipids.[6,17] APs were categorized in three groups: low-risk if they only caused weight gain; intermediate-risk if they caused weight gain plus increased levels of glucose or lipids; and high-risk if they caused weight gain and increased levels of glucose and lipids. For the full list of the antipsychotics included in each group, see **Supplementary material –Table 3.S3**.

COVARIATES

From each ICSR, data on age, sex, region, reporter type, and reporting year was extracted. Age was categorized in four groups: 0–17 years old, 18–44 years old, 45–64 years old, and aged 65 or older. Reporter type was divided into four categories: healthcare professionals, consumer or non-healthcare professionals, manufacturer, and other. Time periods were categorized into three groups: 1968–2009, 2010–2012, and 2013–2017.

DATA ANALYSIS

The unit of analysis in this study was the ICSR. Characteristics of the cases and non-cases were analysed using Chi-square test (age, sex, region, and reporting year). The association between reporting of MACCE and type of AP used (typical vs. atypical) was assessed using logistic regression analysis and expressed as Reporting Odds Ratio (ROR) with 95% confidence intervals (95%CI). The crude ROR was defined as a ratio of the odds of exposure in reports of cases and non-cases, and then adjusted for sex, age, region, and reporting year. TAPs were used as reference group. The analysis was also stratified based on sex and age groups, which are important effect modifiers when studying cardio- and cerebrovascular diseases. Receptor affinity was classified as “higher receptor affinity” when the value was <10 nM, as “intermediate affinity” when the value was between 10 and 1000 nM, and as “lower receptor affinity” when the value was >1000nM (reference group). MSE profile was classified into high-, intermediate- and low-risk (reference) groups. Two sensitivity analyses were performed: (a) the first one where only reportsfrom Europe and other regions were included, as Americas accounted for the majority of cases;
(b) and a second one, where only healthcare professionals’ reports were included.

RESULTS

STUDY POPULATION

By October 2017, out of the total 11,751,594 reports filled in VigiBase, there were 333,894 (2.8%) ICSRs, where APs were suspected drugs. Among these reports, 4,987 (1.5%) cases of MACCE and 328,907 non-cases (all other ADRs) were identified. Of the 4987 reports of MACCE, 2409 (48.3%) reported MI, 1496 (30.0%) reported cerebrovascular events (e.g. stroke and transient ischemic attack) and 1176 (23.6%) reported cardiovascular death (**Figure 3.1.1**).

The characteristics for MACCE-cases and non-cases are presented in **Table 3.1.1**. Cases of MACCE reports were more often from male older patients and reports came predominantly from the Americas (n=3,028; 60.7%).

ASSOCIATION BETWEEN ANTIPSYCHOTICS AND REPORTING OF MACCE

Clozapine was the most frequently suspected drug among MACCE cases (n=1,919; 38.5%), followed by quetiapine (n=901; 18.1%), olanzapine (n=785; 15.7%) and risperidone (n=411; 8.2%).

AAPs were statistically significantly associated with reporting of MACCE (ROR adj. 2.46; 95%CI 2.20–2.74) when compared to TAPs. Ziprasidone (ROR adj. 3.14; 95%CI 2.49–3.97), olanzapine (ROR adj. 2.64; 95%CI 2.22–3.15), and clozapine (ROR adj. 2.64; 95%CI 2.24–3.12) were associated with higher reporting of MACCE compared to haloperidol (**Table 3.1.2**).

ASSOCIATION BETWEEN ANTIPSYCHOTIC RECEPTOR BINDING AFFINITY AND REPORTING OF MACCE

When assessing the effect of receptor binding affinity and risk of MACCE, we found that the increase in the degree of affinity for adrenergic alfa-1 (High – ROR adj. 2.98; 95%CI 1.93–4.59; Intermediate – ROR adj. 2.74; 95%CI 1.78–4.22), histaminic H_1 (High – ROR adj. 2.31; 95%CI 1.98–2.68; Intermediate – ROR adj. 1.64; 95%CI 1.40–1.92), muscarinic M_1 (High – ROR adj. 1.87; 95%CI 1.74–2.01; Intermediate – ROR adj. 1.20; 95%CI 1.10–1.31), and serotoninergic 5-HT_{2A} (High – ROR adj. 3.19; 95%CI 2.07–4.92; Intermediate – ROR adj. 2.20; 95%CI 1.42–3.39), were associated with higher frequency of MACCE compared to low affinity (**Table 3.1.3**).

MACCE reporting rates seem to be related to adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} receptors antagonism given the heat map presented in the **Supplementary material –Table 3.S2**.

When analyzing the contribution of sex in the reporting of MACCE and receptor binding affinity, we found that the increase in the degree of affinity for adrenergic alfa- 1, histaminic H_1, and serotoninergic 5-HT_{2A} were associated with higher frequency of MACCE in men compared to women (adrenergic alfa-1 – men: High – ROR adj. 3.62; 95%CI 1.50–8.74; Intermediate – ROR adj. 3.06; 95%CI 1.27–7.41 vs women: High – ROR adj. 2.93; 95%CI 1.38–6.21; Intermediate – ROR adj. 2.40; 95%CI 1.13–5.08; histaminic H_1 – men: High – ROR adj. 4.31; 95%CI 3.17–5.84; Intermediate – ROR adj. 2.63; 95%CI 1.91–3.62 vs women: High – ROR adj. 2.41; 95%CI 1.84–3.16; Intermediate – ROR adj. 1.80;95%CI 1.36–2.38; serotoninergic 5-HT_{2A} –men: High – ROR adj. 3.78; 95%CI 1.57–9.13; Intermediate – ROR adj. 2.40; 95%CI 0.99–5.83 vs women: High – ROR adj. 2.70; 95%CI 1.27–5.71; Intermediate – ROR adj. 2.58; 95%CI 1.22–5.48). On the other hand, we found that there were no differences between reporting of MACCE and receptor binding affinity within the different age groups (**Supplementary material –Table 3.S10**).

ASSOCIATION BETWEEN ANTIPSYCHOTICS' METABOLIC SIDE EFFECTS PROFILE AND REPORTING OF MACCE

APs associated with intermediate- and high-risk of metabolic side effects (ROR adj. 1.33; 95%CI 1.21–1.46 and ROR adj. 1.88; 95%CI 1.73-2.05, respectively) were associated with higher reporting of MACCE compared to low-risk ones (**Table 3.1.4**).

SENSITIVITY ANALYSES

Results were consistent after excluding reports from the Americas (adjusted ROR for the association between different groups of APs and reporting of MACCE was 2.21, 95%CI 1.91–2.56) and when restricting the analysis to healthcare professionals' reports only (adjusted ROR 2.66, 95%CI 2.29–3.09). Furthermore, there were no major differences with the main analysis with respect to the results of the antipsychotics' receptor binding affinity and MSE profile.

DISCUSSION

In this study, we found an increased frequency of ICSRs AAPs being a suspected drug group in relation to the reporting of MACCE compared with other ADR reports. Our findings also suggest that a high affinity to some receptors, like adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A}, as well as a high MSE profile could explain the occurrence of such events.

The association between AP use and MACCE occurrence has been described for over a decade in the literature. In 2004, clinical trials have shown that olanzapine and risperidone were associated with an increased risk of stroke among the elderly. From 2008, this risk was generalized to all APs and several risk minimization measures were implemented.[6,18,19] Our findings have shown that there is a 2.5-fold increased risk of MACCE reports with AAPs being

the suspected drug group compared to TAPs. This is in line with recognized data that antipsychotic-induced cardiovascular adverse events are commonly linked to AAPs.[11]

In our study, MACCE definition included three main conditions: cerebrovascular events, MI, and cardiovascular death. Cardiovascular diseases are multifactorial conditions and, therefore, multiple mechanisms can be proposed as possible explanations, such as the degree of receptor affinity. We found that an increased degree of affinity for adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} receptors were associated with higher reporting of MACCE. All these receptors seem to play a role in the cardio- vascular system. Adrenergic receptors are a part of our sympathetic system and are normally associated with vasoconstriction, whereas muscarinic receptors act in the opposite direction stimulating a vagal response (vasodilatation and decrease in the heart rate and in the conduction velocity in the atrioventricular node). Interestingly, both types of receptors also seem to play a role in metabolic disorders, such as eating disorder. Histaminic receptors located in the brain are responsible, among others, for the regulation of feeding rhythms and energy metabolism.[11,20,21] Therefore, we hypothesized that APs with a high affinity for such receptors may cause: (a) tachycardia as a result of the blockage of muscarinic M_1; (b) reflex tachycardia as a result of the blockage of adrenergic alfa-1; (c) metabolic syndrome (e.g. weight gain, increased glucose and lipid levels) given the blockage of histaminic H_1. Increased affinity for serotoninergic 5-HT_{2A} receptor may be another possible pathway by which antipsychotics, especially atypical ones, could be linked to MACCE, becausethis receptor is normally present in the membrane of platelets and, therefore, could lead to majorbleedings (e.g. intracranial bleedings).[22] A study undertaken by Verdel et al. (2011) has shown that APs with medium- and high-affinity for 5-HT_{2A} receptor were associated with a higher risk of cerebral haemorrhage.[22] Wu et al. (2013) have also found an association between stroke and high muscarinic M_1 and adrenergic α_2 receptors' affinity.[11] A current meta-regression by Olten etal. (2018) showed that high affinity for M_1, H_1, and M_4 receptors were associated with weight gain in AP users, which may contribute to the development of metabolic syndrome.[20]

Conversely, obesity, diabetes and hypercholesterolemia are well known risk factors for cardiovascular diseases. APs with intermediate- and high-risk of metabolic side effects were associated with more frequent reporting of MACCE. This is in line with findings from a study conducted by Szmulewicz et al., 2017, who have shown that older adult patients using APs may face a higher incidence of major cardiovascular events than those using a low-risk regimen during long-term follow-up. These results support our findings from the receptor affinity analysis showing, that APs with high affinity for receptors involved in metabolic syndrome are a possible pathway for MACCE development.

Studies from our research group have also shown the existence of a time relationship between drug use and event occurrence. Knol et al. (2008) have shown that current users (defined as those finalizing a prescription within 7 days of the index date) had a 60% greater risk of pneumonia com- pared to non-users. They also showed that greater risk had an inversely proportional relationship to duration of treatment.[23] Later in 2011, another study has demonstrated the same results, where current users seem to be at higher risk when compared to non-users.[22]

To our knowledge this is the first study assessing the role of receptor affinity and MSE profile in antipsychotic- induced MACCE using data from the global pharmacovigilance database, VigiBase. Results from this study suggest that different pathways could lead to MACCE occurrence depending on the degree of receptor affinity and MSE profile. However, given that atypical APs are normally more consumed than typical ones, more attention should be given to high affinity to serotoninergic receptors, like 5-HT_{2A} and to APs associated with a high-risk of metabolic side effects.

This study has some limitations worth acknowledging. First, data were obtained through spontaneous reporting without any additional clinical assessment or qualitative validation by the authors. Second, the Weber effect, i.e. severe ADRs or the ones not listed in the Summary of Product Characteristics are more likely to be reported. Third, reporting bias could be present, either by under- or over- reporting. Fourth, the APs were introduced in the market in different time points depending on the country, which may have introduced selection bias. Fifth, the different indications, doses, and durations of treatment were not assessed, which may influence the reporting of the outcome. Given that was not possible to distinguish the different age groups in the paediatric population, it was not possible to assess their contribution to the association between the re- porting of MACCE and receptor binding affinity. Additionally, there was also no available data on doses and drug plasma concentrations, which are likely to modulate receptor binding affinity. Finally, it was not possible to adjust for other potential confounders, such as comorbidities, and lifestyle variables.

CONCLUSION

The reporting of MACCE was disproportionally associated with atypical APs use, when compared to typical ones. We also have shown that increased degree of affinity for adrenergic alfa-1, histaminic H_1, muscarinic M_1, and serotoninergic 5-HT_{2A} were associated with higher reporting of MACCE and as well as APs with intermediate- and high-risk of metabolic side effects. Future studies with prospective designs are needed to confirm these hypotheses.

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There were no funding sources for this study.

CONTRIBUTORS

JPA conceived and designed the study; analysed the data; and drafted, finalized, and submitted the manuscript; FAC contributed to the study design and reviewed all drafts of the manuscript; TE helped on design, data interpretation and reviewed the manuscript; HGM and PS conceived the design of the study, the interpretation of the study findings, provided guidance on writing the manuscript and critically reviewed all drafts of the manuscript.

CONFLICT OF INTEREST

Authors have no conflict of interest to disclose of financial, personal or of any other nature that may bias the work.

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DISCLAIMER

The information in this article does not represent the opinion of the World Health Organization, the Uppsala Monitoring Centre, nor the national pharmacovigilance centres.

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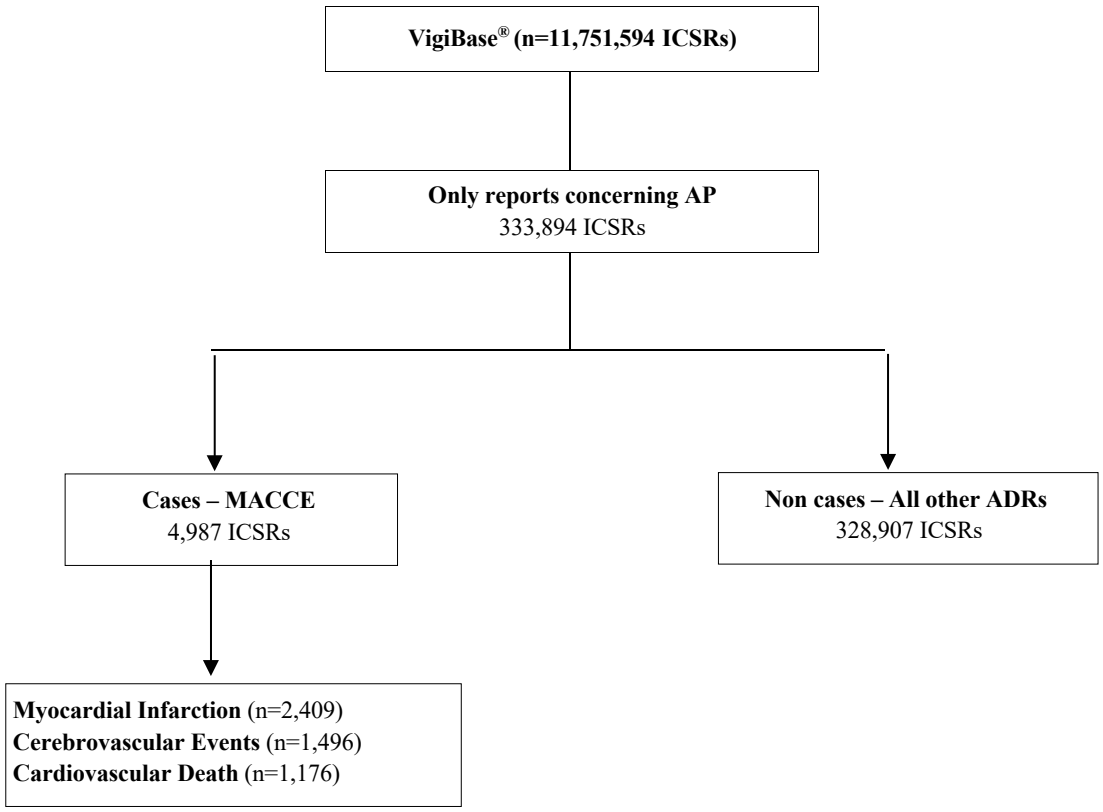


Figure 3.1.1 – The study flowchart

Table 3.1.1 – Baseline characteristics of the study population

Characteristics	Total ICSRs (n=333,894)	
	Cases (n=4,987)	**Non cases (n=328,907)**
Sex, n (%)		
Female	2133 (42.8)	156725 (47.7)
Male	2854 (57.2)	172182 (52.3)
Age, n (%)		
0 – 17 years	45 (0.9)	20691 (6.3)
18 – 64 years	3636 (72.9)	262919 (79.9)
65 – 74 years	583 (11.7)	23209 (7.1)
Aged 75 or older	723 (14.5)	22088 (6.7)
Region, n (%)		
Americas	3028 (60.7)	146043 (44.4)
Europe	1487 (29.8)	119352 (36.3)
Others	472 (9.5)	63512 (19.3)
Reporter type, n (%)		
Healthcare professionals	3150 (76.1)	181887 (67.6)
Consumer or non-healthcare professional	856 (20.7)	44049 (16.4)
Manufacturer	73 (1.8)	3347 (1.2)
Other	63 (1.5)	39939 (14.8)
Reporting year, n (%)		
1968 – 2009	1230 (24.7)	135947 (41.3)
2010 – 2012	2103 (42.2)	79292 (24.1)
2013 – 2017	1654 (33.2)	113668 (34.6)

Abbreviation: ICSRs – Individual Case Safety Reports

Table 3.1.2 – Association between reports of MACCE and exposure to antipsychotics

	Cases (n=4,987)	**Non cases (n=328,907)**	**Crude ROR (95%CI)**	**Adjusted ROR (95%CI)†**
***Type of APs,* n (%)**				
Typical	347 (7.0)	52479 (16.0)	Ref.	Ref.
Atypical	4640 (93.0)	276428 (84.0)	2.54 (2.28-2.83)*	2.46 (2.20-2.74)*
***Individual APs,* n (%)**				
Haloperidol	153 (3.1)	20138 (6.1)	Ref.	Ref.
Clozapine	1919 (38.5)	91543 (27.8)	2.76 (2.34-3.26)*	2.64 (2.24-3.12)*
Olanzapine	785 (15.7)	40386 (12.3)	2.56 (2.15-3.05)*	2.64 (2.22-3.15)*
Risperidone	411 (8.2)	35901 (10.9)	1.51 (1.25-1.82)*	1.66 (1.37-2.00)*
Quetiapine	901 (18.1)	51681 (15.7)	2.30 (1.93-2.73)*	1.90 (1.60-2.27)*
Aripiprazole	248 (5.0)	23672 (7.2)	1.38 (1.13-1.69)*	1.51 (1.23-1.85)*
Ziprasidone	143 (2.9)	6053 (1.8)	3.11 (2.47-3.91)*	3.14 (2.49-3.97)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval
†adjusted for age, sex, region, reporter type, and reporting year
*statistically significant ($p<0.05$)

Table 3.1.3 – Reporting Odds Ratio of MACCE and the receptor binding affinity

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
***Adrenergic alfa-1*, n (%)**				
Low	21 (0.4)	5116 (1.6)	Ref.	Ref.
Intermediate	2297 (47.2)	149733 (47.6)	3.74 (2.43-5.75)*	2.74 (1.78-4.22)*
High	2546 (52.3)	159460 (50.7)	3.89 (2.53-5.98)*	2.98 (1.93-4.59)*
***Adrenergic alfa-2*, n (%)**				
Low	1094 (22.5)	80889 (25.7)	Ref.	Ref.
Intermediate	3228 (66.4)	180598 (57.5)	1.32 (1.23-1.42)*	1.46 (1.36-1.57)*
High	542 (11.1)	52822 (16.8)	0.76 (0.68-0.84)*	0.96 (0.86-1.06)
***Dopaminergic D_1*, n (%)**				
Low	1197 (24.6)	82708 (26.3)	Ref.	Ref.
Intermediate	3622 (74.5)	225206 (71.7)	1.11 (1.04-1.19)*	1.24 (1.15-1.32)*
High	45 (0.9)	6395 (2.0)	0.49 (0.36-0.66)*	0.58 (0.43-0.79)*
***Dopaminergic D_2*, n (%)**				
Low	901 (18.5)	51681 (16.4)	Ref.	Ref.
Intermediate	2783 (57.2)	141547 (45.0)	1.13 (1.05-1.22)*	1.34 (1.24-1.45)*
High	1180 (24.3)	121081 (38.5)	0.56 (0.51-0.61)*	0.74 (0.67-0.81)*
***Dopaminergic D_3*, n (%)**				
Low	901 (19.0)	51681 (17.2)	Ref.	Ref.
Intermediate	2754 (58.0)	135955 (45.3)	1.16 (1.08-1.25)*	1.40 (1.29-1.51)*
High	1097 (23.1)	112381 (37.5)	0.56 (0.51-0.61)*	0.73 (0.67-0.80)*
***Dopaminergic D_4*, n (%)**				
Low	925 (19.0)	57366 (18.3)	Ref.	Ref.
Intermediate	3722 (76.5)	229372 (73.0)	1.01 (0.94-1.08)	1.20 (1.11-1.29)*
High	217 (4.5)	27571 (8.8)	0.49 (0.42-0.57)*	0.58 (0.50-0.68)*
***Histamine H_1*, n (%)**				
Low	185 (3.8)	25937 (8.3)	Ref.	Ref.
Intermediate	982 (20.2)	86842 (27.6)	1.59 (1.35-1.86)*	1.64 (1.40-1.92)*
High	3697 (76.0)	201530 (64.1)	2.57 (2.22-2.98)*	2.31 (1.98-2.68)*

