Universidade de Lisboa

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A cross-sectional study in Slovenia

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Trabalho de Campo orientado pelo Professor Doutor Afonso Miguel das Neves Cavaco, Professor Associado e coorientado pelo Mestre João Rafael Vicente Gonçalves.

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Introdução: O envelhecimento demográfico da população que se espera na europa deve-se ao aumento da esperança de vida, com a diminuição da taxa de fertilidade. Em 2018, 19,41% da população eslovena tinha mais que 65 anos, mas espera-se que esta percentagem atinja os 30,6% em 2050. Uma forma de travar o aumento das despesas públicas é otimizar a utilização de recursos e aumentar a saúde dos cidadãos de maneira que tenham menos morbilidade e assim dependam menos do sistema de saúde. Os padrões de prescrição em idosos tornam-se críticos para a determinação de uma terapêutica eficaz e otimizada, com diminuição da complexidade da terapêutica para o utente idoso, melhores resultados de saúde pública e menos gastos para o sistema financiador. Neste estudo, foram analisados os padrões de prescrição potencialmente inapropriada em utentes idosos e de que forma as caraterísticas demográficas dos prescritores (género, idade e estatuto) influenciam estes padrões. Métodos: Uma base de dados eslovena com todas as prescrições realizadas em 2018 à população maior ou igual a 65 anos, com informação relativa à substância prescrita e com caraterísticas demográficas do utente e do médico prescritor, foi disponibilizada para este estudo. O software informático SPSS IBM Statistics foi utilizado como ferramenta de análise da estatística descritiva, de comparação de médias através do Teste-T independente e de cálculo de frequências sobre o conteúdo da base de dados. As substâncias ativas foram definidas como potencialmente inapropriadas através do Critério de Beers de 2019 e da lista europeia designada por EU(7)PIM list. Discussão: Prescritores com idade maior ou igual a 65 anos, desempregados e mulheres foram os que mais prescreveram medicamentos potencialmente inapropriados. As prevalências de prescrição da maioria dos grupos químicos sofreram influencia do género, idade e/ou estatuto. Conclusão: Há necessidade de incluir idosos em ensaios clínicos de modo a ter mais evidências sobre que medicações são inapropriadas, e de estabelecimento de guidelines terapêuticas em utentes com diversas doenças de forma a evitar a polimedicação e a otimizar recursos.

Doutor Afonso Cavaco, Professor Associado

João Gonçalves, Mestre

Palavras-chave: Medicamentos Potencialmente Inapropriados; Médicos; idade; género; Eslovénia;

Abstract

Introduction: The population demographic ageing that is expected in Europe is due to the increase of life expectancy, combined with the decrease of fertility rates. In 2018, 19,41% of the Slovenian population was over 65 years old, but this share is expected to increase to 30,6% in 2050. One way to prevent the increasing of public investments is to optimize resources and to increase the health of citizens so they have lower morbidity and thus, that they rely less on the public system. The patterns of prescription among the elderly are critical to determine an efficient and optimized therapy, decreasing the complexity of the treatment to the older patient, to obtain better results of public health and lower costs for the financing system. In this study, the patterns of potentially inappropriate prescriptions were analyzed among older adults and in each way the demographic characteristics of physicians (gender and age) influence those patterns. Methods: A Slovenian database with every prescriptions to population equal or older than 65 years old from 2018, with information regarding the chemical substance prescribed and the patients' and physicians' demographic characteristics, was provided for this study. The SPSS IBM statistics software was used as a tool of statistical analysis and mean comparison through the independent t-test over the content of the database. Results were obtained. The chemical substances were defined as potential inappropriate based on AGS Beers Criteria 2019 and the European list named as EU(7) PIM list. Discussion: Female physicians equal or above 65 years old, were the ones who prescribed more potentially inappropriate medications. Most of the chemical groups prevalence of prescription were influenced by age and gender. Conclusion: There is the need to include older adults in clinical trials to have more evidence of the medication that are inappropriate for them, and the need to establish therapy guidelines for patients with multimorbidity so the polypharmacy can be prevented and the resources optimized.

Doutor Afonso Cavaco, Professor Associado

João Gonçalves, Mestre

Keywords: Potentially inappropriate medications; Physicians; Age; Gender; Slovenia

Abbreviations

AAI	Active Ageing Index
EU	European Union
Eurostat	Statistical Office of the European Union
GDP	Gross Domestic Product
HIIS	Health Insurance Institute of Slovenia
NOAC	Novel Oral Anticoagulants
NSAID	Nonsteroidal anti-inflammatory Drugs
OECD	Organization for Economic Co-operation and Development
PIM	Potentially inappropriate medicines
PPIs	Proton-Pump Inhibitors
SHI	Social Health Insurance
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake inhibitor
STA.SI	Republic of Slovenia Statistical Office
WHO	World Health Organization

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1 Introduction

In the next chapter, as an introduction to this study, a description of Slovenia and an overview of its socio-economic and health profile will provide the necessary information to understand the potentially inappropriate prescription patterns among physicians in this European country. Because all the countries on EU follow common guidelines and criteria provided by European organizations such as EMA, it is expected that an overview over Slovenia in this field can serve as a relevant study for the EU panorama.

1.1 Slovenia

Slovenia is an east European country that joined European Union (EU) in 2004.