Table 3.1.3 – (Continued)

***Muscarinic M_1,* n (%)**				
Low	1132 (36.5)	113312 (36.5)	Ref.	Ref.
Intermediate	996 (20.6)	64982 (20.9)	1.53 (1.41-1.67)*	1.20 (1.10-1.31)*
High	2704 (56.0)	131929 (42.5)	2.05 (1.91-2.20)*	1.87 (1.74-2.01)*
***Muscarinic M_2,* n (%)**				
Low	1017 (21.7)	96551 (32.9)	Ref.	Ref.
Intermediate	3680 (78.3)	196487 (67.1)	1.78 (1.66-1.91)*	1.55 (1.44-1.66)*
High	0 (0.0)	0 (0.0)	NE	NE
***Muscarinic M_3,* n (%)**				
Low	1925 (40.7)	148851 (50.6)	Ref.	Ref.
Intermediate	2799 (59.3)	145230 (49.4)	1.49 (1.41-1.58)*	1.52 (1.43-1.61)*
High	0 (0.0)	0 (0.0)	NE	NE
***Muscarinic M_4,* n (%)**				
Low	1003 (21.4)	93229 (32.3)	Ref.	Ref.
Intermediate	3675 (78.6)	195220 (67.7)	1.75 (1.63-1.88)	1.52 (1.41-1.63)*
High	0 (0.0)	0 (0.0)	NE	NE
***Muscarinic M_5,* n (%)**				
Low	1746 (37.3)	123505 (42.8)	Ref.	Ref.
Intermediate	2932 (62.7)	164944 (57.2)	1.26 (1.19-1.34)*	1.29 (1.21-1.37)*
High	0 (0.0)	0 (0.0)	NE	NE
***Serotoninergic 5-HT_{1A},* n (%)**				
Low	1029 (21.2)	80834 (25.7)	Ref.	Ref.
Intermediate	3557 (73.1)	206911 (65.8)	1.35 (1.26-1.45)*	1.24 (1.15-1.33)*
High	278 (5.7)	26564 (8.5)	0.82 (0.72-0.94)*	0.85 (0.74-0.98)*
***Serotoninergic 5-HT_{1B},* n (%)**				
Low	936 (20.0)	60353 (21.0)	Ref.	Ref.
Intermediate	3609 (77.0)	220473 (76.9)	1.06 (0.98-1.14)	1.25 (1.16-1.34)*
High	143 (3.0)	6053 (2.1)	1.52 (1.28-1.82)*	1.79 (1.49-2.14)*
***Serotoninergic 5-HT_{2A},* n (%)**				
Low	21 (0.4)	5116 (1.6)	Ref.	Ref.
Intermediate	1379 (28.4)	105594 (33.6)	3.18 (2.07-4.90)*	2.20 (1.42-3.39)*
High	3464 (71.2)	203599 (64.8)	4.15 (2.70-6.37)*	3.19 (2.07-4.92)*

Table 3.1.3 – (Continued)

***Serotoninergic 5-HT$_{2C}$*, n (%)**				
Low	1094 (22.5)	80506 (25.7)	Ref.	Ref.
Intermediate	3555 (73.2)	220855 (70.6)	1.19 (1.11-1.27)*	1.36 (1.27-1.46)*
High	206 (4.2)	11490 (3.7)	1.32 (1.14-1.53)*	1.51 (1.30-1.76)*
***Serotoninergic 5-HT$_{6}$*, n (%)**				
Low	1492 (31.6)	113204 (38.3)	Ref.	Ref.
Intermediate	3204 (67.8)	180510 (61.2)	1.35 (1.27-1.43)*	1.41 (1.32-1.50)*
High	27 (0.6)	1548 (0.5)	1.32 (0.90-1.94)	1.79 (1.21-2.64)*
***Serotoninergic 5-HT$_{7}$*, n (%)**				
Low	4 (0.1)	2616 (0.9)	Ref.	Ref.
Intermediate	4156 (87.7)	248474 (83.6)	10.94 (4.10-29.18)*	9.30 (3.48-24.83)*
High	578 (12.2)	46143 (15.5)	8.19 (3.06-21.92)*	7.95 (2.97-21.30)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval; NE – Not estimable
†adjusted for age, sex region, reporter type, and reporting year
*statistically significant ($p<0.05$)

Table 3.1.4 – Reporting Odds Ratio of MACCE and the different metabolic side effects profile of antipsychotics

	Cases (n=4,848)	**Non cases (n=309,852)**	**Crude ROR (95%CI)**	**Adjusted ROR (95%CI)†**
***Low-risk of MSE*, n (%)**	656 (13.5)	68022 (22.0)	Ref.	Ref.
Intermediate-risk of MSE	1433 (29.6)	100600 (32.5)	1.48 (1.35-1.62)*	1.33 (1.21-1.46)*
High-risk of MSE	2759 (56.9)	141230 (45.6)	2.03 (1.86-2.21)*	1.88 (1.73-2.05)*

Abbreviation: CI – Confidence Interval; MSE – Metabolic Side Effects; ROR – Reporting Odds Ratio
†adjusted for age, sex region, reporter type, and reporting year
*statistically significant ($p<0.05$)

APPENDICES

SUPPLEMENTARY MATERIAL

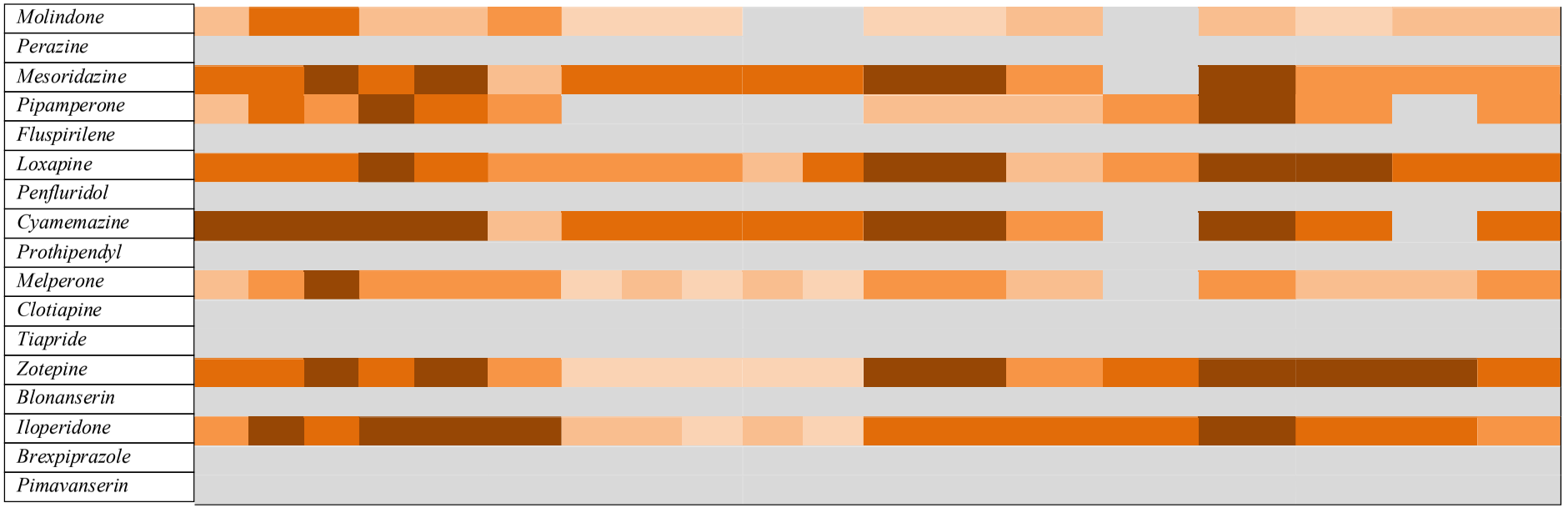
Table 3.S1 – MedDRA terms used when coding the individual conditions included in MACCE

Individual Condition	MedDRA code	MedDRA PT
Myocardial Infarction	10028596	Myocardial infarction
	10049768	Silent myocardial infarction
	10000891	Acute myocardial infarction
	10028600	Myocardial ischaemia
Cerebrovascular Events	10008190	Cerebrovascular accident
	10068644	Brain stem stroke
	10071043	Basal ganglia stroke
	10059613	Stroke in evolution
	10014498	Embolic stroke
	10019016	Haemorrhagic stroke
	10055677	Haemorrhagic transformation stroke
	10061256	Ischaemic stroke
	10076994	Lacunar stroke
	10043647	Thrombotic stroke
	10008118	Cerebral infarction
	10060839	Embolic cerebral infarction
	10019005	Haemorrhagic cerebral infarction
	10060840	Ischaemic cerebral infarction
	10067347	Thrombotic cerebral infarction
	10044390	Transient ischaemic attack
Cardiovascular Death	10049993	Cardiac death
	10049418	Sudden cardiac death
	10042434	Sudden death

Abbreviation: MedDRA – Medical Dictionary for Regulatory Activities; PT – Preferred Terms

Table 3.S2 – Receptor binding affinity (K_a) for the most reported antipsychotics

Antipsychotics	Dopamine				Adrenergic		Muscarinic					Histaminic	Serotoninergic					
	D_1	D_2	D_3	D_4	α_1	α_2	M_1	M_2	M_3	M_4	M_5	H_1	$5HT_{1A}$	$5HT_{1B}$	$5HT_{2A}$	$5HT_{2C}$	$5HT_6$	$5HT_7$
Haloperidol																		
Sertindole																		
Ziprasidone																		
Clozapine													P					
Lurasidone																		
Olanzapine																		
Zuclopenthixol																		
Quetiapine													P					
Risperidone																		
Amisulpride		P																
Aripiprazole	P	P	P	P									P			P		
Thioridazine																		
Asenapine																		
Paliperidone																		
Perphenazine																		
Pimozide																		
Fluphenazine																		
Chlorpromazine																		
Sulpiride																		
Chlorprothixene																		
Periciazine																		
Levomepromazine																		
Promazine																		
Trifluoperazine																		
Droperidol																		
Clopenthixol																		
Benperidol																		
Tiotixene																		
Flupentixol																		



Receptor affinity (K_a) of antagonists:

Receptor affinity (K_a) of agonists:

Table 3.S3 – Metabolic side effects of the antipsychotics of interest

Groups of MSE profile	Weight gain	Increased lipids levels	Increased glucose levels
High-risk of MSE			
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Thioridazine	+++	++	++
Chlorpromazine	+++	+++	++
Intermediate-risk of MSE			
Risperidone	++	+	+/-
Quetiapine	++	+	+/-
Paliperidone	++	+	+/-
Iloperidone	+	+/-	+/-
Lurasidone	+	+/-	+/-
Low-risk of MSE			
Haloperidol	+/-	-	-
Fluphenazine	+/-	-	-
Amisulpride	+	-	-
Aripiprazole	+	-	-
Asenapine	+/-	-	-
Perphenazine	+/-	-	-
Pimozide	+/-	-	-
Sertindole	+/-	-	-
Sulpiride	+/-	-	-
Trifluoperazine	+/-	-	-
Loxapine	+	-	-
Thiothixene	+/-	-	-
Brexpiprazole	+/-	-	-
Cariprazine	+/-	-	-
Ziprasidone	+	-	-

Abbreviation: MSE – Metabolic Side Effects

Legend:

Very low-risk (-) Low-risk (+/-) Intermediate-risk (+) High-risk (++) Very-high risk (+++)

Sensitivity Analysis: Without Americas' reports

Table 3.S4 – Association between reports of MACCE and exposure to antipsychotics

	Cases (n=1959)	Non cases (n=182864)	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Type of APs, n (%)				
Typical	207 (10.6)	36661 (20.0)	Ref.	Ref.
Atypical	1752 (89.4)	146203 (80.0)	2.12 (1.84-2.45)*	2.21 (1.91-2.56)*
Individual APs, n (%)				
Haloperidol	71 (3.6)	13642 (7.5)	Ref.	Ref.
Clozapine	967 (49.3)	56193 (30.7)	3.31 (2.60-4.21)*	2.90 (2.27-3.71)*
Olanzapine	261 (13.3)	24164 (13.2)	2.08 (1.60-2.70)*	2.40 (1.84-3.13)*
Risperidone	195 (10.0)	20623 (11.3)	1.82 (1.38-2.39)*	2.12 (1.61-2.79)*
Quetiapine	135 (6.9)	18710 (10.2)	1.39 (1.04-1.85)*	1.33 (1.00-1.78)
Aripiprazole	65 (3.3)	9262 (5.1)	1.35 (0.96-1.89)	1.88 (1.34-2.64)*
Ziprasidone	23 (1.2)	2030 (1.1)	2.18 (1.36-3.49)*	3.02 (1.88-4.87)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval
†adjusted for age, sex, reporter type, and reporting year
*statistically significant ($p<0.05$)

Table 3.S5 – Reporting Odds Ratio of MACCE and the receptor binding affinity

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Adrenergic alfa-1, n (%)				
Low	18 (0.9)	4917 (2.8)	Ref.	Ref.
Intermediate	606 (31.9)	73060 (42.2)	2.27 (1.42-3.62)*	2.32 (1.45-3.71)*
High	1276 (67.2)	95203 (55.0)	3.66 (2.30-5.84)*	3.32 (2.08-5.30)*
Adrenergic alfa-2, n (%)				
Low	231 (12.2)	40033 (23.1)	Ref.	Ref.
Intermediate	1411 (74.3)	103882 (60.0)	2.35 (2.05-2.71)*	2.32 (2.01-2.68)*
High	258 (13.6)	29265 (16.9)	1.53 (1.28-1.83)*	1.74 (1.45-2.07)*
Dopaminergic D_1, n (%)				
Low	242 (12.7)	34923 (20.2)	Ref.	Ref.
Intermediate	1640 (86.3)	134318 (77.6)	1.76 (1.54-2.02)*	1.75 (1.52-2.01)*
High	18 (0.9)	3939 (2.3)	0.66 (0.41-1.07)	0.65 (0.40-1.05)
Dopaminergic D_2, n (%)				
Low	135 (7.1)	18710 (10.8)	Ref.	Ref.
Intermediate	1282 (67.5)	87517 (50.5)	2.03 (1.70-2.43)*	2.03 (1.69-2.43)*
High	483 (25.4)	66953 (38.7)	1.00 (0.83-1.21)	1.19 (0.99-1.45)
Dopaminergic D_3, n (%)				
Low	135 (7.3)	18710 (11.2)	Ref.	Ref.
Intermediate	1264 (68.4)	82992 (49.8)	2.11 (1.77-2.52)*	2.16 (1.80-2.59)*
High	449 (24.3)	65055 (39.0)	0.96 (0.79-1.16)	1.12 (0.92-1.36)
Dopaminergic D_4, n (%)				
Low	156 (8.2)	24129 (13.9)	Ref.	Ref.
Intermediate	1647 (86.7)	131078 (75.7)	1.94 (1.65-2.29)*	2.07 (1.75-2.45)*
High	97 (5.1)	17973 (10.4)	0.84 (0.65-1.08)	0.91 (0.70-1.17)
Histamine H_1, n (%)				
Low	100 (5.3)	19239 (11.1)	Ref.	Ref.
Intermediate	395 (20.8)	43454 (25.1)	1.75 (1.40-2.18)*	1.91 (1.53-2.39)*
High	1405 (73.9)	110487 (63.8)	2.45 (2.00-3.00)*	2.22 (1.81-2.72)*

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Muscarinic M_1, n (%)				
Low	442 (23.6)	61448 (36.3)	Ref.	Ref.
Intermediate	201 (10.7)	27575 (16.3)	1.01 (0.86-1.20)	0.86 (0.73-1.02)
High	1228 (65.6)	80357 (47.4)	2.13 (1.91-2.37)*	1.83 (1.64-2.05)*
Muscarinic M_2, n (%)				
Low	388 (21.6)	52584 (32.8)	Ref.	Ref.
Intermediate	1409 (78.4)	107511 (67.2)	1.78 (1.59-1.99)*	1.49 (1.33-1.67)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_3, n (%)				
Low	527 (28.9)	71778 (44.6)	Ref.	Ref.
Intermediate	1294 (71.1)	89222 (55.4)	1.98 (1.78-2.19)*	1.77 (1.60-1.97)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_4, n (%)				
Low	382 (21.4)	51108 (32.4)	Ref.	Ref.
Intermediate	1407 (78.6)	106599 (67.6)	1.77 (1.58-1.98)*	1.49 (1.33-1.67)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_5, n (%)				
Low	444 (24.8)	55264 (35.0)	Ref.	Ref.
Intermediate	1345 (75.2)	102443 (65.0)	1.63 (1.47-1.82)*	1.47 (1.31-1.64)*
High	0 (0.0)	0 (0.0)	NE	NE
Serotoninergic 5-HT_{1A}, n (%)				
Low	400 (21.1)	53530 (30.9)	Ref.	Ref.
Intermediate	1432 (75.4)	109871 (63.4)	1.74 (1.56-1.95)*	1.54 (1.37-1.72)*
High	68 (3.6)	9779 (5.6)	0.93 (0.72-1.20)	1.04 (0.80-1.35)
Serotoninergic 5-HT_{1B}, n (%)				
Low	160 (8.9)	25043 (16.0)	Ref.	Ref.
Intermediate	1621 (89.9)	129229 (82.7)	1.96 (1.67-2.31)*	2.00 (1.69-2.35)*
High	23 (1.3)	2030 (1.3)	1.77 (1.14-2.75)*	2.34 (1.50-3.64)*

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Serotoninergic 5-HT$_{2A}$, n (%)				
Low	18 (0.9)	4917 (2.8)	Ref.	Ref.
Intermediate	323 (17.0)	48148 (27.8)	1.83 (1.14-2.95)*	1.77 (1.01-2.85)*
High	1559 (82.1)	120115 (69.4)	3.55 (2.23-5.65)*	3.39 (2.13-5.41)*
Serotoninergic 5-HT$_{2C}$, n (%)				
Low	233 (12.3)	39147 (22.8)	Ref.	Ref.
Intermediate	1605 (84.9)	128083 (74.5)	2.11 (1.83-2.42)*	2.14 (1.86-2.47)*
High	53 (2.8)	4599 (2.7)	1.94 (1.44-2.61)*	2.18 (1.61-2.95)*
Serotoninergic 5-HT$_{6}$, n (%)				
Low	425 (23.4)	58260 (35.9)	Ref.	Ref.
Intermediate	1367 (75.2)	102388 (63.1)	1.83 (1.64-2.04)*	1.76 (1.57-1.97)*
High	27 (1.5)	1505 (0.9)	2.46 (1.66-3.64)*	2.42 (1.63-3.60)*
Serotoninergic 5-HT$_{7}$, n (%)				
Low	2 (0.1)	2442 (1.5)	Ref.	Ref.
Intermediate	1601 (87.3)	136217 (83.0)	14.35 (3.58-57.46)*	14.96 (3.73-59.93)*
High	231 (12.6)	25462 (15.5)	11.08 (2.75-44.59)*	13.66 (3.39-55.02)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval; NE – Not estimable
†adjusted for age, sex, reporter type, and reporting year
*statistically significant ($p<0.05$)

Table 3.S6 – Reporting Odds Ratio of MACCE and the different metabolic side effects profile of antipsychotics

	Cases (n=1,859)	Non cases (n=167,270)	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Low-risk of MSE, n (%)	217 (11.7)	36047 (21.6)	Ref.	Ref.
Intermediate-risk of MSE	380 (20.4)	45472 (27.2)	1.39 (1.17-1.64)*	1.31 (1.11-1.55)*
High-risk of MSE	1262 (67.9)	85751 (51.3)	2.45 (2.12-2.83)*	2.10 (1.81-2.43)*

Abbreviation: CI – Confidence Interval; MSE – Metabolic Side Effects; ROR – Reporting Odds Ratio
†adjusted for age, sex, reporter type, and reporting year
*statistically significant ($p<0.05$)

Sensitivity Analysis: Only healthcare professionals' reports

Table 3.S7 – Association between reports of MACCE and exposure to antipsychotics

	Cases (n=3150)	Non cases (n=181887)	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Type of APs, n (%)				
Typical	186 (5.9)	27926 (15.4)	Ref.	Ref.
Atypical	2964 (94.1)	153961 (84.6)	2.89 (2.49-3.35)*	2.66 (2.29-3.09)*
Individual APs, n (%)				
Haloperidol	92 (2.9)	11037 (6.1)	Ref.	Ref.
Clozapine	1158 (36.8)	49831 (27.4)	2.79 (2.25-3.45)*	2.63 (2.12-3.26)*
Olanzapine	491 (15.6)	21966 (12.1)	2.68 (2.14-3.35)*	2.61 (2.08-3.27)*
Risperidone	268 (8.5)	20038 (11.0)	1.61 (1.27-2.04)*	1.65 (1.30-2.10)*
Quetiapine	636 (20.2)	30252 (16.6)	2.52 (2.03-3.14)*	2.00 (1.60-2.49)*
Aripiprazole	171 (5.4)	13323 (7.3)	1.54 (1.19-1.99)*	1.58 (1.22-2.04)*
Ziprasidone	86 (2.7)	3298 (1.8)	3.13 (2.33-4.21)*	2.91 (2.15-3.93)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval
†adjusted for age, sex, region, and reporting year
*statistically significant ($p<0.05$)

Table 3.S8 – Reporting Odds Ratio of MACCE and the receptor binding affinity

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Adrenergic alfa-1, n (%)				
Low	12 (0.4)	2621 (1.5)	Ref.	Ref.
Intermediate	1514 (49.0)	83940 (48.2)	3.94 (2.23-6.96)*	2.61 (1.47-4.62)*
High	1561 (50.6)	87566 (50.3)	3.89 (2.20-6.88)*	2.76 (1.56-4.88)*
Adrenergic alfa-2, n (%)				
Low	749 (24.3)	45940 (26.4)	Ref.	Ref.
Intermediate	1978 (64.1)	98479 (56.6)	1.23 (1.13-1.34)*	1.37 (1.25-1.49)*
High	360 (11.7)	29708 (17.1)	0.74 (0.66-0.84)*	0.93 (0.81-1.05)
Dopaminergic D_1, n (%)				
Low	832 (27.0)	47432 (27.2)	Ref.	Ref.
Intermediate	2225 (72.1)	123108 (70.7)	1.03 (0.95-1.12)	1.60 (1.11-2.32)*
High	30 (1.0)	3587 (2.1)	0.48 (0.33-0.69)*	1.84 (1.28-2.65)*
Dopaminergic D_2, n (%)				
Low	636 (20.6)	30252 (17.4)	Ref.	Ref.
Intermediate	1686 (54.6)	76776 (44.1)	1.05 (0.95-1.15)	1.26 (1.14-1.38)*
High	765 (24.8)	67099 (38.5)	0.54 (0.49-0.60)*	0.71 (0.64-0.80)*
Dopaminergic D_3, n (%)				
Low	636 (21.1)	30252 (18.2)	Ref.	Ref.
Intermediate	1679 (55.8)	73893 (44.5)	1.08 (0.99-1.19)	1.32 (1.20-1.45)*
High	695 (23.1)	61810 (37.2)	0.54 (0.48-0.60)*	0.70 (0.62-0.78)*
Dopaminergic D_4, n (%)				
Low	648 (21.0)	33165 (19.0)	Ref.	Ref.
Intermediate	2306 (74.7)	125792 (72.2)	0.94 (0.86-1.03)	1.11 (1.02-1.22)*
High	133 (4.3)	15170 (8.7)	0.45 (0.37-0.54)*	0.57 (0.47-0.69)*
Histamine H_1, n (%)				
Low	110 (3.6)	14037 (8.1)	Ref.	Ref.
Intermediate	641 (20.8)	48346 (27.8)	1.69 (1.38-2.07)*	1.63 (1.33-2.00)*
High	2336 (75.7)	111744 (64.2)	2.67 (2.20-3.23)*	2.28 (1.88-2.76)*

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Muscarinic M_1, n (%)				
Low	732 (23.9)	62911 (36.6)	Ref.	Ref.
Intermediate	687 (22.4)	37228 (21.7)	1.59 (1.43-1.76)*	1.25 (1.12-1.39)*
High	1649 (53.7)	71797 (41.8)	1.97 (1.81-2.16)*	1.82 (1.67-1.99)*
Muscarinic M_2, n (%)				
Low	654 (22.0)	53512 (33.0)	Ref.	Ref.
Intermediate	2323 (78.0)	108817 (67.0)	1.75 (1.60-1.91)*	1.54 (1.41-1.68)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_3, n (%)				
Low	1295 (43.2)	84085 (51.6)	Ref.	Ref.
Intermediate	1700 (56.8)	78773 (48.4)	1.40 (1.30-1.51)*	1.45 (1.35-1.57)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_4, n (%)				
Low	643 (21.7)	51687 (32.3)	Ref.	Ref.
Intermediate	2322 (78.3)	108239 (67.7)	1.72 (1.58-1.88)*	1.51 (1.38-1.65)*
High	0 (0.0)	0 (0.0)	NE	NE
Muscarinic M_5, n (%)				
Low	1186 (40.0)	70324 (44.0)	Ref.	Ref.
Intermediate	1779 (60.0)	89602 (56.0)	1.18 (1.09-1.27)*	1.24 (1.15-1.34)*
High	0 (0.0)	0 (0.0)	NE	NE
Serotoninergic 5-HT_{1A}, n (%)				
Low	630 (20.4)	43728 (25.1)	Ref.	Ref.
Intermediate	2266 (73.4)	115301 (66.2)	1.36 (1.25-1.49)*	1.24 (1.13-1.36)*
High	191 (6.2)	15098 (8.7)	0.88 (0.75-1.03)	0.88 (0.75-1.04)
Serotoninergic 5-HT_{1B}, n (%)				
Low	655 (22.0)	34926 (22.0)	Ref.	Ref.
Intermediate	2232 (75.1)	120872 (76.0)	0.99 (0.90-1.08)	1.17 (1.07-1.28)*
High	86 (2.9)	3298 (2.1)	1.39 (1.11-1.75)*	1. 57 (1.25-1.98)*

	Cases	Non cases	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Serotoninergic 5-HT$_{2A}$, n (%)				
Low	12 (0.4)	2621 (1.5)	Ref.	Ref.
Intermediate	941 (30.5)	60022 (34.5)	3.42 (1.94-6.06)*	2.16 (1.22-3.84)*
High	2134 (69.1)	111484 (64.0)	4.18 (2.37-7.38)*	2.95 (1.67-5.23)*
Serotoninergic 5-HT$_{2C}$, n (%)				
Low	750 (24.3)	45840 (26.4)	Ref.	Ref.
Intermediate	2207 (71.6)	121196 (69.9)	1.11 (1.02-1.21)*	1.27 (1.17-1.39)*
High	125 (4.1)	6310 (3.6)	1.21 (1.00-1.47)	1.39 (1.14-1.69)*
Serotoninergic 5-HT$_{6}$, n (%)				
Low	1010 (33.7)	64192 (39.3)	Ref.	Ref.
Intermediate	1966 (65.7)	98453 (60.2)	1.27 (1.18-1.37)*	1.33 (1.23-1.44)*
High	18 (0.6)	827 (0.5)	1.38 (0.86-2.22)	2.74 (1.70-4.42)*
Serotoninergic 5-HT$_{7}$, n (%)				
Low	2 (0.1)	1296 (0.8)	Ref.	Ref.
Intermediate	2630 (87.6)	137607 (83.7)	12.39 (3.09-49.60)*	10.35 (2.58-41.50)*
High	370 (12.3)	25561 (15.5)	9.38 (2.34-37.69)*	8.73 (2.17-35.11)*

Abbreviation: ROR – Reporting Odds Ratio; CI – Confidence Interval; NE – Not estimable
†adjusted for age, sex region, and reporting year
*statistically significant ($p<0.05$)

Table 3.S9 – Reporting Odds Ratio of MACCE and the different metabolic side effects profile of antipsychotics

	Cases (n=)	Non cases (n=)	Crude ROR (95%CI)	Adjusted ROR (95%CI)†
Low-risk of MSE, n (%)	417 (13.5)	37282 (21.7)	Ref.	Ref.
Intermediate-risk of MSE	989 (32.1)	57769 (33.6)	1.53 (1.36-1.72)*	1.36 (1.21-1.53)*
High-risk of MSE	1677 (54.4)	76814 (44.7)	1.95 (1.75-2.17)*	1.82 (1.64-2.04)*

Abbreviation: CI – Confidence Interval; MSE – Metabolic Side Effects; ROR – Reporting Odds Ratio
†adjusted for age, sex region, and reporting year
*statistically significant ($p<0.05$)

CHAPTER 4

From a drug- and disease-centred approach to an individual patient perspective

PERSPECTIVE

The purpose of this chapter was to investigate how can we move from a drug- and disease-centred approach to an individual patient perspective. To accomplish this goal, our first study evaluated possible gaps in the knowledge of different healthcare professionals (e.g., physicians, pharmacists, and nurses) and potential barriers to PIMs management in the elderly. The second study aimed to compile and validate patient-related features that may be used to foster a safe prescribing of APs in the elderly with dementia, and to evaluate their feasibility in clinical practice by analyzing the exhaustiveness of medical records of a mental health specialized hospital. Both studies gather information that may help develop a future intervention, considering, on one hand, a educational approach (Chapter 4.1) and, on the other hand, the structural and process barriers identified in both studies (Chapter 4.1 and Chapter 4.2).

CHAPTER 4.1

Healthcare professionals' views on the management of medication complexities in the elderly with mental disorders: a cross-sectional study

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ABSTRACT

Background: Many challenges in elderly pharmacotherapy are identified, including the use of Potentially Inappropriate Medications (PIMs) which may increase the odds of adverse events, especially in elderly patients with mental health disorders (e. g., behavioral, and psychological symptoms of dementia–BPSD, schizophrenia, bipolar disorder). However, information on the knowledge and practice of healthcare professionals (HCPs) about this topic is still scarce.

Methods: A cross-sectional study was undertaken from July-October 2019. An online questionnaire was specifically designed and validated for this study. We sought HCPs (physicians, pharmacists, and nurses) worldwide, using (a) social media, via Facebook, Twitter, and LinkedIn; and (b) email contacts of the research team (convenience sample). Either way participants were asked to share on their social media or via e-mail the questionnaires with other HCPs (snowballing sample). The survey assessed two main domains: knowledge and practice. Knowledge was evaluated by self-report (perceived knowledge by a 5-item Likert confidence scale) and using three clinical cases, scored between 0 and 30 points (each one rated from 0 to 10 points; real knowledge). Barriers in clinical practice were evaluated using a 5-item Likert scale judging practitioners' opinion.

Results: A total of 165 questionnaires were collected. HCPs were mainly female (n = 114; 69.1%), with a mean age of 35.3 ± 11.3 years old. Seventy-two percent (n = 118) were pharmacists, 21.1% (n = 35) were physicians, and 7.3% (n = 12) nurses. There was a weak correlation, albeit significant, between perceived and real knowledge (r = 0.199; p = 0.001). The mean score of the clinical vignettes regarding elderly patients with dementia and bipolar disorder were 4.59 ± 4.08 and 4.86 ± 2.97 points, respectively. Most HCPs were classified as having an intermediate knowledge (n = 100; 60.6%) about medication complexities in the elderly with mental disorders. Most HCPs agreed that lack of time (81.6%; n = 138), lack of education and training on elderly pharmacotherapy (72.2%; n = 122), and lack of tools adapted to daily practice (61.8%; n = 105) were the main barriers.

Conclusions: Most of the HCPs felt confident to manage medication complexities in elder patients with mental disorders, but only a minority obtained a good score in the knowledge assessment test. The main barriers identified included structural barriers (tools unfit for practice) and process barriers (time).

INTRODUCTION

Population aging has been increasing worldwide in the past decades. In 2010, 524 million people were aged 65 or older – 8.0% of the world's population –, and it is estimated that by 2025 there will be a total of about 1.2 billion people aged 60 or older.[1,2] Individuals aged 80 or older are the fastest growing fraction of the population and are expected to reach 30.0% of the overall population in industrialized countries by 2050.[3,4] Older individuals tend to present multiple chronic conditions (multimorbidity), requiring the use of multiple medications. Aging has introduced several changes in patients' physiology, which contributed to different pharmacokinetics/pharmacodynamics (PK/PD) patterns.[5]

Polypharmacy can be defined based on the number of medications taken by the patient, where it is normally considered as the use of 5 or more drugs, or based on the appropriateness of the medications included, as appropriate or inappropriate polypharmacy.[1,6] Inappropriate polypharmacy is defined as the use of too many medications, including medicines where the risk of adverse drug events (ADE) outweighs the clinical benefit.[7,8] On the other hand, we can have patients that may be using potentially inappropriate medications (PIMs), i.e., medications where the risk of ADEs may outweigh the clinical benefit of its use. These medications can be classified as PIMs independently from comorbidities, or because there is a potentially inappropriate interaction with an underlying condition or another medication. Since polypharmacy includes the use of multiple drugs (normally 5 or more), at least one of them may be considered a PIM.[9]

The complexity of care required by elder individuals, increase their use of healthcare services and to consult different Healthcare Professionals (HCPs). This results in the need for interprofessional collaboration among general practitioners, different specialist physicians, pharmacists, nurses, and other HCPs. However, interprofessional communication is nowadays uncoordinated and may result in an increased risk of polypharmacy and inappropriate medication use. A study conducted by Mahlknecht et al. has shown that systematic education of HCPs and structured interprofessional medication review may decrease the mean number of severe drug-drug interactions as well as a decreased agitated behavior in older adults in nursing homes.[10,11]

In psychiatry, polypharmacy is normally a reality that physicians struggle to handle since many of the clinical guidelines and treatment algorithms prefer a monotherapy approach. However, in some cases, polypharmacy is clinically needed to handle persistent symptoms and nonresponse to monotherapy.[12] Some studies have investigated the prevalence of polypharmacy and clinical features that may be associated with this issue and concluded that polypharmacy can be a risk in some subgroups of patients.[13,14] For example, a systematic review identified that elderly with bipolar disorder are exposed to polypharmacy, but it may be a risk depending on the type and mood episode phase of illness that the patient present. They also have shown that it depends on the type of medications used (e.g., lithium, antipsychotics).[13] Many types of polypharmacy have been

identified in this area, namely, same class (e.g., the use of medication from the same class), multi-class (e.g., full dose of different medications from different classes), adjunctive (e.g., one medicine is used to treat an ADE of another), augmentation (e.g., the use of one medication at a lower dose with another at full dose) or total polypharmacy.[12] Even though, it seems beneficial to use polypharmacy in patients with mental disorders (to control negative, positive, cognitive, or behavioral symptoms), there seems to be scarce evidence to support that. Some studies have shown that healthcare professionals, especially clinicians, should evaluate if polypharmacy enhances clinical outcomes or whether it promotes ADEs.[12,15]

Since some of the medications identified in several PIM-lists are used to treat several mental disorders and knowing that in older individuals they may increase the odds of ADEs, it seems to be relevant to evaluate the knowledge of healthcare professionals on the management of polypharmacy and PIMs in older patients with mental health disorders and to identify potential barriers in clinical practice.

METHODS

STUDY DESING

This study follows the STROBE reporting guidelines.[16] A cross-sectional study was undertaken, using an online questionnaire from July to October 2019.

POPULATION AND SAMPLE

The target population for this study was defined as HCPs that have an active role in medication review for the elderly. Therefore, we selected physicians, pharmacists, and nurses as the main HCPs of interest. Given the difficulty in defining the theoretical sample of HCPs necessary to reach, due to limited data on the number or percentage of HCPs that have access to social media or even to the internet, we have applied a snowball sampling technique by disseminating the questionnaire via social media and via email. The database of email contacts included 17 pharmacists, 16 physicians, and 16 nurses. These participants were a mix of HCPs actively practicing at the time of study and HCPs known to have some expertise in geriatrics. We have deliberately excluded all participants that did not fit in one of those three professional categories, including students (given that they were not practicing yet), interns, and retired professionals. Our goal was to obtain at least 100 HCPs, with a balanced number between the different professions.

DEVELOPMENT AND VALIDATION OF THE QUESTIONNAIRE

The self-administered online questionnaire was developed from scratch following literature review and made available bilingually (English and Portuguese).[17–19] This questionnaire collected sociodemographic characteristics and consisted of three domains: (a) perceived knowledge; (b) actual knowledge; and (c) potential barriers to PIMs' management in clinical practice.

Sociodemographic variables collected included age, sex, country, professional category, practice setting, academic degree, and years of practice. The perceived knowledge domain was implemented through the presentation of statements focused on perceived facility of identifying PIMs when undertaking medication reviews, and on frequency of use of any tool to guide medication review (e.g., Beers criteria, START/STOPP criteria, PRISCUS criteria, Medscape) and then searching for agreement of HCPs. The actual knowledge domain was implemented by presenting three clinical vignettes based on real-life clinical cases where Beers criteria 2019 version had been applied. The first and second vignettes concerned the identification of psychiatric, and non-steroidal anti-inflammatory drugs in patients with mental disorders, namely dementia and bipolar disorder, and the third vignette concerned a cardiovascular drug in a patient with dementia. The third domain focused on barriers in practice and was implemented by asking HCPs the proportion of patients to whom they normally review pharmacotherapeutic records; and by listing potential barriers to PIMs' management in clinical practice, to be ranked on a 5-point agreement Likert scale. The first and third domains were assessed using a 5-item Likert scale, ranging from "Strongly disagree," to "Strongly agree." In the domain evaluating actual knowledge, for each clinical vignette, there were four questions scored from 0 to 2.5 points, which accounted for a maximum of 10 points.

Face and content validity were established by an expert panel composed of 12 HCPs from different fields of practice (2 physicians, 5 pharmacists, 2 nurses and 3 academics/researchers). The draft questionnaire was modified following the comments made by the experts. The final version of the questionnaire is available as **Supplementary Material S1**.