In Slovenia, a social health insurance system is financed by a single public insurer (the Health Insurance Institute of Slovenia: HIIIS), who provides universal mandatory health insurance. In addition, complementary health insurance is purchased by most of the population. Health services can be supplied by public providers (a network of health care centres, hospitals and outpatient clinics) and by private providers (1, 2).

1.1.1 Country Statistics and Population Demographics

In the last few years, the population growth in Slovenia has been around 0,1% and 0,2%. In 2018, Slovenia surpassed EU growth rates for the first time since 2013 and its growth annual rates are currently increasing compared to the relatively stable values for the EU (3). The GDP per capita has also increased from 2012 to 2018 (4.0 for 2018), following the trend of the EU, although Slovenia's achievements were more pronounced (4).

The statistical office of the European Union (Eurostat) released a report related to the *Structure of population and ageing* across the EU member states in 2019. The main conclusion of the report is that the population is ageing as a result of a higher life expectancy combined with lower births. The percentage of the younger population in Slovenia (0-14 years old) increased over time, showing a percentage close to the EU (15,1 and 15,2, respectively). On the contrary, the percentage of the working-age population (15-64 years old) decreased over time but it showed a higher percentage than the EU (65,2 and 64,6, respectively). In 2018, according to the Republic of Slovenia Statistical Office

(STA.SI), Slovenia had a population of 2 066 880 individuals, of which 19,41% were over 65 years while the EU had an average of 20,3% (1,2). As a result, the median age in Slovenia was slightly lower than in the EU (43.2, compared to 43,7, respectively) (5). Since the 90s, the life expectancy in Slovenia increased more than nine years, which is causing a significant change in the share of the population by age. From 2009, the increase of the share of people equal or above 65 years old was close to 3%, whereas Slovenia showed an increase of almost 3,5% in the same group. As a consequence, it is expected that the percentage of older adults in Slovenia reaches to 30,6% in 2050, while in the EU is expected to reach to 28,7 % (7).

Table Erro! Não existe nenhum texto com o estilo especificado no documento**..3 Proportion of total population, mean age and proportion of older adults per gender in Slovenia**

Demographics in 2018	**Slovenia (SI.STAT)**(6)	**EU (World bank)** (3)
Population - TOTAL	2 066 880	*
Population – Men (%)	49,69 %	48,85%
Population – Women (%)	50,31 %	51,15%
Mean age (years) - TOTAL	43,2 years	43,7 years
Mean age (years) - Men	41,7 years	*
Mean age (years) - Women	44,7 years	*
Proportion of population aged 65 or more (%) - TOTAL	19,4 %	19,7%
Proportion of population aged 65 or more (%) - Men	42,5 %	43,09%
Proportion of population aged 65 or more (%) - Women	57,5 %	56,91%
Ageing growth	3,5%	3%
Proportion of population aged 65 or more in 2050 (%)	30,6%	28,7%

Notes:*No data available

1.1.2 *State of Health: Country Profile 2019*(8)

Since the last two decades, Slovenia has had a major development in health over the years. In 2017, life expectancy at birth had a great increase to 81.2 years and turned relatively higher than the EU average although there was still a great gap between gender (78.2 for males and 84 for females). Besides the lower public investment in health (2 060€ per capita, compared to an EU average of 2884 €), Slovenia managed to decrease mortality for some of the main causes of death in the country, such as ischaemic heart disease and stroke, to invest in mental health awareness and in the treatment to decrease the high discrepancy in suicide rates, particularly among men, when compared to Europe. These challenges are still very prevalent in the population, despite the efforts. Other main worries in the country are the incidence of lung cancer which is also a leading cause of death in Slovenia and the highest one for cancer, the growing incidence of pancreatic cancer, and the low numbers of healthy life years for older people, especially for women.

In general, and according to the country profile published by the European Commission, 37% of deaths in Slovenia can be attributed to behavioral risk factors, such as smoking habits, binge drinking, and obesity which relates to the lack of fruit and vegetables in the diet and the low physical exercise. In 2017 the incidence of all the mentioned risk factors was similar between Slovenia and the EU, varying only 1% between them, except for the alcohol consumption, where Slovenia shows half of the consumption of the average in the EU.

One of the strongest ambitions for Slovenia, in the health field, seems to be focused on the ageing population and its pressure on long-term care expenses especially since its mostly supported by contributions paid to HIIS, shaking the sustainability of the system.

1.1.3 Epidemiology

In 2017, consistently with the trend for high-income countries, non-communicable diseases represented the largest share of illness in society and the major cause of burden over people's quality of life and health expenses in Europe (9). Within this group, which includes all the non-transmissible diseases, the diseases of the circulatory system were the main cause of death for the majority of OECD countries which was also the case for Slovenia, while cancer was the second one for the country (31.1)% with a significantly

higher incidence than the average for OECD countries (10,11). In Slovenia, for men, lung cancer and prostate cancer were the main causes of cancer deaths, while among women it was breast cancer and lung cancer. Following neoplasms, also in Slovenia, injury and poisoning, diseases of the respiratory system, and diseases of the digestive system were the top causes of death by descending order (11).

Limited studies are approaching the most prescribed chemical groups and substances in Europe. In 2018, the British Journal of Clinical Pharmacology released an article named "The top 100 drugs and classes in England". On that research, for the overall population, the top 10 drug classes and the main drugs prescribed within each one of them were: proton pump inhibitors like omeprazole and lansoprazole; statins such simvastatin, atorvastatin, and pravastatin; beta-blockers like bisoprolol, atenolol and propranolol; calcium and vitamin D; calcium-channel blockers such amlodipine, felodipine, diltiazem, nifedipine and lercanidipine; antihistaminics including cetirizine, loratadine and chlorphenamine; acetylsalycilic acid; weak to moderate opioids like tramadol and codeine; strong opioids like morphine (12). Although this research was not focused on drugs prescribed to the elderly, many of the chemical groups mentioned treat conditions that affect mostly older adults, such hypertension, dyslipidaemia, arrhythmia, osteotrophy and pain, and for the need to prevent circulatory emergencies such strokes. It is thereby reasonable to say that older adults are likely to be responsible for a great share of the medicines used.

1.1.4 Physicians

There is limited information regarding the distribution of physicians per medical specialties either in Slovenia or Europe, and only few studies analyze the prescribing patterns per physicians rather than the ones that study the prescribing patterns among patients in a certain population or facility.

In Slovenia, the ratio of doctors per thousand inhabitants is low compared to the EU ratio, however, the number has increased considerably in the last few years. The share of physicians above 55 years old in Slovenia is below the OECD countries average. On the contrary, the share of females is one of the highest in OECD(13,14).

A table of the distribution of physicians in Slovenia per age and gender is presented below (13,14).

Table 1.2 Physicians' Distribution per age and gender in Slovenia and the EU

Physicians' Distribution 2018	Slovenia	EU Average
Less than 35 years	24.7 %	20,82%
35-44 years	25.6 %	21,92%
45-54 years	20.3 %	21,56 %
55-64 years	21.9 %	24,84 %
65 years of more	7,5 %	10,86%
Females	63 %	52,92%
Males	37 %	47,08%

1.2 Ageing Physiology

With ageing significant structural and functional changes happen in the body that leads to metabolic, cell performance, and tissue variations. The challenges in the management of older patients come not only from these variations but from assessing how profound these changes appear in each organ and each individual. The ageing process is extremely heterogeneous among people which hinders the establishment of harmonized criteria and guidelines on treatments (15).

Most frequently the ageing process is faster for organs where elastic tissue prevails, such as the cardiovascular, the respiratory, and the cutaneous systems, while it is expected to be slower for the nervous one (16).

For the cardiovascular system, the ageing process starts with the thickening of arteries' walls, a decrease in elasticity and collagen, and an increase in smooth muscle tone on the vascular tissue. As a result, the compliance of vessels diminishes which leads to high systolic pressures, sometimes in comparison with mild diastolic blood pressures. A high systolic pressure burdens the cardiac activity since the heart contraction must constantly overcome the arterial blood pressure. The effort of the left ventricle to eject blood is the reason why it frequently leads to its hypertrophy with age. This hypertrophy and the need for a strong ejection from the left ventricle consequently affect the ventricular relaxation, leading to a diastolic dysfunction which ultimately burdens the left atrial, which can also result in general left side hypertrophy and atrial fibrillation. The pacemaker cells' automaticity can also be affected, which explains why arrhythmia is common in older adults. Finally, as the efficiency of the cardiovascular decreases, the blood flow can be compromised for different organs in the body. On the other hand, because the plasma renin activity and the aldosterone response tend to decrease with age, there is an ineffective response to post-prandial and postural blood pressure decrease which can lead to syncope and falls. The elderly also tend to be intolerant to intravascular variations since the strictness of the venous system cannot adapt to these changes. (15,16)

There is a decrease in the number of nerve cells, in the nervous system. A decrease in the blood flow due to vascular resistance in the brain is one of the possible causes, among many others. Changes in blood pressure can also be due to changes in the autonomic nervous system since there is an increase of sympathetic tone which causes a higher vascular resistance. The lack of response to beta-adrenergic stimuli also explains the difficulty of responding to changes in the blood pressure that lead to syncope or falls. The parasympathetic system disfunction can lead to gastrointestinal changes, such as constipation, and lower secretion of fluids and enzymes. (15–17) Some neurotransmitters, such dopamine, catecholamine, serotonin, and acetylcholine are less produced which compromise the motor and cognitive function, memory and provokes behavioral changes. There are fewer muscle cells connected to the nervous system (denervation) which causes muscle atrophy and there is a postural reflex impairment in the elderly which can both

also lead to falls. (15,16,18) The quality of sleep declines with age due to changes in the REM and NREM that provoke insomnia and premature awakening. (15,16,19)

As it happens in other systems, the musculoskeletal system is greatly influenced by age. The bone density decreases significantly with age which can be due to endocrine changes, the lower synthesis of vitamin D in the skin, and the malabsorption of nutrients such as calcium in the gastrointestinal system. The decrease in bone density predisposes to fractures in the elderly. Also, the decrease in cartilage and arthrosis is one of the main reasons for the decrease in the quality of life. (15,16)