DATA COLLECTION

Data was collected using two different approaches: the first one included the dissemination of the e-questionnaire through the social media, which included Facebook, LinkedIn, and Twitter; the second included the dissemination of the questionnaire through a list of e-mails from our research team. In the first approach, all researchers from our team shared the link in their personal pages, and in private and open social media groups addressing the selected HCPs (e.g., wenurses, wepharmacists, wedoctors). These publications were shared every two weeks, and we asked all participants to share the link in their personal pages. In the second approach, the questionnaire was sent via email to a list of professional contacts from the research team. We invited all colleagues that were eligible for the study and asked them to forward the link to other HCPs fitting the inclusion criteria. Reminders were made every two weeks in both approaches.

DATA ANALYSIS

Descriptive statistics were used, where numerical variables were expressed using central tendency and dispersion measures and categorical variables as absolute and relative frequencies. The Kolmogorov-Smirnov was used to test the sample distribution. Regarding our main outcome (real

knowledge), the median was considered to set the threshold between positive and negative scores. For the total score the threshold was set at 13.75 out of 30 points, and for each individual vignette the threshold was 4 out of 10 points. Therefore, knowledge was divided in three categories (total score over 30): "poor knowledge" (<13.75 points); "intermediate knowledge" ([13.75–20[points; and "advanced knowledge" (≥21 points). Pearson correlation coefficient was calculated to evaluate the strength of correlation between perceived and real knowledge (considering normal distribution of both variables). A value of $p < 0.05$ was considered for Chi-squared test (when comparing categorical variables) and ANOVA test (when comparing numerical variables). Both tests were used to compare perceived and real knowledge and barriers identified between the different professions. IBM SPSS v.21 was used to run the statistical analysis.

SENSITIVITY ANALYSIS

Since the questionnaire was disseminated to different countries, we were expecting that differences may be seen, especially if one of the countries had more representativeness comparing to others. Therefore, we performed a sensitivity analysis excluding the responses from other countries to see if there were differences, when analyzing all countries vs. only Portugal.

RESULTS

PARTICIPANTS' CHARACTERISTICS

By the end of the study period, we had 180 HCPs' responses. From those, 3 did not qualify because HCPs did not agree to participate, 5 questionnaires were left blank, and 7 were working exclusively as researcher/lecturer. Thus, our final sample consisted of 165 questionnaires. HCPs were mainly females (n=114; 69.1%), with a mean age of 35.3±11.3 years old {21;76}. They were practicing in 26 different countries.

From the 165 HCPs that completed the questionnaire, 71.5% (n=118) were pharmacists, 21.2% (n=35) were physicians, and 7.3% (n=12) were nurses. Most HCPs were practicing in the outpatient setting (n=95; 57.6%), followed by inpatient setting (n=70; 42.4%). Sixty-six percent (n=109) had less than 10 years of experience, and 64.6% (n=106) had a master's degree. Full details are available in **Table 4.1.1**.

KNWOLEDGE OF DIFFERENT HCPs ABOUT PIMs: PERCEIVED VS REAL KNOWLEDGE

One-hundred and thirty (76.0%) HCPs confirmed having the knowledge to identify and evaluate the use of PIMs in the elderly in their daily practice, and 70.9% (n=122) considered their knowledge was enough to perform a medication review in elder patients. There were no differences between the different professional classes regarding statement 1 and 2 (p=0.115 and p=0.057, respectively) (**Table 4.1.2**). When exploring differences between the different professional classes on the type of tool used to optimize the pharmacotherapy in older adults, including for PIMs' management, pharmacists seem to more commonly use START/STOPP or Beers criteria when compared to the other two HCPs classes (p=0.023). Conversely, physicians normally use Up-to-date, Medscape, Dynamed, and BMJ-Best Practice (p=0.030).

Concerning actual knowledge, only 15.4% (n=25) of HCPs were classified as having advanced knowledge, but no statistically significant differences were found between different professions (p=0.987). Overall, the mean score of the three clinical vignettes was 13.04±7.69 points {0.0;30.0}. Pharmacists scored a mean of 13.16±8.08 points, physicians scored 14.29±5.50 points, and nurses scored 10.10±9.07 points, but no differences were found between them (p=0.269) (**Table 4.1.2**). There was a weak correlation between perceived and real knowledge, even though statistically significant (r=0.199; p<0.001) (**Figure 4.1.1**). Similar results were obtained when analyzing the different professions (Pharmacists – r=0.205; p=0.027; Physicians – r=0.025; p=0.887; and Nurses – r=0.118; p=0.714).

Regarding the clinical vignettes concerning older individuals with dementia and bipolar disorders, the mean score was 4.59±4.08 and 4.86±2.97 points, respectively. Most HCPs were classified as having an intermediate knowledge (n=100; 60.6%) regarding medication complexities in the elderly with mental disorders.

POTENTIAL BARRIERS TO PIMS' MANAGEMENT IN CLINICAL PRACTICE: ARE THERE ANY DIFFERENCES BETWEEN HCPs?

Fifty-seven percent (n=93) of HCPs normally review the pharmacotherapeutic regimen in less than two out of 10 patients in their clinical practice. Differences were found in the average number of patients where the pharmacotherapeutic regimen is reviewed, where physicians tend to review the medication in at least 6 out of 10 patients compared to pharmacists and nurses (p<0.001) (**Table 4.1.2**). Participants agreed that limited time of appointments (81.6%; n=138), lack of a specific curricular unit on gerontology in their bachelor/master degree (72.2%; n=122), and scarce clinical tools adjusted to clinical practice (61.8%; n=105) were the major potential barriers to PIMs' management in clinical practice. There were no differences between the perceived barriers by the different HCPs (**Table 4.1.2**).

Other barriers, including lack of interprofessional collaboration, limited access to clinical and laboratory information, no remuneration, fear of deprescribing drugs, and lack of confidence in their own recommendations, were also listed as barriers to clinical management of PIMs.

SENSITIVITY ANALYSIS

There were no differences in the results when considering only Portugal in the analysis.

DISCUSSION

MAIN FINDINGS

In this study, we found that most participants felt confident in managing PIMs and no differences were found between physicians, pharmacists, and nurses. However, when evaluated by clinical vignettes, only 15.4% (n=25) of HCPs were considered to have advanced knowledge and no statistical differences were found between different professions. However, there was a weak correlation between perceived and real knowledge, even though statistically significant. When looking to the clinical vignettes concerning examples of patients with mental health disorders, we found that even though participants felt confident in managing their therapeutic complexities, only a minority obtained a good score in the knowledge assessment test. Moreover, HCPs agreed that limited time for appointments, lack of a specific curricular unit on gerontology in their bachelor/master's degree, and scarce clinical tools adjusted to clinical practice were major potential barriers to PIMs' management in clinical practice.

In this study, most participants felt confident that their knowledge was enough to perform a medication review in their older patients, which is in accordance with previous studies. Ramaswamy et al. (2010) assessed the knowledge, confidence, and barriers to appropriate prescribing in the elderly among family and internal medicine residents and attending doctors in three teaching hospitals in the US and found that 75% felt confident about their prescribing patterns.[22] Another study, conducted by Akkawi and Mohamed (2018), found a lower degree of confidence (34%) in the ability to recommend appropriate medications for elderly patients; however, no differences were found between physicians and clinical pharmacists.[20] These results corroborate our findings. When asked how often HCPs use specific tools that may help in identifying and managing PIMs, most respondents stated to hardly use them (between 0.0 and 20.0%). Other studies have shown similar results, despite HCPs being aware of the existence of such tools.[19,20,18] This suggests that only a small proportion of HCPs may have heard of explicit tools, and an even smaller proportion may have used it. According to our results, two potential barriers were identified as possible determinants: lack a specific curricular unit on gerontology in the pre-graduated studies, and limited availability of clinical tools adjusted to clinical practice.

This means that probably we can have two scenarios: the first one, where they never heard of explicit tools, because they did not have a specific curricular unit of gerontology or appropriate pharmacotherapy for the elderly; and the second one, where they heard of explicit tools and they know where to find them, but they think that these tools are not adapted to clinical practice as they are mostly available as extensive tables. This last finding associated to the fact that most participants agreed that limited time for appointments is a relevant constraint for PIMs' management in clinical practice, seems to corroborate out second hypothesis.

Pharmacists were the professional class that reported more frequent use of explicit criteria, compared to physicians, and nurses. This may be linked to the fact that some curricular programmes of the pharmacy degree have changed in recent years, including topics on medicines management in the elderly, including medication review. However, there was no statistically significant differences between the scores obtained by pharmacists and the other two professional classes.

When evaluating actual knowledge using clinical vignettes, we observed that only a small proportion of the sample was classified as having advanced knowledge, in accordance with previous studies.[19,20,22] In our study physicians showed a better knowledge in the first vignette focusing on psychiatric drugs in elderly patients with cardiovascular disease, whereas pharmacists showed a better score in the second vignette focusing on NSAIDs and benzodiazepines in patients with osteoarticular disease. This could mean that pharmacists are more aware of the potential adverse drug events (ADEs) of these drugs, whereas physicians are more used to deal with certain medications that may increase the cardiovascular risk; however, some of these potential ADEs may be found in other platforms like Up-to-date or Medscape, which were the most frequently used tools by physicians. The use of benzodiazepines and the risk of falls and the risk of gastrointestinal bleeding associated with the use of NSAIDs are associations very well established, particularly for the elderly population. However, there was a weak correlation between perceived and real knowledge, including between the different professions. This may suggest that in the future, changes on how future HCPs are evaluated should be adapted to a more real-world situation using case studies, instead of theoretical examination only. This has been defended by Miller since the 90s, and later adapted by various researchers and professional organizations focused on competency training and continuous professional development, to highlight the difference between knowledge and competency, knowing how and being able to competently deliver.[23]

IMPACT ON PRACTICE

To our best knowledge, this is one of the few studies assessing knowledge and practice of different HCPs (physicians, pharmacists, and nurses) on pharmacotherapy optimization for older adults

with mental health disorders, including PIMs' management. Considering global ageing, it is imperative for HCPs to be prepared to manage multimorbidity and polypharmacy as new challenges in clinical practice. PIMs are one example of another challenge that HCPs are very likely to face in practice and demand specific knowledge and skills. Therefore, future work will focus on the inclusion of these extensive lists in digital clinical-decision support systems to more efficiently help HCPs to manage medication in the elderly, and also to foster more intense interprofessional collaboration where all contribute along the patient pathway, avoiding silos and information mismatches.

LIMITATIONS

This study has some limitations worth acknowledging, including the inability to estimate a sample size given the absence of data on physicians, pharmacists, and nurses accessing social media worldwide. It is also important to mention that the study period (July-October 2019) may have influenced our sample size, since most of those months are coincident with summer holidays, where HCPs are less available to participate in research studies. Additionally, this sample may represent a self-selected sample, as many of the participants seem to be HCPs involved in the Geriatric field and, therefore, their knowledge may be higher when compared to others less involved. There is also a disproportionality in terms of the number of different HCPs included, i.e., pharmacist represents most of the sample (72.0%), which may influence the results. There are also no differences between different medical specialties, which may be justified by the self-selected sample in which most of the physicians that agreed to participate, may have a higher knowledge on geriatrics or even a subspeciality in this field. It is also important to acknowledge that the different undergraduate curriculum of the different healthcare professions may influence their knowledge in this field. Clinical vignettes were based on the Beers criteria, but the assessment of clinical knowledge considered may be questioned. However, we do believe that this approach is a better way than using implicit criteria that lies more on the clinical judgement and hence in previous knowledge of pharmacotherapy. The fact that most of the criteria presented on those lists is related to ADRs known to be commonly experienced by the elderly (e.g., NSAIDs should be avoided due to an increased risk of bleeding) was considered a proof of validity per se. A more qualitative approach to access the potential barriers to PIMs could have been considered and would eventually result in more in-depth material for future work. Finally, our results cannot be generalized given the limited sample.

CONCLUSION

Most of the HCPs felt confident to manage medication complexities in elder patients with mental disorders, but only a minority obtained a good score in the knowledge assessment test. There were no differences between physicians, pharmacists, and nurses concerning their confidence and knowledge about optimizing the pharmacotherapy in older adults, including PIMs management. Additionally, a weak correlation between perceived and real knowledge was found. Main barriers

identified included structural barriers (tools unfit for practice) and process barriers (time), suggesting education per se will not necessarily lead to optimised pharmacotherapy in the elderly.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Faculty of Pharmacy, University of Lisbon. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FAC, HL, and JA conceived and designed the study. JA and JGM collected, analyzed, and interpreted the data. JA prepared the manuscript. All the authors have critically reviewed the manuscript until its final version. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 4.1.1 – Sociodemographic characteristics

Characteristics	Total of questionnaires (n=165)
Age, Mean±SD (years)	35.3±11.3
Female respondents, n (%)	114 (69.1)
Occupation, n (%)	
Pharmacist	118 (71.5)
Physician	35 (21.1)
Nurse	12 (7.3)
Setting where HCPs do their practice, n (%)	
Ambulatory	95 (57.6)
Hospital	70 (42.4)
Years of practice, n (%)	
Less than 5 years	57 (34.5)
5 to 10 years	52 (31.5)
11 to 15 years	10 (6.1)
16 to 20 years	21 (12.7)
More than 20 years	25 (15.2)
Degree, n (%)	
Bachelor	28 (17.1)
Integrated Master	62 (37.8)
Master	44 (26.8)
PhD	30 (18.3)
Missing values: 1	

Abbreviations: HCPs – Healthcare Professionals; SD – Standard Deviation

Table 4.1.2 – Knowledge assessment and practice of physicians, pharmacists, and nurses regarding PIMs management

Domain	Total sample (n=165)	Physicians (n=35)	Pharmacists (n=118)	Nurses (n=12)	*p*-value
Knowledge					
Statement 1 – I have knowledge to identify and evaluate the use of PIMs in the elderly in my daily practice, % (n)	75.6 (124)	80.0 (28)	77.0 (90)	50.0 (6)	0.115
Statement 2 – I think my knowledge is enough to perform a medication review of my elder patients' therapy, including the use of PIMs, % (n)	71 (117)	77.2 (27)	72.1 (85)	41.7 (5)	0.057
Advanced knowledge, % (n)	15.4 (25)	14.3 (5)	16.5 (19)	8.3 (1)	0.987
Mean score in the clinical cases, mean±SD	13.17±7.70	14.29±5.50	13.16±8.08	10.10±9.07	0.269
Mean score in the vignette 1, mean±SD	4.59±4.08	6.07±3.75	4.32±4.05	2.92±4.37	0.135
Mean score in the vignette 2, mean±SD	4.86±2.97	4.64±2.30	5.06±3.17	3.44±2.39	0.543
Mean score in the vignette 3, mean±SD	3.73±3.59	3.57±3.80	3.77±3.49	3.75±4.20	0.959
Practice					
Therapeutic regimen revised in less than two out of 10 patients, % (n)	56.7 (93)	25.0 (9)	67.5 (77)	41.7 (5)	<0.001
Lack of a specific curricular unit on gerontology in their bachelor/master's degree, % (n)	72.8 (118)	77.1 (27)	72.2 (83)	66.7 (8)	0.601
Limited time of appointments/counselling	82.1 (133)	77.2 (27)	83.4 (96)	83.3 (10)	0.884
Scarce clinical tools adjusted to clinical practice	62.6 (102)	60.0 (11)	64.6 (75)	50.0 (6)	0.123

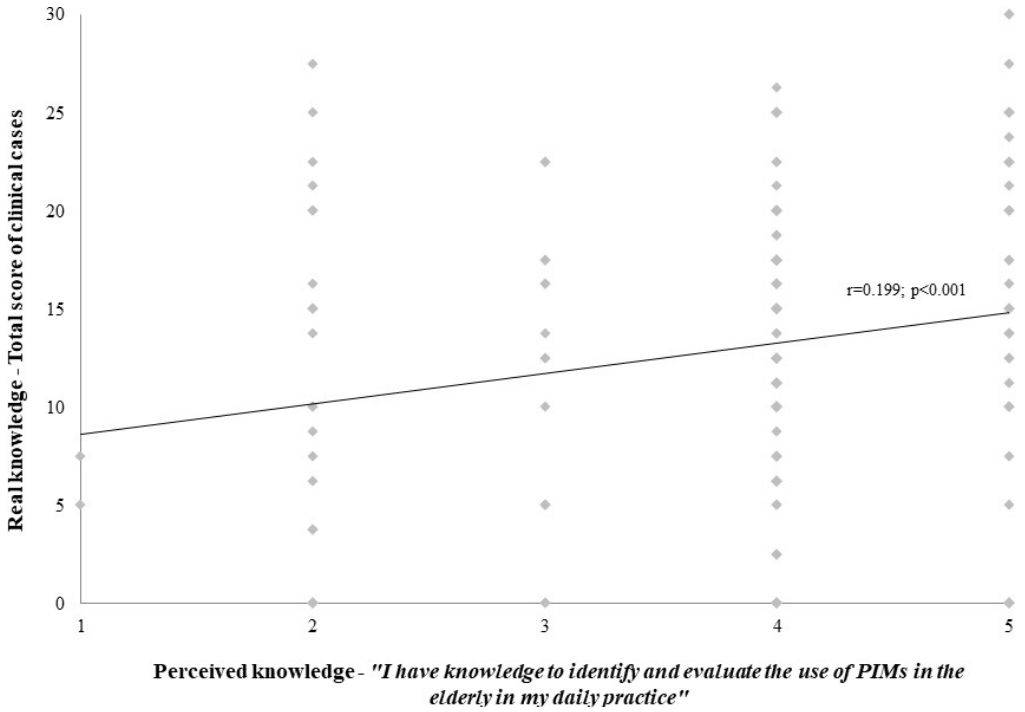

Figure 4.1.1 – Real knowledge vs perceived knowledge of healthcare professionals included in the study (1-Strongly disagree, 2-Partially disagree, 3-Do not disagree/do not agree, 4-Partially agree, 5-Strongly disagree)

APPENDICES

SUPPLEMENTARY MATERIAL

Supplementary Material – S1: Questionnaires specifically developed for this study to evaluate knowledge and practice of HCPs about PIMs management in the elderly

English Version:

Population aging marks an important advancement in demography. The elderly (individuals aged ≥ 65) are a challenge for clinical practice given their intrinsic features, their complexity and heterogeneity, all of which contribute to higher odds of experiencing multimorbidity and polypharmacy. Since the 90s, many lists based on explicit criteria have been developed to access and manage Potentially Inappropriate Medications (PIMs), i.e. medicines where the risk of adverse events overweights the clinical benefit of its use. However, information on the knowledge and practice of different healthcare professionals on PIMs is still scarce.

This study is part of a Master thesis that is being undertaken in Faculdade de Farmácia, Universidade de Lisboa (FFULisboa), by Marta Franco Santos, supervised by Professor Filipa Alves da Costa (FFULisboa), Dr. João Pedro Aguiar (FFULisboa), and Dr. João Gama Marques (Faculdade de Medicina da Universidade de Lisboa). Our main goals are: (a) to evaluate the knowledge and practice of healthcare professionals around PIMs; and (b) to identify possible barriers that may affect healthcare professionals' clinical practice. This study does not intend to judge your clinical practice, but rather to collect valuable information that may contribute to develop a tool/system to assist prescribing in practice. No personal identifiable data is being collected and all answers will be analysed collectively.

If you intend to proceed, do you consent the research team to use your answers collectively in the future?

Yes

No

If you intend to proceed, do you agree to participate in the study?

Yes

No

(If you have selected "No" in any of the questions, the questionnaire ends here)

Section 1 – Sociodemographic data

1 – Age

2 – Country

3 – Sex:

Male

Female

4 – Occupation:

Physician

Pharmacist

Nurse

Other. Please state which:

4.1. – If you selected “Physician”, please indicate which specialty you have (or area you work in)

4.2. – If you selected “Pharmacist”, please indicate which specialty you have (or area you work in)

4.3. – If you selected “Nurse”, please indicate which specialty you have (or area you work in)

5 – For how many years have you been working?