The respiratory system is another system that suffers from the loss of elasticity which compromises the ventilation, due to the collapsibility of alveoli. Deficient production of surfactants and a decline in cilia compromises gas exchanges which also decrease ventilation effectiveness. The lung expansion turns less effective and there is a desynchronization between ventilation and perfusion which lowers arterial oxygen tension. Finally, there is a decrease in the cough reflex which can lead to aspiration. (15,16)

The kidneys tend to be greatly influenced by age. There is a loss in cortical renal mass that causes the sclerosis of the glomeruli, decreasing the surface area for filtration. Besides the decline of the glomerular filtration rates, there is a higher permeability which leads to albuminuria or even proteinuria. As seen in the cardiovascular system section, the vascular changes compromise the vasodilation of the afferent renal artery to compensate for the decline of the glomerular filtration rates. The renal blood flow and urinary excretion also decline with age, which lowers the ability of renal clearance. (15,16)

The weakening of vesicle smooth muscle and sphincters is the reason for the difficulty in retaining urine and bladder emptying. (15,16)

There is a tendency for gastric PH to increase with age caused by a decrease in the secretion of hydrochloric acid. Proteolytic, hepatic, and pancreatic enzymes, pepsin, and saliva also tend to be less secreted, and substances obtained through active mechanisms tend to be less absorbed. The calcium absorption diminishes due to either the decline of vitamin D or malabsorption. (15,16)

Ageing predisposes to infections and compromises recovery. Immune innate and acquired responses are affected by age because white blood cells lose their function (macrophages,

B and T cells) or decline (dendritic cells), and because there is a decrease of mediators such the tumor necrosis factor-a, interleukin-1 and nitric oxide. One of the reasons for the loss of function of T cells in the thymic involution prevents an effective differentiation and proliferation of these cells. On the contrary, autoimmune reactions tend to be more frequent and pronounced in the elderly. (15,16)

Usually, in the elderly, the endocrine system tends to be more affected at the target organs like what it happens with the resistance to insulin with age. Besides the variations mentioned before, the production and clearance of thyroxine declines, the activation of the vitamin D is ineffective, and the antidiuretic hormone concentration increases with age. The renin, aldosterone, and antidiuretic hormone changes can lead to hyponatremia in the elderly. (15,16)

1.3 Changes in Pharmacokinetics and Pharmacodynamics

The variations that occur in the ageing body can affect pharmacokinetics, changing the physiological response to medicines. Thereby, to know these changes is extremely important to determine the appropriate prescribing among the elderly, minimizing adverse side effects and optimizing the health outcomes among this population.

A reduction in the production of saliva, gastric acidity, blood flow, and motility can compromise the dissolution and absorption of substances (20–22).

The lean body mass, muscle, and water decrease while and the fat tissue increases with age. These variations cause an increase in the distribution of liposoluble substances, which leads to a lower concentration of these substances and a slower excretion. The time to reach the therapeutic effect can be delayed and there can be an accumulation of the substances due to their slower excretion. Benzodiazepines, beta-adrenergic blockers, valproic acid, and phenytoin are examples of these substances and their associated side effects can be intensified when taken chronically, such as the depression of the nervous system by benzodiazepines. On the contrary, hydrophile substances have a decreased distribution in the body which leads to higher concentrations. Substances with a narrow margin such as lithium and digoxin become potentially dangerous for the elderly if they are not adjusted to them (16,22–26).

Albumin concentration tends to decline with age while alpha-1-glycoprotein tends to increase. As a result, the unbound fraction of acidic substances tends to increase (warfarin, phenytoin, valproic acid, acetylsalicylic acid, naproxen) while the unbound fraction of alkaline substances tends to decrease (chlorpromazine, imipramine). These variations must be considered especially for substances that are extensively linked to these plasma proteins and/or have a narrow margin (like phenytoin) (16,22–26).

The metabolism of certain substances that are highly metabolized by the liver (like benzodiazepines) can be affected due to a decrease in liver mass and blood flow (16,22–26).

Phase II metabolism is not age-dependent and thus it is not affecting the elderly. However, phase I metabolism which includes oxidation, reduction, hydroxylation, and demethylation can be reduced with age and affect the metabolism of some substances (amiodarone, amitriptyline, nifedipine, verapamil, warfarin, and fentanyl, for example). Some substances originate metabolites that are active for a long time, such as diazepam and amitriptyline. The prescriber may have to consider the replacement of these substances for others that are safer for older adults (16,20,26).

Hydrophile substances with a narrow margin (digoxin, aminoglycoside, lithium) and nephrotoxic drugs (nonsteroid anti-inflammatories, metformin, aminoglycosides, acyclovir, amphotericin B) must be carefully prescribed to the elderly. There is a decrease in the kidney blood flow and its functions (filtration, excretion, clearance) which can lead to an increase in the concentration of the mentioned substances or to damage of an organ there is more fragile already (20,21,26).

There is a higher risk of dehydration in the elderly because they do not feel thirst and so diuretics must be carefully prescribed to them. Due to the decrease in respiratory performance, drugs that cause respiratory depression are potentially dangerous, which also happens to the drugs that increase the risk of falls for having a central nervous depression. For this reason and their influence over mood and behavior, psychotropics are responsible for a great share of side effects that come from the overuse of potentially inappropriate substances (15,27).

1.4 The burden of Disease and Medication

For the year 2015 pharmaceuticals were on average responsible for 16% of health costs, which was the third-highest share of health expenditures in OECD countries. Because this cost is mostly covered by public financing, governments have been putting efforts to reduce the investment in pharmaceuticals. Between 2009 and 2015 these efforts were able to decrease the expenditures annually by 0,5% for OECD on average and in Slovenia 0,9%, mostly due to the use of generic medicines (2,10).

Still, in the last 20 years polypharmacy (defined as taking more than 5 different medicines) increased by four times, while the amount of older people that do not take medication decreased significantly. This is related to a higher life expectancy, which leads to the prevalence of multiple chronic diseases due to ageing (multimorbidity). Clinical guidelines usually focus on a single disease so the management and the establishment of therapy on these patients are multiplied by several guidelines for each one of the conditions (28,29). Besides, a Swedish study concluded that during the year before dying, drug usage rose by 30,3% to 47,2%, and the increase remained significant after analgesics were excluded. The findings reveal that some medications were focused on long-term preventive treatments with a questionable benefit (30). An example of this is the use of statins in older patients with no reasonable benefit since these treatments focus on preventing cardiovascular diseases in many years and show no life expectancy enhances when used in older patients. There was another study that showed considerable improvements in the quality of life and no changes in death rates and life expectancy after discontinuing statins (28,30).

The tendency to take several medicines with age is a risk for the older patients who are frailer due to pharmacokinetic and pharmacodynamic changes in the ageing body which can lead to side effects and errors since their medication is more complex and adherence is a challenge (28,31). In the United Kingdom adverse reactions to medicines caused around 2400 deaths per year and 17% of hospital admissions of older adults are related to adverse reactions, with more than 70% most likely avoidable (28).

An adverse drug reaction can happen due to inappropriate use or dosage, length of use, interactions, and use is contraindicated circumstances. Adverse drug reactions represent economic and clinical expenses because they can lead to hospital admissions, medications to deal with the consequences of another, a longer stay hospitalization missed days at

work by relatives responsible for the older patient, and morbidity due to anxiety from the emergency episode. As examples of the usage of medications to deal with the adverse reactions of others happens commonly in patients with Parkinson's disease treated with dopaminergics when they are prescribed with antipsychotics or to patients with Alzheimer's disease are prescribed with anticholinergic medications for urinary retention (29,31).

Nonsteroid anti-inflammatories, coumarins, antibiotics, and beta-blockers are some of the therapeutic groups more associated with adverse reactions while the most common adverse drug reactions are falls, fever, diarrhea, bleeding, and cardiac arrhythmia (29,31).

1.5 Justification of the study

Illness and chronic diseases are highly present in older adults which makes the elderly the most dependent on health services. This is the reason why the costs of healthcare tend to be higher for this population. With the growing share of elderly people in Europe and the increasing in life expectancy, it is expected that the public expenditure on health continues to rise which represents a tremendous economic challenge to countries. Disability and the need for long-term care and services can be diminished if technology and pharmaceutical usage are optimized and efficient in lowering morbidity and raising the quality of life of older people. Older adults are the ones who use more medication and the most susceptible to adverse side effects. Since doctors are the ones who prescribe their medication, this current research intends to investigate physicians' prescribing patterns of potentially inappropriate medicines in order to gather further insights on their demographic influence on prescribing patterns. This study intends to be part of the efforts on providing the correct management of older people and the establishment of a proper therapy adapted to their physiology and complexity, which is crucial to reduce adverse drug reactions and improve health status, finally helping to achieve a sustainable future of healthcare.

There was an interest in evaluating the appropriateness of prescription patterns among older adults in an ageing population such as the Slovenian one which reassembled the entire European Union panorama. The research was conducted due to the availability of the national database that was able to provide information on the demographics of patients and physicians, together with the prescriptions involved.

1.6 Objectives

The main goal of this study was to weigh how the demographic characteristics of the physicians (such as age and gender) could influence the incidence of potentially inappropriate medications. Studies in the field of potentially inappropriate medications in older adults usually focus on the patients to whom the medication prescribed is for. In this study, however, the aim was to evaluate the appropriateness of medications prescribed by the physicians, how often the potentially inappropriate medications were prescribed by doctors, and which are the substances and chemical groups more often prescribed that can lead to a potentially disadvantageous outcome.

2 Methods

2.1 Data Source

The study was conducted through a nationwide cross-sectional study using data from the Slovenian National Prescription Database.

Within the database, a case corresponded to a prescribed medicine that was coded by the ATC Classification System. In this nomenclature, active substances are divided into groups depending on the respective targetted organ or system and their therapeutic, pharmacological and chemical properties. Drugs are then distributed in groups at five different categories: anatomical main group, therapeutic group, pharmacological subgroup, chemical subgroup and finally, in the chemical substance. In this paper, the chemical substances and therapeutic groups where decoded and referred by their designation.

The correspondent patient of each prescription and the physician who prescribed it were identified by a code and their identity was anonymous. The demographic characteristics of both patient and physician, such as gender and age were also presented as variables. Gender was defined as female or male and age was calculated from the date of birth.

The study period for the cross-sectional analysis was the year of 2018.

2.2 Data Management Software

The database was managed and analyzed using the IBM SPSS Statistics Software, version 25.