Less than 5 years

5 to 10 years

11-15 years

16-20 years

More than 20

I am not currently working

6 – Academic degree

Bachelor

Integrated Master

Second Cycle Master

PhD

Section 2 – Perceived knowledge

Please consider the following definition of medication review (adapted from Griese-Mammen, 2018): is a structured evaluation of patient's medication with the aim of optimizing medicines use and improving health outcomes. This entails detecting PIMs or contraindicated medications and recommending or implementing interventions.

1 – Considering a PIM as a medicine where the risk of adverse drug reactions (ADRs) overweights the clinical benefit and for which there is a safer alternative available, I have the knowledge to identify and evaluate the use of PIMs in the elderly in my daily practice

Strongly disagree

Partially disagree

Do not disagree/do not agree

Partially agree

Strongly agree

2 – I think my knowledge is enough to perform a medication review of my elder patients' therapy, including the use of PIMs.

Strongly disagree

Partially disagree

Do not disagree/do not agree

Partially agree

Strongly agree

3 – How often do you use clinical decision support systems to perform medication review in your elder patients?

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4 – How often do you use each of the following tools?

4.1. Beers Criteria

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.2. START/STOPP criteria

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.3. PRISCUS List

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.4. Up to date

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.5. Medscape

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.6. Dynamed

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

4.7. BMJ – Best Practice

Never (0-20%)

Rarely (20-40%)

Sometimes (40-60%)

Most of the times (60-80%)

Always (80-100%)

Section 3 – Real Knowledge

In this section you can find three clinical cases, where you should answer according to what you would do in your clinical practice.

1 – Ms. DS, 77 years old, with hypertension, dyslipidaemia, type 2 diabetes, and dementia, has been prescribed with atorvastatin 20 mg (once daily), perindopril 4 mg (once daily), sitagliptin 100 mg (once daily), and olanzapine 5 mg (once daily).

1.1. Among the medication list, do you identify any PIM?

Yes

No

1.2. Which medicine(s) would you classify as PIM?

Atorvastatin

Perindopril

Sitagliptin

Olanzapine

1.3. What do you consider to be the reason why the previously medicine(s) is(are) considered as PIM?

Atorvastatin – risk of muscular pain and, in more severe cases, rhabdomyolysis

Association of olanzapine with sitagliptin – high risk of hyperglycaemia with olanzapine use

Association of perindopril with atorvastatin – risk of renal failure

Olanzapine – increase of cardiovascular risk in patients with previous history of cardiovascular disease

Other reasons. Which?

1.4. What do you think would be the most appropriate action in this case?

Inform the treating physician/prescriber of the need to deprescribe the medication(s) and suggest a safer alternative (in case of being the prescriber, I would deprescribe the medicine myself)

Suggest dose adjustment of the medicine(s)

Suggest keeping the medicine(s), because there is no effective alternative available, even though is not safe

There is no need to make any suggestion

Other actions. Which?

2. Mr. MC, 79 years old, with bipolar disorder and musculoskeletal disease, has been prescribed with lithium 200 mg (once daily), alprazolam 1 mg (thrice daily), paracetamol 1000mg (thrice daily), and naproxen 500mg (twice daily when needed).

2.1. Among the medication list, do you identify any PIM?

Yes

No

2.2. Which medicine(s) would you classify as PIM?

Lithium

Alprazolam

Paracetamol

Naproxen

2.3. What do you consider to be the reason why the previous medicine(s) is(are) considered as PIM?

Lithium – risk of toxicity in patients with renal failure

Alprazolam – high risk of falls in the elderly

Paracetamol – contraindicated in patients with heart failure

Naproxen – risk of GI bleeding in patients aged 75 or older

Other reasons. Which?

2.4. What do you think would be the most appropriate action in this case?

Inform the physician/prescriber of the need to deprescribed the medication and suggest a safer alternative (in case of being the prescriber, I would deprescribed the medicine myself)

Suggest dose adjustment of the medicine

Suggest keeping the medicine, because there is no effective alternative available, even though is not safe

There is no need to make any suggestion

Other actions. Which?

3. Mr. HN, 88 years old, with dyslipidaemia, heart failure, previous history of myocardial infarction, and dementia, has been prescribed with rosuvastatin 10 mg (once daily), enalapril 5 mg (once daily), furosemide 40 mg (once daily), bisoprolol 5 mg (once daily), digoxin 0.25 mg (once daily), and galantamine 8 mg (once daily). This patient does not have renal failure.

3.1. Among the medication list, do you identify any PIM?

Yes

No

3.2. Which medicine(s) would you classify as PIM?

Galantamine

Rosuvastatin

Bisoprolol

Digoxin

There are no PIMs

3.3. What do you consider to be the reason why the previous medicine(s) is(are) considered as PIM?

Association of rosuvastatin with digoxin – increased risk of rhabdomyolysis

Digoxin – in doses ≥ 0.125mg can cause toxicity in older patients with heart failure

Association of digoxin with bisoprolol – increased risk of hyperkalaemia

Association of galantamine with bisoprolol – increased risk of bradycardia

Other reasons. Which?

3.4. What do you think would be the most appropriate action in this case?

Inform the physician/prescriber of the need to deprescribed the medication and suggest a safer alternative (in case of being the prescriber, I would deprescribed the medicine myself)

Suggest dose adjustment of the medicine

Suggest keeping the medicine, because there is no effective alternative available, even though is not safe

There is no need to make any suggestion

Other actions. Which?

Section 4 - Structural or procedural barriers in clinical practice

1. Considering the last 10 patients you saw, in how many of them, did you undertake a medication review?

Less than 2 patients

3 to 4 patients

5 to 6 patients

7 to 8 patients

9 to 10 patients

2. Please select your level of agreement on the barriers around the knowledge of PIMs

2.1. Lack of a specific curricular unit on gerontology in your bachelor/master degree

Strongly disagree

Partially disagree

Do not disagree/do not agree

Partially agree

Strongly agree

2.2. Lack of clinical tools adjusted to clinical practice

Strongly disagree

Partially disagree

Do not disagree/do not agree

Partially agree

Strongly agree

2.3. Lack of time available for each patient

Strongly disagree

Partially disagree

Do not disagree/do not agree

Partially agree

Strongly agree

2.4. Please list any other barriers you consider relevant.

Versão Portuguesa:

Nas últimas décadas tem-se assistido a um importante marco demográfico: o envelhecimento acentuado da população a nível mundial. O doente idoso, definido como um indivíduo com idade ≥ a 65 anos, constitui, um desafio para a prática clínica, não só pelas suas características intrínsecas, mas pela complexidade e heterogeneidade da população em causa. Dada a dificuldade de avaliar o rácio benefício/risco, desde os anos 90 têm sido desenvolvidas listas de apoio à prescrição, identificando medicamentos potencialmente inadequados (PIM – Potentially Inappropriate Medications), ou seja, medicamentos que poderão, quando usados neste subgrupo populacional, aumentar o risco de ocorrência de reações adversas a medicamentos (RAM), ainda que não sejam considerados contraindicados. Contudo, é, ainda, desconhecido o grau de conhecimento e prática dos profissionais de saúde portugueses em relação a este tipo de medicamentos.

Este projeto de investigação está a ser desenvolvido no âmbito de uma dissertação de Mestrado Integrado para a obtenção do grau de Mestre em Ciências Farmacêuticas pela Faculdade de Farmácia, Universidade de Lisboa (FFULisboa), sendo orientada pela Prof. Dra. Filipa Alves da Costa e co-orientada pelo Mestre João Pedro Aguiar, em colaboração com o Dr. João Gama Marques (Faculdade de Medicina, Universidade de Lisboa). Os objetivos primários são: (a) avaliar o conhecimento dos profissionais de saúde portugueses em relação aos PIM; e (b) identificar possíveis barreiras à otimização do histórico farmacoterapêutico dos doentes idosos relativamente a este tipo de medicamentos na sua prática clínica. Importa frisar que não se pretende julgar a prática diária em relação a esta temática, mas sim obter dados que nos permitam auxiliar no desenvolvimento de uma futura intervenção, tendo em conta as necessidades expressas pelos profissionais de saúde face ao tema. Todas as respostas são de carácter voluntário e opcional e a não resposta a qualquer uma das questões, não tem qualquer tipo de contrapartida. No entanto, apela-se à resposta atenta de forma que todos os dados obtidos sejam válidos e passíveis de análise. Os dados serão tratados de forma agregada, não havendo qualquer item que identifique o respondente e, por isso é totalmente anónimo.

Ao prosseguir, terá tomado conhecimento da informação acima mencionada e a autorizar a sua participação no estudo. Pretende fazer parte do estudo?

Sim

Não

Secção 1 – Caracterização Sociodemográfica

1 – Idade (em anos)

2 – Sexo:

Feminino

Masculino

3 – Profissão:

Médico(a)

Farmacêutico(a)

Enfermeiro(a)

Outra (Qual?)

3.1. Se anteriormente respondeu médico(a), indique a especialidade (ou área em que exerce)

3.2. Se anteriormente respondeu farmacêutico(a), indique a especialidade (ou área em que exerce)

3.3. Se anteriormente respondeu enfermeiro(a), indique a especialidade (ou área em que exerce)

4 – Qual a região do país onde exerce:

Norte

Centro

Área Metropolitana de Lisboa

Alentejo

Algarve

Região Autónoma da Madeira

Região Autónoma dos Açores

5 – Anos do exercício profissional:

Menos de 5 anos

5-10 anos

15-20 anos

Mais de 20 anos

Não exerce atualmente

6 – Grau académico:

Licenciatura (incluindo pré-Bolonha)

Mestrado Integrado

Mestrado 2º Ciclo

Doutoramento

Secção 2 – Conhecimento Percecionado

Por favor considere a seguinte definição de revisão da medicação (adaptado de Griese-Mammen, 2018): é uma avaliação estruturada dos medicamentos de um doente que tem como principal objetivo otimizar a utilização dos medicamentos e melhorar outcomes em saúde. Esta abordagem pressupões a deteção de Medicamentos Potencialmente Inadequados e a recomendação e implementação de intervenções.

1 – Considerando que se define Medicamento Potencialmente Inadequado como um medicamento com potencial risco de evento adverso associado e para o qual existe uma alternativa mais segura, na minha prática diária, tenho conhecimentos para identificar e avaliar a utilização de PIM em doentes idosos.

Discordo totalmente

Discordo parcialmente

Não concordo nem discordo

Concordo parcialmente

Concordo totalmente

2 – Sinto que tenho os conhecimentos necessários para proceder à revisão da medicação dos utentes idosos, incluindo a utilização de Medicamentos Potencialmente Inadequados.

Discordo totalmente

Discordo parcialmente

Não concordo nem discordo

Concordo parcialmente

Concordo totalmente

3 – Com que frequência utiliza instrumentos de apoio à decisão clínica para rever (alterar ou modificar) a terapêutica dos utentes idosos?

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4 – Com que frequência utiliza cada uma das seguintes plataformas de apoio à decisão clínica:

4.1. Critérios de Beers

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.2. Critérios START/STOPP

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.3. Lista Priscus

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.4. Up-to-date

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.5. Medscape

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.6. Dynamed

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

4.7. BMJ – Best Practice

Nunca (0-20%)

Raramente (20-40%)

Às vezes (40-60%)

Muitas vezes (60-80%)

Sempre (80-100%)

Secção 3 – Conhecimento Real

Irão ser-lhe apresentados alguns casos práticos, para cada um deles, pedimos-lhe que indique, como procederia.

1 – A Sra. DS, 77 anos, apresenta como antecedentes pessoais dislipidémia, hipertensão, diabetes mellitus tipo 2 e demência, encontrando-se medicada com os seguintes medicamentos: atorvastatina 20 mg (1x/dia), perindopril 4 mg (1x/dia), sitagliptina 100 mg (1x/dia) e olanzapina 5 mg (1x/dia).

1.1 – Tendo em conta o regime farmacoterapêutico da doente, identifica algum medicamento que considere potencialmente inadequado?

Sim

Não

1.2 – Qual/quais dos seguintes medicamentos selecionaria como potencialmente inadequado na situação em causa?

Atorvastatina

Perindopril

Sitagliptina

Olanzapina

1.3 – Qual/quais considera ser a razão pela qual o medicamento anteriormente assinalado é considerado potencialmente inadequado?

Atorvastatina – risco de dores musculares severas e, em casos graves, rabdomiólise.

Combinação de olanzapina com sitagliptina – aumento do risco de hiperglicémias com a utilização de olanzapina

Risco de insuficiência renal, devido à interação entre o perindopril e a atorvastatina

Olanzapina – aumento do risco cardiovascular em doentes com história de doença cardiovascular.

Outra razão. Qual?

1.4 – Qual das seguintes ações iria sugerir?

Comunicar ao médico prescritor a necessidade de retirar o medicamento e escolher uma opção mais segura (ou em caso de ser o próprio o prescritor, retirava o medicamento).

Sugeria ajustar a dose ou o intervalo posológico do medicamento selecionado.

Sugeria manter o medicamento dado não existir uma alternativa tão efetiva, ainda que menos segura.

Não sente necessidade de fazer sugestões

Outra ação. Qual?

2 – O Sr. MC, 79 anos, apresenta como antecedentes pessoais doença bipolar e patologia osteoarticular encontrando-se medicado com os seguintes fármacos lítio 200mg (1x/dia), alprazolam 1mg (3x/dia), paracetamol 1000mg (3x/dia) e naproxeno 500mg (2x/dia em SOS).

2.1 – Tendo em conta o regime farmacoterapêutico da doente, identifica algum medicamento que considere potencialmente inadequado?

Sim

Não

2.2 – Qual/quais dos seguintes medicamentos selecionaria como potencialmente inadequado na situação em causa?

Lítio

Alprazolam

Paracetamol

Naproxeno

2.3 – Qual/quais considera ser a razão pela qual o medicamento anteriormente assinalado é considerado potencialmente inadequado?

Lítio – risco de toxicidade em doentes com insuficiência renal.

Alprazolam – risco de quedas dada a hipersensibilidade do doente idoso a este tipo de fármacos psicoativos.

Paracetamol – contra-indicado em situações de insuficiência cardíaca.

Naproxeno – risco de hemorragias gastrointestinais em doentes com idade superior ou igual a 75 anos.

Outra razão. Qual?

2.4 – Qual das seguintes ações iria sugerir?

Comunicar ao médico prescritor a necessidade de retirar o medicamento e escolher uma opção mais segura (ou em caso de ser o próprio o prescritor, retirava o medicamento).

Sugeria ajustar a dose ou o intervalo posológico do medicamento selecionado.

Sugeria manter o medicamento dado não existir uma alternativa tão efetiva, ainda que menos segura.

Não sente necessidade de fazer sugestões

Outra ação. Qual?

3 – O Sr. HN, 88 anos, apresenta como antecedentes pessoais dislipidémia, insuficiência cardíaca, história de enfarte do miocárdio e doença de Alzheimer, encontrando-se medicado com os seguintes fármacos: rosuvastatina 10 mg (1x/dia), enalapril 5 mg (1x/dia), furosemida 40 mg (1x/dia), bisoprolol 5 mg (1x/dia), digoxina 0.25 mg (1x/dia) e galantamina 8 mg (1x/dia). Salienta-se que o doente não apresenta insuficiência renal.

3.1 – Tendo em conta o regime farmacoterapêutico da doente, identifica algum medicamento que considere potencialmente inadequado?

Sim

Não

3.2 – Qual/quais dos seguintes medicamentos selecionaria como potencialmente inadequado na situação em causa?

Galantamina

Rosuvastatina

Bisoprolol

Digoxina

3.3 – Qual/quais considera ser a razão pela qual o medicamento anteriormente assinalado é considerado potencialmente inadequado?

Combinação de rosuvastatina com digoxina – aumento do risco de rabdomiólise

Digoxina – em doses superiores a 0.125mg pode causar toxicidade digitálica em doentes idosos com insuficiência cardíaca.

Combinação de digoxina com bisoprolol – aumento do risco de hipercaliémia.

Combinação da galantamina com o bisoprolol – aumento do risco de bradicardia.

3.4 – Qual das seguintes ações iria sugerir?

Comunicar ao médico prescritor a necessidade de retirar o medicamento e escolher uma opção mais segura (ou em caso de ser o próprio o prescritor, retirava o medicamento).

Sugeria ajustar a dose ou o intervalo posológico do medicamento selecionado.

Sugeria manter o medicamento dado não existir uma alternativa tão efetiva, ainda que menos segura.

Não sente necessidade de fazer sugestões

Outra ação. Qual?

Secção 4 – Obstáculos estruturais ou processuais existentes na prática clínica

1 – Considerando uma amostra de 10 doentes, em quantos costuma rever (alterar ou modificar) a terapêutica?

Menos de 2 doentes

3 a 4 doentes

5 a 6 doentes

7 a 8 doentes

9 a 10 doentes

Outro

2 – Indique, o seu grau de concordância com os seguintes fatores, referentes às barreiras à aplicabilidade do seu conhecimento acerca de Medicamentos Potencialmente Inadequados de acordo com a seguinte escala

2.1. Falta de ferramentas ajustadas à prática diária

Discordo totalmente

Discordo parcialmente

Não concordo nem discordo

Concordo parcialmente

Concordo totalmente

2.2. Pouco tempo disponível para cada doente

Discordo totalmente

Discordo parcialmente

Não concordo nem discordo

Concordo parcialmente

Concordo totalmente

2.3. Falta de ênfase dado à temática aquando da formação pré e pós-graduada

Discordo totalmente

Discordo parcialmente

Não concordo nem discordo

Concordo parcialmente

Concordo totalmente

2.4. Outras sugestões que queira indicar:

CHAPTER 4.2

Identification of a set of patient-related features to foster safe prescribing of specific antipsychotics in the elderly with dementia

João Pedro Aguiar, Catarina Bernardo, João Gama Marques, Hubert G.M. Leufkens, and Filipa Alves da Costa

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doi: 10.3389/fpsyt.2020.604201
Impact Factor: 4.157

ABSTRACT

Background: Antipsychotics (APs) are widely used to manage behavioural and psychiatric symptoms in dementia, although with a variety of adverse drug reactions. Therefore, it is important to know which patient-related features should be considered to foster a safe prescribing of these medications.

Objectives: To compile and validate a set of patient-related features (PRFs) to foster safe prescribing of specific APs in the elderly with dementia; and to evaluate the feasibility of using them in clinical practice by analysing the exhaustiveness of medical records.

Method: A rapid literature review was the starting point, where PRFs were identified through a search in PubMed combined with information from the Summary of Product Characteristics (SmPCs). In the next step, a two-round e-Delphi survey was undertaken, where a total of 450 participants were invited by e-mail, including prescribers and specialists in benefit-risk assessment. Finally, a cross-sectional study was undertaken, where 100 patients were randomly extracted from the psychiatric hospital database. Outcomes were defined as the assessment of the clinical relevance and feasibility of the PRFs, and the level of exhaustiveness of these features in medical records. Data analysis was performed using univariate statistics (IBM SPSS v.23.0).

Results: A total of 92 experts participated in the e-Delphi. Forty-seven PRFs obtained consensus, where 12 were applicable to haloperidol, 14 to olanzapine/risperidone, 13 to quetiapine, and 8 to aripiprazole. Age, comorbidities, and co-medications were rated as important features regardless of the prescribed drug. All PRFs were rated as always or frequently available and, if not, they were easy or partially easy to obtain. Age, comorbidities, and co-medications were always available in the medical records, whereas cognitive status (between 41.4 and 78.8%) or hepatic function (between 17.2 and 30.4%) presented a low-level of exhaustiveness.

Conclusions: Even though a high number of PRFs were rated as clinically relevant, some of them were identified as frequently missing from medical records. This may suggest that medical records should be complemented with other sources (e.g., nursing and pharmacy records) to ensure a safe prescribing of APs.

INTRODUCTION

Antipsychotic (AP) medication is frequently used in several psychiatric conditions, including behavioural and psychiatric symptoms in dementia (BPSD), schizophrenia, and bipolar disorder.[1] APs are commonly divided into two groups: typical and atypical. The first group has been on the market since 1950's and were associated with extrapyramidal symptoms (EPS). Over the years, atypical APs have been widely used compared to the typical group, given their lower risk of EPS.[2,3] However, they have been associated with metabolic syndrome and cardio- and cerebrovascular events.[4-6]

Prescribing these medications to older individuals is common, particularly in nursing homes. The use of such medications in this age group is most of the times done off-label, as most of the evidence about their effectiveness and safety was extrapolated from younger adults. They can be used in the elderly to manage BPSD, which may affect up to 90% of the patients.[1,7] A systematic review found that risperidone, olanzapine, and aripiprazole showed greater efficacy than quetiapine, including the more severe cases. However, there is little evidence to suggest optimal duration of AP treatment, suggesting that a maximum of 6 weeks of treatment may be enough.[8] Even though APs may have a greater benefit compared to non-pharmacologic measures, they also carry a greater risk.[1]

Adverse drug reactions (ADRs) are common among the elderly, especially with psychotropic drugs.[9] Multimorbidity, polypharmacy, and the use of inappropriate medications (PIMs – potentially inappropriate medications) are well-known risk factors associated with an increased risk of ADRs and, therefore, with higher costs, hospitalizations, and mortality.[10,11] In order to avoid ADRs, prescribing indicators have been identified and validated. Prescribing indicators are useful to: (a) optimize quality of healthcare delivery; (b) evaluate if medications are rationally used; (c) to audit and monitor practices in the context e.g., of quality circles, to describe and benchmark differences in practices; and (d) may also be used within clinical decision support systems.[12-15] Different indicators may be divided according to different domains, such as safety (prescribing safety indicators) or quality (prescribing quality indicators). The first group has been defined as statements that describe prescribing events that may increase the risk of harm in patients.[16] Prescribing safety indicators in mental health have been explored in a recent systematic review, where authors found that presence of PIMs, high risk medications, drug-disease interactions, and drug-related problems are examples of indicators that should be considered. They also found that 15.5% of those indicators were applicable to APs.[17] A recent Delphi-study has developed prescribing safety indicators for medications used in mental health disorders, reporting 42 indicators considered to be of high or extreme risk for patient care. These included

drug-disease and drug-drug interactions, inadequate monitoring, inappropriate dose, omissions, PIMs, and polypharmacy, most of which were applicable to APs.[18]

Even though some studies have been conducted to develop and validate prescribing safety indicators related to mental health, there is still the need to move from a population-based approach to patient-centred care. APs are a good example of a medication class with a wide range of receptor binding affinities, which may contribute to different ADR profile for each drug.[19] Therefore, it may be important to know which patient-related features (PRFs) should be taken into account when prescribing specific APs to older patients with dementia. Therefore, our aims were to compile and validate a set of patient-features to foster safe prescribing of APs in older individuals with dementia and to evaluate the level exhaustiveness of such features in medical records of a mental health specialized hospital in Portugal.

METHODS

STUDY DESIGN

This study was divided into three steps: a rapid literature review to identify and compile possible PRFs, i.e., individual characteristics from the patients that may be used to foster safe prescribing of specific APs (*e.g.*, quetiapine, olanzapine/risperidone, haloperidol, and aripiprazole) in the elderly with dementia; a consensus study to select the most clinically relevant PRFs for each drug; and a cross-sectional study where medical records from a Portuguese Psychiatry Hospital were reviewed to access their exhaustiveness regarding the features previously validated among comprehensively and validate PRFs.

COMPILATION OF DIFFERENT PRFs REGARDING AP PRESCRIPTION FOR THE ELDERLY WITH DEMENTIA

Quetiapine, olanzapine/risperidone, haloperidol, and aripiprazole were chosen either based on their consumption pattern in older individuals with dementia or on their innovative mechanism of action, which may be an advantage on the risk-benefit ratio when prescribing the drug. A rapid literature review was performed using PubMed.[20] Papers describing either PRFs used when prescribing APs or PRFs that should be monitored while using this medication in demented patients were included, considering the drug marketing authorizations of the selected APs. Summary of Product Characteristics (SmPCs) were used to supplement the results extracted from the rapid literature review. Age, renal and hepatic function, presence of comorbidities, and electrocardiogram results (EKG) were common features for all the selected drugs. PRFs specific for each drug were also extracted and summarized in **Table 4.2.1**.

DELPHI SURVEY AND PARTICIPANTS

To validate which PRFs would be more suitable to ensure a safe prescription of the previous selected APs in the elderly with dementia, a two-round Delphi survey were undertaken from July to September 2019. This method provides a systematic way to converge the expertise of individuals working in a specific area and gives guidance that is readily applicable to a particular context.[21] A total of 450 participants were invited to participate in order to obtain a final sample of 100. Participants should be prescribers (which physicians and pharmacists from countries where this profession is allowed to prescribe) that may have a role in the management of elderly patients with dementia and experiencing BPSD or healthcare professionals specialized in the benefit-risk assessment. The panel size was a convenient sample number that was likely to yield stable results.[21]

An initial sample of 38 features (7 for haloperidol, 10 for olanzapine/risperidone, 11 for quetiapine, and 10 for aripiprazole) were presented to the expert panel so they could rate them in terms of: (a) clinical relevance; (b) accessibility, i.e., how often they have access to the selected PRFs and, if needed, how easy it is to obtain them from elsewhere. Rating scores were given according to a 5-item Likert scale: for clinical relevance assessment – 1=Very important; 2=Important; 3=Equivocal; 4=Less important; 5=Not important; for how often do they have access – 1=Always; 2=Frequently; 3=Sometimes; 4=Rarely; 5=Never; for how easy is to have them available – 1=Very easy; 2=Partially easy; 3=Equivocal; 4=Partially difficult; 5=Difficult). The questionnaires were sent by e-mail and answered using a specific link generated by One Click Survey v. 19.08.91.

CONSENSUS VALIDATION

When judging the clinical relevance, a mean score of 2 was used as the cut-off point to be agreed on and 75% as the consensus cut-off.[22] In round one, scores ≤ 2 with a $\geq 75\%$ consensus were automatically retained as important PRFs to be considered when prescribing APs for older individuals with dementia, whereas all others were included in round two together with new indicators suggested by the participants on the first round.

EXHAUSTIVENESS OF THE PRFs IN MEDICAL RECORDS OF A PORTUGUESE PSYCHIATRIC HOSPITAL

The second part of this study was undertaken at a Portuguese Psychiatry Hospital – Hospital Júlio de Matos, Centro Hospitalar Psiquiátrico de Lisboa – between October and December of 2019. A sample of 100 patients were selected using a systematic method of choosing randomly the first patients of each month hospitalized in the psychogeriatric department between January of 2018 and December of 2019 who met the inclusion criteria (individuals aged 65 or older with dementia diagnosis and prescribed with APs). Data were extracted from medical records, which included

sociodemographic information (age, sex, and education level), anthropometric measures (height, weight, and body mass index), clinical and laboratory data (comorbidities, medications, allergies, EKG, Minimal Mental Status – MMS, glycaemia, glycated hemoglobin – HbA1c, urea, creatinine, aspartate transaminase – AST, alanine aminotransferase – ALT, gamma-glutamyltransferase – gamma-GT, cholesterol, HDL, LDL triglycerides, sodium, potassium, and chloride), and drug- related data (co-medication, antipsychotic used, frequency, route of administration, and safety-related data – previous experience of ADRs).

DATA ANALYSIS

Statistical analysis was performed using IBM SPSSv.26.0. Descriptive statistics were used for sociodemographic characterization of Delphi participants and to access responses obtained as well as to document the exhaustiveness of the PRFs in the medical records. Numerical variables were expressed using central tendency and dispersion measures (either as mean and standard deviations, whichever was applicable), and categorical variables as absolute and relative frequencies.

To assess the exhaustiveness of data entry, a specific classification was used based in a previous study: high (<1% missing values), medium (missing values between 1 and 15%), and low exhaustiveness (>15% missing values).[23] Anthropometric measures, EKG, MMS, and sociodemographic variables were considered present if described in medical records at the time of admission to the psychogeriatric department. For variables such as comorbidities, co-medications, and AP-related data, high-exhaustiveness was considered if those variables were available in the last update of the medical record. Laboratory values and biomarkers assessment (*e.g.*, blood pressure) were searched for a 6-months period prior to the index date (i.e., date of last medical record update during the study period) and were considered to present high-exhaustiveness if they had at least 3 measurements. For indicators that may result in a final score (*e.g.*, cardio and cerebrovascular risk, frailty/risk of falls) were classified based on the exhaustiveness of the individual data needed to calculate them.

RESULTS

CONSENSUS RESULTS

Participants' characteristics

From the initial 126 participants who agree to participate, there were three dropouts from the study and 31 incomplete questionnaires which were excluded. A total of 92 participants were retained, where 53.3% (n=49) were male and 39.1% (n=36) belonged to the age group of 30–39 years old. Almost half of the sample (43.5%; n=40) had a PhD degree and had < 10 years of

working experience (43.4%; n = 40). The majority of participants were either psychiatrists (25.0%; n=23) or internal medicine physicians (25.0; n=23), followed by pharmacists able to prescribe (15.2%; n=14), pharmacologists (10.0%; n=9), gerontologists (9.8%; n=7), general practitioners (6.5%; n=6), epidemiologists (5.4%; n=5), cardiologists (2.2%; n=2), neurologists (2.2%; n=2), and palliative care physicians (1.1%; n=1). **Table 4.2.2** summarizes the sociodemographic characterization of the panel experts.

PRFs selected in the two-round Delphi survey

A total of 61 PRFs (13 for haloperidol, 18 for olanzapine/risperidone, 21 for quetiapine, and 20 for aripiprazole) were presented to the expert panel, where 38 were retrieved from the literature and 23 were suggested by the participants after the first round. In the end of the second round, 47 PRFs were retained, where 12 (25.5%) were selected for haloperidol, 14 (29.8%) for olanzapine/risperidone, 13 (27.7%) for quetiapine, and 8 (17.0%) for aripiprazole.

Age, comorbidities, and co-medications were rated as important features for safe prescribing of antipsychotics in the elderly and were found in all the selected drugs. **Table 4.2.3** summarizes the clinical relevance, availability of specific PRFs in medical records or possibility for obtaining them when not available. All the selected features were either always or frequently available in daily practice and, if not, all of them were easy or partially easy to request.

EXHAUSTIVENESS OF PRFs IN MEDICAL RECORDS

Age, comorbidities, co-medications, and the indication for which the drug was being used presented a high-level exhaustiveness in the medical records independently of the drug used. For haloperidol, electrolyte disturbances and the presence of Parkinson disease were also extensively described in the charts, whereas for olanzapine/risperidone the same result was found for the presence of diabetes. Conversely, hepatic function (haloperidol–22.2%; olanzapine–30.4%; risperidone–17.2%; quetiapine–30.3%), EKG (haloperidol–44.4%; quetiapine–42.4%), cognitive status (haloperidol–66.7%; olanzapine–60.9%; risperidone–41.4%; quetiapine–78.8%), and weight (olanzapine–100.0%; risperidone–100.0%) presented a low-level of exhaustiveness. Renal function (olanzapine–12.5%; risperidone–6.9%) and blood pressure (12.1%) presented a medium-level of exhaustiveness. **Table 4.2.4** summarizes all the results described.

DISCUSSION

Main Results

In this study, we found that 47 of the initial 61 PRFs were retained as relevant in clinical practice to safely prescribe an AP to an older individual with dementia. Of those indicators, most of them

were specific for the selected drugs, and participants reported that all of them were always or frequently available in the medical records. If not available, all of them were easy or partially easy to request. When evaluating their exhaustiveness in the medical records, we found that age, comorbidities, and co-medications were always available, whereas cognitive status or hepatic function presented a low-level of exhaustiveness.

To ensure safe prescribing of APs in the elderly, it is important to consider not only drug-related issues, but also patient-related features. As most other psychotropic drugs, APs are known to have different mechanisms of action, given their binding affinity to specific receptors, which may lead to different ADRs. For instance, haloperidol is known to cause QT-prolongation or parkinsonism, whereas olanzapine and risperidone are known to be associated with metabolic syndrome.[24,25] For this reason, data on EKG, glycemia, cholesterol, and other laboratory values should be available in order not only to monitor patients already instituted therapy, but also to make sure that the AP being prescribed for the first time will not increase the risk of ADRs. We found that EKG was an important feature when prescribing haloperidol or quetiapine, even though a low-level of exhaustiveness was obtained, albeit reported as easy to request. Similar results were found for olanzapine and risperidone when evaluating the presence of hyperglycaemia, hypercholesterolemia, and weight. This indicates that prescribers know what is important to consider when prescribing these drugs, but data may not be fully available given the organization of the healthcare system. In Portugal, data from in- and out-patient settings are not always integrated, which leads to a different level of exhaustiveness when both settings are compared. Most importantly, this gap makes the data available different for each prescriber, i.e., a general practitioner may have different access to a certain type of indicators in comparison with a psychiatrist.

Another indicator rated as important was cognitive status, which was absent in most medical records. It is known that in patients with cognitive impairment, like demented patients, the assessment of cognitive status is important when prescribing APs.[26] These safety issues are crucial when prescribing medications to older adults, especially in patients with psychiatric symptoms where multiple medications may interact with each other, resulting in exacerbation of cognitive impairment.

Even though frailty status, and cardio- and cerebrovascular risk were not available in the medical records, these scores were rated as clinically relevant when prescribing APs to elderly patients with dementia. It is known that these drugs may be associated with an increased risk of cardio- and cerebrovascular events.[4-6] These scores sometimes are not available directly in the medical record of the hospital, but nowadays many online calculators are available. Therefore, if the data needed to calculate the scores is available in the medical records, prescribers may be able to

calculate them and take these risks into account when prescribing, especially atypical APs (e.g., olanzapine, risperidone, and quetiapine). Another important aspect is the fact that some PRFs may be available in the nursing records (e.g., blood pressure, weight), which may be missed if prescribers do not look for it when prescribing atypical APs, where the risk of developing metabolic syndrome is high. So, it is important to acknowledge the contribution of different patient information sources to ensure a safe prescribing of such medications.[27]

Few studies have evaluated the need to validate prescribing quality and safety indicators, i.e., indicators for evaluating the quality of prescribing (e.g., adherence, presence of polypharmacy), and the safety when prescribing to older individuals (e.g., presence of drug-drug interactions, concurrent use of more than one AP). One of the aims of developing a set of such indicators was to prevent/minimize the occurrence of ADRs. However, such indicators are mostly population-oriented, and do not consider the need to look for specific features that may be important when prescribing a specific AP, e.g., relevant for haloperidol, but not so important, for instance, for olanzapine. As some of these elder patients may be on more than one AP, a combination of features may need to be accessed prior to a prescription. Moreover, knowing that this population is highly heterogeneous, there may be some patients where specific features may be more important than in others. For instance, in patients with previous history of cardiac arrhythmias, an EKG for evaluating the QT segment may be needed ahead of the prescription, so that prescribers may select among APs that do not increase the risk of heart block.

To the authors' best knowledge, this is one of the few studies validating patient-related features that may contribute to a safer prescribing pattern of specific APs, like haloperidol, olanzapine, risperidone, quetiapine, and aripiprazole. Current prescribing culture is more focused on effectiveness rather than safety, which in older patients with dementia may increase their odds of experiencing ADRs. Even though prescribers have identified a set of patient-related features with clinical relevance, a low-level of exhaustiveness in our country was found which may be a reality in other countries with a similar healthcare system. This may show the current need not only to integrate the different healthcare software, but also to unify the entire healthcare setting in order to optimize patient medications, especially psychotropic drugs. Future work will include the development of an algorithm to be integrated in a digital tool or app, that may be able to include all these important variables in order to ensure safe prescribing of APs in this population group.

Limitations

Some limitations have been identified and are worth acknowledging. First, selection bias may be present in both samples (expert panel and in-hospital patients). However, we believe that in the sample retrieved from the hospital this bias may be reduced, given that we used a quasi-random methodology and patients were extracted from a specialized hospital in psychiatric illness, which

may contribute to a more homogeneous distribution of patients' characteristics. Secondly, misclassification bias may be present given that most information was retrieved from medical charts of different

physicians. We believe that this bias was minimized given that the authors have coded the variables according to a pre-defined dataset, which may have contributed to a more homogeneous coding system. Finally, this data may not be generalized for a larger population.

Conclusions

To conclude, this study has validated a set of patient-related features, like age, comorbidities, co-medications, renal and hepatic function, and cognitive status as relevant items to consider in daily practice when prescribing specific APs to older individuals with dementia. All of them always or frequently were available in medical records and, when absent, considered easy to request. However, a low-level of exhaustiveness was found in medical records for certain features, such as cognitive status, hepatic function, and weight. Future work will focus on the development of drug-specific algorithms to be included in a digital platform or app to foster safe prescribing of such medications in older individuals with dementia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Egas Moniz (658/2018) and the Ethics Committee of Centro Hospitalar Psiquiátrico de Lisboa (0019/2019). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FAC, HL, and JPA conceived and designed the study. CB, JA, and JGM collected, analysed, and interpreted the data. JPA prepared the manuscript. All the authors have critically reviewed the manuscript until its final version.

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Table 4.2.1 – Drug-specific indicators extracted from the rapid literature review for the APs included in this study

Drug	Indicators specific for each of the selected drugs
Haloperidol	Aged 65 or older Renal function Hepatic function Comorbidities EKG Concomitant medication Electrolyte disturbances (especially with potassium and magnesium)
Olanzapine/Risperidone	Aged 65 or older Renal function Hepatic function Comorbidities EKG Hyperglycaemia/diabetes mellitus BMI > 30 kg/m^2 Hypercholesterolemia High risk for metabolic syndrome High cardiovascular risk
Quetiapine	Aged 65 or older Renal function Hepatic function Comorbidities EKG Blood pressure High cardiovascular risk High risk for metabolic syndrome Hyperglycaemia/diabetes mellitus Hypercholesterolemia
Aripiprazole	Aged 65 or older Renal function Hepatic function EKG Sex Smoking habits High cardiovascular risk Hyperglycaemia/diabetes mellitus BMI > 30 kg/m^2

BMI – Body Mass Index; EKG – electrocardiogram.