Microsoft Excel Office 16 was also used as a tool to manage data obtained from SPSS analysis and to create graphs that allowed a different and clearer view of the results.

2.3 Criteria to Assess the Potential Inappropriate Medicines Prescribed

The EU(7)-PIM list and American Geriatrics Society 2019 Updated AGS Beers Criteria (from now on referred to as 2019 Beers Criteria) were the tools used to identify a PIM in the database. A prescribed medicine was considered a PIM if it was present in at least one

of the two lists. When it comes to the 2019 Beers Criteria, only the medicines classified as PIM regardless of dose or indication were accounted for, as these variables are not known from the data.

The EU(7)-PIM list is a 2015 consensus on potentially inappropriate medications for older people by experts from seven European countries. This tool was considered suitable because it was developed to compare prescribing patterns across European countries and it is adapted to the European guidelines and the medicines that are approved and commercialized in Europe. The 2019 Beers Criteria list was also considered suitable for this study for being more recent and thereby updated with the latest findings in this field of study. There is another consensus for PIM, but they are known as being a derivative from the Beers Criteria and so they were not included in this research.

2.4 Data Analyses

Only the medications prescribed to adults equal or more than 65 years old were submitted to the analysis, while others were excluded. Missing values were also excluded. As a result the number of medicines submitted to the analysis was 8 635 081. The prescriptions were then classified as PIM or non-PIM.

The database was transposed so each case represented a physician, while the variables described their demographic characteristics and their prescription patterns. There were 7352 physicians in the database and the variables describing them were age, gender and the variables used to describe their prescribing patterns, such as the total number of prescriptions (from now on referred to as “Total of prescribed medicines per doctor”), the number of PIM prescribed (from now on referred as ”Total PIM prescribed per doctor”), the number of different chemical substances prescribed (from now on referred as “Different Substances prescribed per doctor”), the number of different chemical substances identified as PIM prescribed (from now on referred as “Different PIM prescribed per doctor”), and finally the number of PIM prescriptions per ATC level 2. From these variables, the ratio of Different PIM prescribed per doctor, the ratio of Total PIM prescribed per doctor, and the ratio of each ATC level 2 chemical group prescriptions, were calculated per physician, so the size of the sample did not influence with the results.

The IBM SPSS Statistics software was used to analyze the descriptive statistics and the distribution of physicians per gender and age. The gender was defined as “Female” or “Male” and the age was defined into groups- group 0 for the physicians below 65 and group 1 for physicians equal or above 65. This decision was taken so the effect on the ageing physician could be assessed in this study.

The independent sample T-Test was used to study the effect of gender and age on the variables that were describing the prescription patterns of the physicians, such as the ratio of Different PIM prescribed per doctor and the ratio of Total PIM prescribed per doctor.

To assess how the patterns of prescription per chemical group were influenced by the physicians’ characteristics, the ratio of PIM prescriptions per each ATC level 2 code was also submitted to the independent T-Test.

The frequency of PIM prescriptions per ATC 2 (which classifies chemical groups) and per ATC 5 (which classifies chemical substance) were obtained through descriptive analysis to be further analyzed and to conclude which chemical groups or substances were more prescribed during the year 2018.

3 Results

3.1 Demographic Distribution

The number of older patients in the sample was 395215. The analyses of the distribution of patients on their demographic characteristics showed that most of the patients in this study were female (57,9%) and between 65 and 74 years old (50,7%). Overall, the patients were in average 75 years old. Table 3.1 below presents a detailed view of the results.

The number of physicians in the sample was 7352. The analyses of the distribution of physicians on their demographic characteristics showed that most of the professionals in this study were below 65 years old (73,6%) and females (60,1%). Table 3.2 on the next page presents a detailed view of the results.

Table 3.1 Patients' distribution per age and gender

Patient Demographics		**Frequencies, (%)**	**Average Age (years old)**	**Standard Deviation (years old)**
Age (years old)	[65, 109]	395215, (100%)	75,35	7,71
Age group (years old)	1: [65, 74]	200572, (50,7%)	68,99	2,79
	2: [75, 84]	137156, (34,7%)	79,06	2,83
	3: [85, 94]	53778, (13,6%)	88,15	2,57
	4: [95, 109]	3709, (0,9%)	96,55	1,84
Gender	Male	166393, (42,1%)	74,11	7,06
	Female	228822, (57,9%)	76,26	8,03

Table 3.2 Physicians' distribution per age and gender.

Physician Demographics		Frequencies, (%)	Average Age (years old)	Standard Deviation (years old)
Age (years old)	[25,98]	7352, (100%)	51,91	16,62
Age group (years old)	0: [25,64]	5412 (73,6%)	44,08	11,28
	1: [65,98]	1940 (26,4%)	73,77	6,48
Gender	Male	2934, (39,9%)	54,03	17,26
	Female	4418, (60,1%)	50,50	16,01

3.2 Descriptive Statistics

The table below presents an overview of the descriptive statistics of the variables of interest for this study in the database. These variables include values determined for physicians and each value corresponds to a prescription which means one single medicine prescribed. All the data refers to the year of 2018.