Table 4.2.2 – Sociodemographic characteristics of the Delphi survey participants

Sociodemographic characteristics	**N=92**
Sex, n (%)	
Male	49 (53.3)
Female	43 (46.7)
Age, n (%)	
20-29	14 (15.2)
30-39	36 (39.1)
40-49	15 (16.3)
50-59	13 (14.1)
≥ 60	14 (15.2)
Educational degree, n (%)	
Bachelor	15 (16.3)
Master	32 (34.8)
PhD	40 (43.5)
Other	5 (5.4)
Speciality/Area of expertise, n (%)	
Psychiatry	23 (25.0)
Internal Medicine	23 (25.0)
Clinical Pharmacy	14 (15.2)
Pharmacology	9 (10.0)
Gerontology	7 (9.8)
General Practice	6 (6.5)
Public Health	5 (5.4)
Cardiology	2 (2.2)
Neurology	2 (2.2)
Palliative Care	1 (1.1)

Table 4.2.3 – PFRs selected through the Delphi survey for each drug as the most important ones to foster safe prescribing of APs in older individuals

Indicators	Panel survey score (mean±SD)		
	Clinical relevance*	**Accessibility†**	**Availability when asked‡**
Haloperidol			
Age	1.05±0.7	1.25±0.76	1.10±0,39
Hepatic function	2.00±0.9	1.73±0.80	1.81±0.72
Comorbidities	1.50±0.6	1.48±0.59	1.73±0.54
EKG	1.60±0.6	1.94±0.77	2.16±0.76
Electrolyte disturbances	1.90±0.9	1.20±0.86	1.91±0.74
Co-medications	1.30±0.7	1.41±0.81	1.78±0.76
Labelled indication	1.50±0.7	1.27±0.54	1.67±0.87
Frailty/Risk of falls	1.60±0.7	1.77±0.76	1.91±0.85
Previous ADRs	1.40±0.5	1.92±0.78	2.24±1.06
Cognitive status	1.80±0.8	1.66±0.57	1.97±0.78
Benefit-risk ratio assessment	1.30±0.5	1.51±0.64	1.92±0.89
Presence of Parkinson Disease	2.00±0.80	1.89±0.77	1.75±0.74
Olanzapine/Risperidone			
Age	1.03±0.24	1.03±0.24	1.06±0.33
Renal function	1.78±0.58	1.78±0.58	1.63±0.69
Hepatic function	1.90±0.67	1.90±0.97	1.67±0.67
Comorbidities	1.40±0.54	1.40±0.54	1.63±0.51
Co-medications	1.50±0.79	1.50±0.79	1.70±0.51
Hyperglycaemia/diabetes mellitus	1.76±0.55	1.76±0.55	1.59±0.54
Weight	2.16±0.95	2.16±0.95	1.80±0.65
Cardiovascular risk	2.03±0.68	2.03±0.68	1.97±0.72
Labelled indication	1.56±0.87	1.56±0.87	1.58±0.76
Frailty/Risk of falls	1.82±0.91	1.82±0.91	1.84±0.82
Previous ADRs	1.94±0.94	1.94±0.94	2.06±0.77
Cognitive status	1.71±0.80	1.71±0.80	1.63±0.66
Benefit-risk ratio assessment	1.64±0.77	1.64±0.77	1.68±0.77
Cerebrovascular risk	1.93±0.48	1.93±0.88	1.87±0.89
Quetiapine			
Age	1.60±0.80	1.15±0.35	1.06±0.33
Hepatic function	1.90±0.80	1.69±0.68	1.64±0.61

Table 4.2.3 – (Continued)

Comorbidities	1.50±0.60	1.41±0.63	1.49±0.50
EKG	2.00±0.70	2.10±0.74	1.77±0.62
Co-medication	1.40±0.50	1.44±0.70	1.64±0.51
Cardiovascular risk	1.90±0.70	2.20±1.00	1.94±0.68
Blood pressure	2.00±0.80	1.46±0.60	1.25±0.61
Labelled indication	1.50±0.60	1.49±0.61	1.59±0.81
Frailty/Risk of falls	1.60±0.70	1.79±0.75	1.71±0.74
Previous ADRs	1.60±0.80	1.82±0.72	1.92±0.81
Cognitive status	1.70±0.80	1.65±0.61	1.68±0.74
Benefit-risk ratio assessment	1.50±0.70	1.59±0.63	1.67±0.81
Cerebrovascular risk	1.80±0.80	1.89±0.82	1.93±0.92
Aripiprazole			
Age	1.60±0.80	1.12±0.31	1.03±0.24
Comorbidities	1.60±0.80	1.49±0.55	1.66±0.57
Co-medications	1.60±0.70	1.69±0.95	1.69±0.95
Cardiovascular risk	2.00±0.80	2.20±1.00	1.99±0.79
Labelled indication	1.60±0.70	1.77±1.03	1.77±0.98
Benefit-risk ratio assessment	1.50±0.70	1.71±1.01	1.96±0.98
Cerebrovascular risk	1.90±0.70	2.01±0.99	1.82±0.93
Clinical response and tolerability to previous APs	1.60±0.70	2.04±0.99	2.16±0.91

ADRs – Adverse Drug Reactions; APs – Antipsychotics; EKG – Electrocardiogram.

* Feasibility in clinical practice means how often do healthcare professionals, namely prescribers, have access to the selected indicators in their daily practice; Rating scale: 1 – very important; 2 – important; 3 – equivocal; 4 – less important; 5 – not important.

† Rating scale: 1 – always; 2 – frequently; 3 – sometimes; 4 – rarely; 5 – never.

‡ Rating scale: 1 – very easy; 2 – partially easy; 3 – equivocal; 4 – partially difficult; 5 – difficult.

Table 4.2.4 – Exhaustiveness of PQIs selected through the Delphi survey in medical records of older individuals with dementia

Indicators	Exhaustiveness of medical records		
	n	%	Description*
Haloperidol **(n=9)**			
Age	0	0.0	High
Hepatic function	2	22.2	Low
Comorbidities	0	0.0	High
EKG	4	44.4	Low
Electrolyte disturbances	0	0.0	High
Co-medications	0	0.0	High
Labelled indication	0	0.0	High
Frailty/Risk of falls	n/a	n/a	n/a
Previous ADRs	n/a	n/a	n/a
Cognitive status	6	66.7	Low
Benefit-risk ratio assessment	n/a	n/a	n/a
Presence of Parkinson Disease	0	0.0	High
Olanzapine **(n=23)**			
Age	0	0.0	High
Renal function	3	12.5	Medium
Hepatic function	7	30.4	Low
Comorbidities	0	0.0	High
Co-medications	0	0.0	High
Presence of hyperglycaemia	6	26.1	Low
Presence of diabetes mellitus	0	0.0	High
Weight	23	100.0	Low
Cardiovascular risk	n/a	n/a	n/a
Labelled indication	0	0.0	High
Frailty/Risk of falls	n/a	n/a	n/a
Previous ADRs	n/a	n/a	n/a
Cognitive status	14	60.9	Low
Benefit-risk ratio assessment	n/a	n/a	n/a
Cerebrovascular risk	n/a	n/a	n/a
Risperidone **(n=29)**			
Age	0	0.0	High

Table 4.2.4 – (Continued)

Renal function	2	6.9	Medium
Hepatic function	5	17.2	Low
Comorbidities	0	0.0	High
Co-medications	0	0.0	High
Presence of hyperglycaemia	3	10.3	Medium
Presence of diabetes mellitus	0	0.0	High
Weight	29	100.0	Low
Cardiovascular risk	n/a	n/a	n/a
Labelled indication	0	0.0	High
Frailty/Risk of falls	n/a	n/a	n/a
Previous ADRs	n/a	n/a	n/a
Cognitive status	12	41.4	Low
Benefit-risk ratio assessment	n/a	n/a	n/a
Cerebrovascular risk	n/a	n/a	n/a
***Quetiapine* (n=33)**			
Age	0	0.0	High
Hepatic function	10	30.3	Low
Comorbidities	0	0.0	High
EKG	14	42.4	Low
Co-medication	0	0.0	High
Cardiovascular risk	n/a	n/a	n/a
Blood pressure	4	12.1	Medium
Labelled indication	0	0.0	High
Frailty/Risk of falls	n/a	n/a	n/a
Previous ADRs	n/a	n/a	n/a
Cognitive status	26	78.8	Low
Benefit-risk ratio assessment	n/a	n/a	n/a
Cerebrovascular risk	n/a	n/a	n/a
***Aripiprazole* (n=6)**			
Age	0	0.0	High
Comorbidities	0	0.0	High
Co-medications	0	0.0	High
Cardiovascular risk	n/a	n/a	n/a
Labelled indication	0	0.0	High

Table 4.2.4 – (Continued)

Benefit-risk ratio assessment	n/a	n/a	n/a
Cerebrovascular risk	n/a	n/a	n/a
Clinical response and tolerability to previous APs	n/a	n/a	n/a

EKG – electrocardiogram; n/a – not available

* High exhaustiveness: <1% missing values; medium exhaustiveness: between 1 and 15%; low exhaustiveness: >15% missing values.

CHAPTER 5

General Discussion

SCOPE OF THESIS

Potentially Inappropriate Medications (PIMs) are nowadays a reality in the elderly and an important challenge for healthcare professionals when managing their therapeutic regimen. They are defined as medications where the risk of possible adverse drug reactions (ADRs) outweighs the clinical benefit of its use.[1-5] Therefore, efforts to prevent or deprescribe such medications in clinical practice are needed to avoid the occurrence of adverse events, such as Major Adverse Cardio and Cerebrovascular Events (MACCE).

MAIN FINDINGS

PIMs WITH MACCE RISK – WHICH MEDICATIONS SHOULD WE BE AWARE?

During the last decades, several PIM-lists have been published, describing extensive tables of medications that should be avoided in older individuals. In a sample of 24 PIM-lists, we found that 15.3% of the PIMs reported in those lists had the potential to cause cardio and cerebrovascular adverse events, and nearly half of them were associated with MACCE. The most frequently described PIMs with MACCE risk were NSAIDs, antiarrhythmics (Class I and III), selective calcium channel blockers with vascular effects, and antipsychotics (**Chapter 2.1 – Systematic review**). When looking at their prevalence of use in the ambulatory setting and in LTCFs, we found that nearly 40.0% of the sample was using such medications (51.8% in LTCFs and 35.5% in ambulatory care). From those, 30.0% of patients had previous history of cardiovascular diseases (CVD). Non-steroidal anti-inflammatory drugs (NSAIDs) and antipsychotics (APs) werethe most prevalent drug classes found in this sample (**Chapter 2.2 – Prevalence study**).

Considering the vast body of research around NSAIDs and knowing that APs are widely used in older individuals to manage behavioural and psychiatric symptoms in dementia (BPSD) and that they should be avoided in this specific population, this drug class was chosen to be used as a case-study. We found that more than half (53.4%) of patients from the ambulatory setting and LTCFs were using APs, and when restricting the analysis to LTCFs, the prevalence identified was 88%. We also found that the type of AP (typical vs. atypical APs) used in both setting was slightly different. In long-term care facilities we found that patients were using mainly typical APs, whereas in ambulatory setting atypical ones were more commonly found (**Chapter 2.2 – Prevalence study**). Since they were described in the PIM-lists as medications associated with increased risk of stroke, we evaluated the potential association between the different receptor binding affinity and metabolic side effects profile and the reporting of MACCE. We found that APs with high affinity for adrenergic alfa-1 (ROR adj. 2.98; 95%CI 1.93-4.59), histaminic H_1 (ROR adj. 2.31; 95%CI 1.98-2.68), muscarinic M_1 (ROR adj. 1.87; 95%CI 1.74-2.01), and serotoninergic 5-HT_{2A} (ROR adj. 3.19; 95%CI 2.07-4.92) were associated with a higher risk of

reporting of MACCE compared to low affinity. APs with higher risk of metabolic side effects profile (ROR adj. 1.88; 95%CI 1.73-2.05) were associated with higher reporting of MACCE compared with those with a lower risk of metabolic side effects (**Chapter 3.1 – VigiBase study**).

PIMs WITH MACCE RISK – HOW CAN WE BUILD THE BRIDGE FROM A POPULATION PERSPECTIVE TO A PATIENT-CENTRED APPROACH?

To design a future successful intervention, it is important to consider different factors before the implementation phase. Therefore, we evaluated two factors: a) education and practice of different HCPs; and b) patient-related features that should be used to foster safe prescribing in a specific individual of advanced age. We found that perceived knowledge of HCPs does not correlate well with their real knowledge. In both these domains, there were no significant differences between the different HCPs' ability to manage therapeutic complexities in the elderly. All HCPs in general familiar with ADRs associated with commonly used medications in the elderly, like NSAIDs and benzodiazepines. Most respondents agreed that limited time, insufficient education and training on geriatrics, and scarce tools adapted to daily practice were the main barriers identified in their daily practice (**Chapter 4.1 – HCPs' knowledge and barriers study**).

As shown in **Chapter 2.2 – Prevalence study**, APs were widely used in elderly with dementia and described as PIMs with increased risk of stroke in **Chapter 2.1 – Systematic review**. In **Chapter 4.2 – PRFs study**, we focused on specific APs (*e.g.,* haloperidol, olanzapine/risperidone, quetiapine, and aripiprazole) and consensus was reached for 47 patient-related features that may be used to foster safe prescribing of these medications (12 were applicable to haloperidol, 14 to olanzapine/risperidone, 13 to quetiapine, and 8 to aripiprazole). All the patient-related features were rated by experts as always or frequently available and, if not, they were easy or partially easy to obtain. However, some of those features were frequently missing from the electronic medical records (*e.g.*, cognitive status or hepatic function).

NEW INSIGHTS INTO INAPPROPRIATE PRESCRIBING – WHAT HAVE WE LEARNED?

Inappropriate prescribing is common among the elderly and is associated with an increased risk of ADRs.[6] Potentially inappropriate prescribing has been associated with adverse events, hospitalizations, morbidity and mortality, increased costs in the healthcare system.[7,8] A recent systematic review has shown a significant association between ADRs and PIMs (OR 1.44; 95%CI 1.33-1.56), being this association stronger when considering the use of STOPP criteria to define PIMs (OR 1.66; 95%CI 1.34-1.56). The authors have also performed a subgroup analysis by continent, which showed that the risk of ADRs resulting from PIMs was more evident in European elderly individuals than in American elderly individuals (OR 1.88; 95%CI 1.54-2.29 vs OR1.47;

95%CI 1.35-1.60, respectively). They also found that patients taking more than two PIMs were at higher risk of ADRs. Conversely, the authors have found no statistically significant association between mortality and PIMs (OR 1.04; 95%CI 0.75-1.45).[7] Several tools have been developed, since the 90s, in different countries and they show major differences in terms of structure and content. These tools present an extensive list of medications that should be avoided in the elderly and are normally organized by the organ system where the drug acts, regardless of the ADR that they may cause.[9-37] To authors' best knowledge there is no PIM-list focusing on medications with risk of cardiac and cerebrovascular adverse events, which made our work pioneer in this setting.[38] We have compiled an extensive list of medications with risk of MACCE and CCVAEs and assessed the number of times each medication was reported in the tools. Even though these lists can be useful to alert healthcare professionals during medication review, they also lack some important new pharmacovigilance signals arising as important safety concerns for the elderly (*e.g.*, the example of new oral anticoagulants and the risk of cerebrovascular bleeding). This was also discussed in a recently published paper of our research team on the utility and limitations of STOPP criteria for psychiatric older patients.[39] Despite the drug market differences, these lists also do not reflect the individual features of patients and are based on a population-based approach, disregarding that the individual risk may be different between patients.

The most prescribed PIMs were drugs that may exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatremia (27.3%), NSAIDs use in patients under anticoagulants (21.2%), use of PIPs for more than 8 weeks (10.5%), and benzodiazepines (5.7%).[40] Another study, using the same criteria, conducted in Pakistan has found that 67.4% of elderly cardiac patients were exposed to at least one PIM, being the most prescribed hydrochlorothiazide (21.5%), furosemide (17.1%), omeprazole (13.7%), and orphenadrine (6.7%).[41] Even though our results do not tackle PIMs in general, but PIMs with cardiac and cerebrovascular risk, our prevalence of PIMs use in patients with previous history of cardiovascular diseases is slightly lower (reaching almost 50.0%). Differences were found when comparing patients from long-term care facilities with patients from the ambulatory setting, which was also shown in the literature.[42,43] Since there were no previous studies on the prevalence of use of such PIMs associated with specific adverse events (minor and major ones), this study was also pioneer in this context.[44] It also provided an in-depth analysis of the prevalence of use of such medications among patients with previous history of cardiac and cerebrovascular diseases (which may exacerbate those previous conditions), but also their prevalence among patients with dementia. APs have been one of the groups where we have focused our attention since they can have a negative impact on demented patients by deteriorating their cognitive function, but also because of their cardiac and cerebrovascular risk of adverse events. Most of these events are not clearly understood since they are a result of multifactorial events. Studies have shown that APs-

related cardiac and cerebrovascular adverse events may be the result of complex interactions between patients-related features, such as previous comorbidities, age, sex, with drug-related features, which may include the risk of metabolic syndrome (especially common among atypical APs), QT prolongation, or haemorrhagic events associated with serotoninergic receptors' binding affinity.[45-49] Our results have shown that either high affinity for specific receptors (e.g., adrenergic, histaminic, serotoninergic, or muscarinic receptors), or their increased risk of metabolic side effects can be possible explanations of the occurrence of MACCE. However, additional observational prospective studies should be conducted to confirm these findings.[50]

As previously mentioned, PIM-lists are a useful way to alert healthcare professionals for potentially harmful drugs that may cause adverse events or ADRs in the elderly population. Since these lists are normally population-based and require no or little clinical judgment there is the need to adapt them for a more patient-centred approach. Moreover, these tools are normally presented to healthcare professionals as extensive lists of medications with different drugs depending on the country where they were developed, which may be a barrier in practice for the implementation of interventions that aim at deprescribing such medications. This hypothesis was supported by results presented in **Chapter 4.1 – HCPs' knowledge and barriers study**, where most HCPs agreed that there were scarce clinical tools adjusted to clinical practice. It also seems that most of the healthcare professionals do not use the current tools, and tend to more frequently base their decisions on online tools, such as Up-to-date, Medscape, Dynamed, and BMJ-Best Practice as described in previous studies.[51-54] An interesting result from this chapter was the weak correlation found between perceived and real knowledge, which may suggest that practice-based methods of evaluation should be favoured in clinical teaching, moving from knowledge-acquisition to competence-demonstration, as suggested by Miller.[55]

With the intent of going from a population-based to a patient-centred approach on the field of APs as PIMs in the elderly with dementia, we carried out a mixed method approach to deliver a possible set of patient-related features that could be used in clinical practice to foster safe prescribing of these medications (**Chapter 4.2 – PRFs study**). The relevance of this study for the actual knowledge is that few studies have evaluated the need to validate quality and safety prescribing indicators, i.e., indicators for evaluating the quality of prescribing (*e.g.*, presence of polypharmacy), and the safety when prescribing to older individuals (e.g., presence of drug-drug interactions, concurrent use of more than one AP).[56-60] Therefore, some of the indicators that are normally available in the literature are mostly population-oriented and do not consider the need to look at specific features that may be important when prescribing a specific AP, e.g., relevant for haloperidol, but not so important, for instance, for olanzapine. With these set of patient-related features we may be able to tackle in which patient the drug can really be considered potentially inappropriate and use a risk stratification tool to decide which elder patients with dementia are

really at higher risk of ADRs, especially cardiac and cerebrovascular ones. Also, with the results from **Chapter 4.1 – HCPs' knowledge and barriers**, we believe that more user-friendly digital tools adapted to a more patient-centred approach could lead to safer prescribing practices, particularly in elderly patients. A worrisome finding retrieved from **Chapter 4.2 – PRFs study** was the low-level of exhaustiveness found in the medical records concerning basic patient-related features that should be considered when prescribing a specific AP. This may show the need to integrate different healthcare data to accomplish a more complete patient profile concerning not only specific patient-related, but also drug-related features (including medication adherence and previous ADRs, which are most of the times missed).

METHODOLOGICAL ISSUES IN OBSERVATIONAL STUDIES

All studies conducted were based in real-word data, using electronic healthcare databases, or healthcare records from different settings (e.g., ambulatory setting, hospital-based, and long-term care facilities).

During this project, we have used three types of data: primary data (**Chapter 2.1 – Systematic review, Chapter 2.2 – Prevalence study, Chapter 4.1 – HCPs' knowledge and barriers study, and Chapter 4.2 – PRFs study**), secondary data (**Chapter 2.2 – Prevalence study**) and electronic healthcare data (**Chapter 3.1 – VigiBase study**).

Primary data has the advantage to specifically answer the research question addressed in the study but may require more time and resources for data collection. On the other hand, secondary data may require less human or finances resources but are more prone to some bias (e.g., misclassification bias) and data is not collected primarily to answer the research question. Finally, electronic healthcare data may have the advantage of being integrated with other databases that may be beneficial for extracting complementary data and the large amount of data that can be extracted, ensuring a good external validity. However, a quality data analysis should be performed to ensure the exhaustiveness of the variables of interest and these data may be more prone to confounding and bias that may affect the internal validity of studies.