Table 3.3 Descriptive Statistics

Variable	Average	Std Dev	Min	Max
Total of prescribed medicines per doctor	1170,43	2629,04	1	21499
Total PIM prescribed per doctor	285,76	656,06	1	5390
Different Substances prescribed per doctor	65,22	91,90	1	345
Different PIM prescribed per doctor	15,66	21,01	0	76
Total PIM prescribed per doctor / Total of prescribed medicines per doctor (%)	28,86	20,68	0	100
Different PIM prescribed per doctor/ Different Substances Prescribed per doctor (%)	24,41	17,10	0	100

3.3 Independent Sample T-Test

In this chapter, the results of the independent T-Test analyses are going to be displayed as a table followed by an explanation of the values obtained.

3.3.1 Age

Table 3.4 Independent T-Test: Age Effect

Variable		**Independent T-Test Results**	
Total PIM prescribed per doctor / Total of prescribed medicines per doctor	Group 0 (below 65 years old)	(M= 28.26, SD= 20,85)	t(3533,69)= -4.24, p= .018
	Group 1 (equal or more than 65 years old)	(M=30.53, SD= 20.11)	
Different PIM prescribed per doctor / Different Substances Prescribed per doctor	Group 0 (below 65 years old)	(M=24.27, SD=16.56)	t(3114)= -1,17, p=.000
	Group 1 (equal or more than 65 years old)	(M=24.82, SD= 18,55)	

The analyses reveal that all the tests showed a significant influence of the age group on the prescription patterns among physicians. The physicians in group 0 compared to the physicians in group 1, demonstrated significantly lower values on the ratio of Total PIM prescribed per doctor. The same result was observed between the same groups for Different PIM prescribed per doctor, showing a stronger significance, but a smaller gap between both.

3.3.2 Gender

Table 3.5 Independent T-Test: Gender Effect

Variable		Independent T-Test Results	
Total PIM prescribed per doctor/ Total of prescribed medicines per doctor	Male	(M=27.72, SD=20.02)	t(6500.87)= -3.9, p=0,04
	Female	(M=29.61, SD=21.08)	
Different PIM prescribed per doctor/ Different Substances Prescribed per doctor	Male	(M=24.79, SD=16.37)	t(6581.02)= 1.57, p=0,04
	Female	(M=24.16, SD=17.58)	

The analyses reveal that all the tests showed a significant influence of gender on the prescription patterns among physicians.

In this study, females showed higher values for the Total PIM prescribed per doctor. The ratio of Different PIM prescribed per doctor however showed lower values for females.

3.3.3 ATC level 2: Chemical Groups

In this chapter, the ratios of PIM prescriptions per each ATC level 2 group were submitted to the independent T-Test analyses so the influence of age and gender could be assessed on each chemical group level individually.

Before a detailed description of the results, a table will be displayed to show an overview of which chemical groups were affected by each one of the variables.

Table 3.7 Demographic variables influence on the patterns of prescribing different Chemical Groups

Chemical Group	Age	Gender
Drugs for acid related disorders	[25,64]<[65,98]	
Drugs for functional gastrointestinal disorders	[25,64]>[65,98]	
Antiemetics and antinauseants		
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	[25,64]<[65,98]	M>F
Drugs used in diabetes		M<F
Mineral supplements		M<F
Antithrombotic agents	[25,64]>[65,98]	M>F
Antianemic drugs	[25,64]>[65,98]	
Cardiac therapy		M>F
Antihypertensive drugs		M>F
Diuretic drugs	[25,64]>[65,98]	M>F
Beta blocking agents	[25,64]<[65,98]	
Calcium channel blockers	[25,64]<[65,98]	M<F
Sex hormones and modulators of the genital system		
Urological drugs	[25,64]>[65,98]	
Antibacterial drugs	[25,64]<[65,98]	M<F
Endocrine therapy	[25,64]>[65,98]	
Anti-inflammatory and antirheumatic drugs		

Drugs affecting bone structure and mineralization		
Analgesic drugs		
Antiepileptic drugs		M>F
Antiparkinson drugs	[25,64]<[65,98]	
Psycholeptics drugs	[25,64]<[65,98]	M<F
Psychoanaleptics	[25,64]>[65,98]	M<F
Drugs for obstructive airway diseases	[25,64]>[65,98]	
Cough and cold drugs	[25,64]>[65,98]	
Ophthalmological drugs	[25,64]<[65,98]	

Notes: A colored box means that the chemical group was influenced by the respective variable while a white one means no significant effect was observed. For the Age variable, physicians are referred according to their age interval which means that younger physicians from group 0 are referred as [25,64], while the older physicians from age group 1 are referred as [65,98]. In the Gender variable, "M" stands for Male while "F" stands for "Female".

As seen in the table above, the Antiemetics and antinauseants group and the Analgesic drugs group were not influenced either by age or gender, so they will not be mentioned in the analyses anymore.

Looking closer to the effect of age on the prescribing patterns for different chemical groups, the independent T-Test analyses were able to show that group 0 (below 65 years old) tends to prescribe significantly more PIM, when compared to group 1, in the following groups: Drugs for Functional gastrointestinal Disorder group, Antithrombotic Agents group, Antianemic Drugs group, Diuretic Drugs group, Urological Drugs group, Endocrine Therapy group, Psychoanaleptics group, Drugs for obstructive airway diseases group and at last, the Cough and cold drugs group, which was only influenced by age nor gender.