For the studies described in **Chapters 2.1 – Systematic review, 4.1 – HCPs' knowledge and barriers study and 4.2 – PRFs study**, primary data were collected. In **Chapter 2.1**, data was collected from different search databases (e.g., PubMed, Ovid® – Medline, Google Scholar) and in **Chapter 2.2 – Prevalence study, 4.1 – HCPs' knowledge and barriers study and 4.2 – PRFs study** data were collected from dispensing records of a community pharmacy, from healthcare professionals using questionnaires and from the medical charts of a psychiatric hospital, respectively.

For the study described in **Chapter 2.2 – Prevalence study**, secondary data were collected from previous databases specifically designed during previous studies of our research team, using data from long-term care facilities.

For the study described in **Chapter 3.1 – VigiBase study**, we used VigiBase, a spontaneous report database for ADRs globally. This database contains individual case safety reports (ICSR) of ADRs from pharmacovigilance centres of more than 150 member countries of the WHO Program for the International Drug Monitoring representing more than 90% of the global population.[61]

Despite all the advantages shown above, several limitations in performing observational studies should be considered to access the internal and external validity of the findings. One of the most important aspects that should be highlighted is the information bias due to misclassification bias. In **Chapter 2.2 – Prevalence study**., since data from ambulatory was extracted from dispensing records of community pharmacy, our ability to extract accurate information on patients' comorbidities was limited. Therefore, data on the number of comorbidities, previous history of cardiovascular diseases, and the presence of dementia were solely based on the pharmacotherapeutic regimens of each patient. Another issue, in **Chapter 2.2 – Prevalence study and 4.2 – PRFs study**, was the inability to access drug use (medication adherence). Drugs were prescribed (**Chapter 4.2 – PRFs study**) and dispensed (**Chapter 2.2 – Prevalence study**), but there was no guarantee that the drug was being used by the patients. Also, there were some missing data on the frequency of drug exposure, which did not allow the difference between as needed or for regular use. Information bias was also important in **Chapter 3.1 – VigiBase study.**Since we were using spontaneous reporting, some data (e.g., different indications, doses, and durations of treatment) were missed, because they are not mandatory when reporting an ADR, which may influence the reporting of the outcome.

The second potential problem is selection bias. In **Chapter 2.1 – Systematic review**, this bias may have occurred since we have only included lists that were published in English. So, all other lists in different languages were missed. In **Chapter 3.1 – VigiBase study**, the different APs were introduced in the market in different time points depending on the country, which may have introduced selection bias. Also, since the age of the person experiencing the ADR was not available, it was not possible to assess the relative contribution of the paediatric population to the association between the reporting of the outcome and the exposure. In **Chapter 4.1 – HCPs' knowledge and barriers study**, self-selection bias was present since the questionnaire was available in social media and, therefore, the HCPs that had a differentiated knowledge or worked in the geriatric field would be more participative. Finally, in **Chapter 4.2 – PRFs study**, selection bias was also present, either in the expert panel or in the in-hospital patients.

The third potential problem is confounding. This was especially important in **Chapter 3.1**, where the lack of information on potential confounders, such as comorbidities and lifestyle variables, may impact the reporting of the outcome.

To minimize the influence of bias, several strategies were used. Information bias due to misclassification bias was minimized in different studies using either universal coding systems (*e.g.*, ATC Coding System, ICD-10) and the help of a clinician who independently revised all medical charts (**Chapter 2.2 – Prevalence study and Chapter 4.2 – PRFs study**) to ensure that information extracted was homogeneous. We have also used a quasi-random extraction of in-hospital patients, in **Chapter 4.2 – PRFs study**, which may also help to reduce the selection bias. Finally, in **Chapter 3.1 – VigiBase**, matching, multivariable adjustment, stratification, restriction, or using an active comparator design were applied to reduce confounding and bias.

Finally, chance finding because of small sample sizes were often a limitation, which may reduce the power to detect small significant associations (**Chapter 2.2 – Prevalence study, Chapter 4.1 – HCPs' knowledge and barriers study, and Chapter 4.2 – PRFs study**).

POTENTIAL CLINICAL IMPLICATIONS, CONCLUSIONS AND FUTURE STUDIES

Current prescribing culture is more focused on effectiveness rather than on safety, which in older patients may increase their odds of experiencing ADRs. We believe that the tools available nowadays are valuable instruments to alert HCPs about the presence of PIMs and the potential need to deprescribe them. However, it also seems that they should be revised in terms of their structure, be continuously updated to include new safety signals that are sometimes missed and perhaps above all, refine their specificity by focusing on identifying relevant and likely to happen negative outcomes. It also seems that HCPs prefer more digital solutions that may help them to overcome the limited time of appointments. Another important issue found in this project is the need to move from a population-based to a more patient-centred approach. The tools available nowadays present more information and are starting to move to a more patient-centred approach, compared to the ones initially developed. For example, the last updates of Beers criteria started to include lists of medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults.[30,62] However, most of the drugs themselves constitute a PIM if they are present in the pharmacotherapeutic regimen of the patient, regardless of patients' features. This may show the need to adapt these tools to a more risk stratification measure, where different patients will have different risks in terms of developing cardiac and cerebrovascular adverse events.

A current review of the trends and concerns of PIM use in patients with cardiovascular diseases have highlighted that deprescribing, implementation of systematic electronic records, pharmacist-led medication review, and collaboration among cardiologists, internists, geriatricians, clinical pharmacologists, pharmacists, and other HCPs are the basis of multidisciplinary assessment teams to ensure safe prescribing among these patients.[63]

In the beginning of this project, our intention was to move to a more patient-centred approach and include the digital world in such a transition. These digital solutions can be great options either for HCPs or for their patients/carers. For HCPs, digitalisation may be a way to overcome the limitations presented in **Chapter 4.1 – HCPs' knowledge and barriers study**, such as limited time, scarce adapted tools, and for patients or their carers, digitalisation seems to favour empowerment and enhance involvement in shared decision making. Mobile health (mHealth) has become a fast-growing assistive technology in the treatment of people with chronic diseases, providing plain and efficient healthcare solutions to people and healthcare professionals.[64,65] So, new interventions targeted either at deprescribing PIMs with cardiac and cerebrovascular risk of adverse events or to foster safe prescribing of specific medication, like APs, may need not only to include the correct data inserted in the software, but also quality health education should be considered for both type of users: HCPs and patients/carers. Before translating all this knowledge into practice, we need to reflect on how we can include this CDSS into the software that are already used in practice, instead of creating new ones or online versions. We also need to reflect on how we can manage confidentiality issues regarding patient and HCPs' data. This work had viewed the safety problems from HCPs or system's views and, for a short-term perspective, the inclusion of this data as a CDSS directed to detect patients that may be at high-risk of experiencing specific ADRs (e.g., MACCE) would be of great value. Moreover, as a long-term perspective, we should also address the safety problems from the patient's view. Here we should reflect on how we could empower patients to have a more active role in the medication cycle and the extent to which mHealth could be a good option to serve as an additional source of information to tackle safety issues after drug exposure.

To begin this translation of knowledge from the previous study to a more digital perspective, we conducted a pilot study that aimed to identify a set of features for digital tools that should be considered when developing a new app to help carers of patients living with dementia in daily disease management. Using a mixed-methods approach, a systematic overview of the literature was undertaken to evaluate how many apps are currently available for patients living with dementia and for their carers and which features they contained. After that, we conducted semi-structured interviews with three carers to explore their difficulties and discuss the extent to which digital solutions can overcome them; finally, we conducted a nominal group technique to explore the needs perceived by the HCPs on the characteristics considered more relevant to be included

in a mobile app. We observed that most of the tools described in the literature were not available in practice and most of the features integrated in those tools included educational contents and socialization support. Features related to medication management were scarce among the tools identified and included medication alarms. Most of the difficulties perceived by caregivers were related to the management of the disease and some of the participants did not know that digital tools were already available. HCPs recommended that easy-to-use and more tailored tools with specific features, especially in terms of medication management, may be useful to help either people living with dementia or caregivers.[66]

In conclusion, all the knowledge built in this work should be integrated and included in a future digital tool to which all involved stakeholders actively contribute, and which must be adapted to the Portuguese healthcare system, be interoperable across the multiple systems along the patient pathway, to support HCPs in increasing patient safety (**Figure 5.1**).

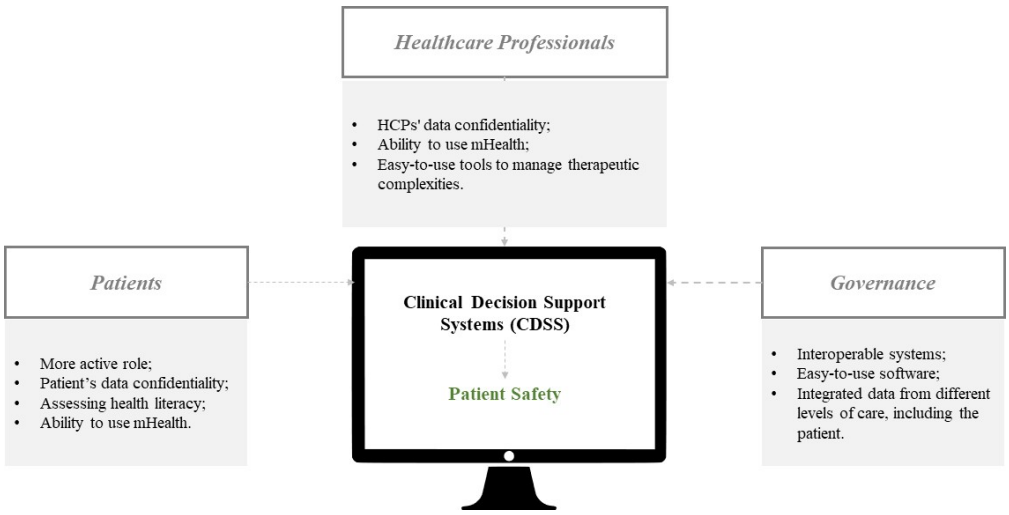

Figure 5.1 – Conceptual framework for future research

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APPENDICES

APPENDIX 1

Publications and Scientific Communications

PUBLICATIONS RELATED TO THIS THESIS

Aguiar JP, Gama Marques J, Alves da Costa F. Utility and limitations of a screening tool of older person's prescription among psychiatric elder patients: A comprehensive review. Aging and Health Research. 2021.

doi: https://doi.org/10.1016/j.ahr.2021.100031.

Aguiar JP, Bernardo C, Gama Marques J, Leufkens HGM, Alves da Costa F. Identification of a set of patient-related features to foster a safe prescribing of antipsychotics in the elderly with dementia. Frontiers in Psychiatry. 2020. 11:604201.

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Aguiar JP, Gama Marques J, Leufkens HGM, Alves da Costa F. Physicians, pharmacists, and nurses are equally able to handle medication complexities in the elderly. Frontiers in Psychiatry. 2022. Submitted and under review.

Aguiar JP, Alves da Costa F, Egberts T, Leufkens HGM, Souverein P. The association between receptor binding affinity and metabolic side effects profile of antipsychotics and major cardio- and cerebrovascular events: a case/non-case study using VigiBase. European Neuropsychopharmacology. 2020. 35:30-38.

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Aguiar JP, Heitor Costa L, Alves da Costa F, Leufkens HGM, Martins AP. Identification of potentially inappropriate medications with risk of major adverse cardiac and cerebrovascular events among elderly patients in ambulatory setting and long-term care facilities. Clinical Interventions in Aging. 2019. 14: 535-547.

doi: https://doi.org/10.2147/CIA.S192252

Aguiar JP, Brito AM, Martins AP, Leufkens HGM, Alves da Costa F. Potentially inappropriate medications with risk of cardiovascular adverse events in the elderly: a systematic review of tools addressing inappropriate prescribing. Journal of Clinical Pharmacy and Therapeutics. 2019. 44: 349-360.

doi: https://doi.org/10.1111/jcpt.12811

PUBLICATIONS UNRELATED TO THIS THESIS

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Alves da Costa F, Vaz J. Estarão os Doentes com Fibrilhação Auricular Correctamente Anticoagulados? Um Retrato de um Hospital Português do Interior. Revista Portuguesa de Medicina Interna. 2021. 28(4): 344-9.

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Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Alves da Costa F, Vaz J. Fast-track management of acute chest pain: experience gained in Beja Hospital. Revista de Medicina Interna. 2021.28(3): 224-229.

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Aguiar JP, Ribeiro M, Pedro AR, Martins AP, Alves da Costa F. Awareness about barriers to medication adherence in cardiovascular patients and strategies used in clinical practice by Portuguese clinicians: a nationwide study. International Journal of Clinical Pharmacy. 2021. 43(3): 629-636.

doi: https://doi.org/10.1007/s11096-020-01174-2

Aguiar JP, Cardoso Borges F, Murteira R, Ramos C, Gouveia E, Passos MJ, Miranda A, Alves da Costa F. Using a cancer registry to capture signals of adverse events following immune and target therapy for melanoma. International Journal of Clinical Pharmacy. 2018. 40: 852-861.

doi: https://doi.org/10.1007/s11096-018-0665-1

ORAL COMMUNICATIONS

Aguiar JP, Franco M, Gama Marques J, Alves da Costa F. Healthcare professionals' views about potentially inappropriate medications: from knowledge to practice. Presented at 7th PCNE Working Symposium 2020. Egmond aan Zee, the Netherlands. 2020. Published in International Journal of Clinical Pharmacy.

doi: https://doi.org/10.1007/s11096-020-01009-0

Bernardo C, **Aguiar JP**, Alves da Costa F. Management of clinically relevant drug-drug interactions with antipsychotics in nursing homes. Presented at 4th International Congress of CiiEM: Health, well-being, and ageing in the XXI century. Caparica, Portugal. 2019.

Bernardo C, **Aguiar JP**, Alves da Costa F. The role of the pharmacist in optimizing antipsychotic use among elderly patients with dementia in nursing homes: is there enough exhaustiveness in medical records? Presented at 48th European Symposium on Clinical Pharmacy, Ljubljana, Slovenia. 2019. Published in International Journal of Clinical Pharmacy.

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Aguiar JP, Alves da Costa F, Leufkens H, Martins AP. Potentially Inappropriate Medications with risk of Major Adverse Cardiac and Cerebrovascular Events. Presented at 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences. Scottish Event Campus (SEC), Glasgow, United Kingdom. 2018.

Aguiar JP, Brito AM, Alves da Costa F, Leufkens H, Martins AP. Cardiac and Cerebrovascular risk of Major Adverse Events (MACCE) following exposure to Potentially Inappropriate Medications (PIMs). Presented at 1st International Conference – FIP Pharmacy Practice Research: postgraduate students, postdoctoral fellows, and supervisors. Lisboa, Portugal. 2018.

Aguiar JP, Alves da Costa F, Leufkens HGM, Martins AP. Patient Safety: Risk of Major Adverse Cardio and Cerebrovascular Events following exposure to Potentially Inappropriate Medications. Presented at 9th iMED.ULisboa Postgraduate Students' Meeting and 2nd i3DU Meeting. Lisbon, Portugal. 2017.

Aguiar JP, Alves da Costa F, Leufkens HGM, Martins AP. Development of a Core Set of Potentially Inappropriate Medications associated with Major Adverse Cardio andCerebrovascular Events. Presented at Translational Research and Innovation in Human and Health Sciences: 2nd International Congress of CiiEM. Caparica, Portugal. 2017. Published in Annals of Medicine.

doi: https://doi.org/10.1080/07853890.2018.1427460

POSTER PRESENTATIONS RELATED TO THIS THESIS

Bernardo C, **Aguiar JP**, Alves da Costa F. Clinically relevant interactions with antipsychotics in nursing homes. Presented at 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences. Abu Dhabi, United Arab Emirates. 2019

Aguiar JP, Alves da Costa F, Martins AP, Egberts T, Leufkens HGM, Souverein P. The association between receptor binding affinity and metabolic side effects profile of antipsychotics and major adverse cardiac and cerebrovascular events: a case/non-case study in VigiBase. Presented at 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE). Philadelphia, US. 2019.

Aguiar JP, Alves da Costa F, Martins AP, Egberts T, Leufkens HGM, Souverein P. Antipsychotic use and Major Adverse Cardiovascular Events: a case/non-case study in VigiBase. Presented at ISPE's 2019: Mid-Year Meeting. Rome, Italy. 2019.

Bernardo C, **Aguiar JP**, Alves da Costa F. Antipsychotic drug consumption in Portugal: a nationwide trend from 2008 to 2017. Presented at 11th PCNE Working Conference 2019 – Targeting patients and tailoring Pharmaceutical Care: how to be outstanding? Egmond aan Zee, the Netherlands. 2019. Published in International Journal of Clinical Pharmacy.

doi: https://doi.org/10.1007/s11096-019-00805-7

Bernardo C, **Aguiar JP**, Costa AM, Alves da Costa F. Optimizing antipsychotic medicines use among the elderly: preliminary results of the potential use of web-based tools for cardiovascular safety. Presented at 11th PCNE Working Conference 2019 – Targeting patients and tailoring Pharmaceutical Care: how to be outstanding? Egmond aan Zee, the Netherlands. 2019. Published in International Journal of Clinical Pharmacy.

doi: https://doi.org/10.1007/s11096-019-00805-7

Aguiar JP, Alves da Costa, Leufkens HGM, Martins AP. Prevalence of potentially inappropriate medications with risk of cardiovascular events in the elderly. Presented at XIII Congresso da Associação Portuguesa de Epidemiologia e XXXVI Reunión Científica de la SEE. Lisboa, Portugal. 2018.

Aguiar JP, Brito AM, Alves da Costa F, Leufkens HGM, Martins AP. A systematic overview of Potentially Inappropriate Medications (PIMs) with risk of Major Adverse Cardio and Cerebrovascular Events (MACCE). Presented at 6th PCNE Working Symposium 2018. Malaga, Spain. 2018. Published in International Journal of Clinical Pharmacy.

doi: https://doi.org/10.13140/RG.2.2.35311.94884

Aguiar JP, Aves da Costa F, Leufkens HGM, Martins AP. How to define a Potentially Inappropriate Medication (PIM)? Antipsychotics as a case-study. Presented at 6th PCNE Working Symposium 2018. Malaga, Spain. 2018. Published in International Journal of Clinical Pharmacy.

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POSTER PRESENTATIONS UNRELATED TO THIS THESIS

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Vaz J. The association between HbA1c and the presence of metabolic complications in diabetic patients: a study in a Portuguese hospital. Presented at 18th European Congress of Internal Medicine. Lisboa, Portugal. 2019.

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Vaz J. "Via Verde Coronária" – a fast approach protocol for chest pain patients: what have we learned in the last 6 months? Presented at 18th European Congress of Internal Medicine. Lisboa, Portugal. 2019.

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Vaz J. Severity of diabetic ketoacidosis in patients admitted in the emergency department of a Portuguese hospital: a cross-sectional study. Presented at 18th European Congress of Internal Medicine. Lisboa, Portugal. 2019.

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Vaz J. Oral anticoagulation on patients with atrial fibrillation: are we doing a good job? Presented at 4th International Congress of CiiEM: Health, well-being, and ageing in the XXI century. Caparica, Portugal. 2019.

Lima JCF, **Aguiar JP**, Paixão Ferreira M, Calixto R, Cesário V, Vaz J. Identification of Potentially Inappropriate Medications with risk of Major Adverse Cardio- and Cerebrovascular Events among elderly patients. Presented at 4th International Congress of CiiEM: Health, well-being, and ageing in the XXI century. Caparica, Portugal. 2019.