On the contrary, the independent T-Test analyses showed that group 1 also tends to prescribe more PIM in other chemical groups such as Drugs for acid related disorders

group, Antidiarrheals, intestinal Anti-inflammatory/anti-infective agents group, Beta blocking agents group, Calcium channel blockers group, Antibacterial drugs group, Antiparkinson drugs group, Psycholeptics drugs group and Ophthalmological drugs.

When it comes to the gender effect on the PIM prescribing patterns, it was noticed that it significantly influenced many chemical groups where age remained neutral, and on the contrary, that it did not influence few chemical groups that age had an influenced on. The PIM prescriptions in the Drugs used in the diabetes group and the Mineral supplements group were not influenced by age, but they were significantly influenced by gender as females tended to prescribe more PIM in these groups than males. On the other hand, males tended to prescribe more PIM in the Cardiac therapy group, in the Antihypertensive drugs, and the Antiepileptic drugs group, while age was also neutral. The Drugs for acid related disorders group, Drugs for functional gastrointestinal disorders group, the Antianemic drugs group, the Beta blocking agents group, the Urological drugs group, the Psycholeptics drugs group, the Drugs for obstructive airway diseases group, and the Ophthalmological drugs group are the mentioned cases where only age had a significant influence on while gender remained neutral. Also, the cases that were only affected by age individually were mentioned before and so it is known by now that gender did not influence them too.

At last, regarding the chemical groups that were affected by both variables (age and gender), the Antidiarrheals, intestinal Anti-inflammatory/anti-infective agents group, Antithrombotic agents group, and Diuretic drugs group were significantly more prescribed by males, while the Calcium channel blockers group, Antibacterial drugs group, the Psycholeptics drugs group and the Psychoanaleptics group were significantly more prescribed by females.

3.4 The most prescribed chemical groups /substances

The five chemical groups with more prescriptions found in the database were Drugs for Acid Related Disorders, Psycholeptics, Diuretic Drugs, Anti-inflammatory, and Antirheumatic Drugs, and Psychoanaleptics by descending order. Consistently with these results, the ten most prescribed chemical substances were, also by descending order, Pantoprazole, Furosemide, Zolpidem, Diclofenac, Indapamide, Naproxen, Alprazolam, Bromazepam, Esomeprazole, and Espironolactone.

A table is presented below with the frequencies in percentage for each one of this chemical groups/substances in the database.

Table 3.7 The most prescribed Chemical Groups

Chemical Groups	Frequencies (%)
Drugs for Acid Related Disordes	22,10
Psychleptics	17,36
Diuretic Drugs	16,00
Anti-inflammatory and Antirheumatic Drugs	12,90
Psychoanaleptics	10,81
Cumulative Frequency (%)	79,18

Table 3.8 The most prescribed Chemical Substances

Chemical Substances	Frequencies (%)
Pantoprazole	14,74
Furosemide	7,02
Zolpidem	5,21
Diclofenac	4,36
Indapamide	4,19
Naproxen	3,96
Alprazolam	3,51
Bromazepam	3,43
Esomeprazole	3,32
Spironolactone	2,45
Cumulative Frequency (%)	52,2%

The main chemical groups and substances per group (gender and age) were also analyzed but the results showed no significant difference from the general analysis. All the chemical groups and substances mentioned were consistently the most prescribed for every group.

The next chapter will be focused on the discussion of the results obtained in this study.

4 Discussion

Before delving into discussing the results, it is important to first outline certain limitations of this research. The research was limited by the information available in the used database, as this database did not include data on the prescribed dosages. Furthermore, there was also no data available on indication, patient profile, and medical specialty of the physician. The lack of this information prevents further depth to the results and any conclusions derived from them.

The results show that over one year (2018) on average more than 1170 prescriptions were prescribed per doctor, 285 of them defined as PIM based on the two criteria used for the study- the EU(7) PIM list and the AGS Beers Criteria 2019. From an average of more than 65 chemical substances prescribed per doctor, more than 15 were defined as PIM (24%). It is relatively complex to compare these results with other European ones because the prevalence of PIM depends on the study design, the sample size, context (type of facility), and criteria used (which in the case of the beers criteria is updated every 3 years). Results range from 10% (32) to 60% PIM prescriptions (33,34)**,** while the number of PIM chemical substances is calculated per patient instead of the prescriber.

The study of the influence of the physicians' demographic characteristics over the number of PIM showed that older age (equal or above 65 years old) and female gender were the determinants to have more PIM prescriptions over 2018 in Slovenia. However, even though females had more prevalence of PIM prescriptions, they prescribed a lower number of different chemical substances which means that the substances they prescribed, they prescribed more often. Few studies were found to correlate the prescription patterns per age or gender, especially focused on PIM. Several studies concluded that females tended to prescribe more carefully, conservatively, and at lower dosages, focusing more on preventive, engaging, and actively listening more to their patients which lead to more screenings and monitoring, better adherence, change of habits, and better health outcomes (35–37). These research results are not consistent with the findings of the studies mentioned, as females tended to prescribe more PIM. From another perspective, however, as females tend to be more conservative, they are less likely to switch their patients medications for recent ones which can show safer profile for older adults.

Several studies are approaching the challenges and likely compromises in the ageing physician. It is frequently argued that having more experience positively influences a

performance, however, in 2005 a systematic review that studied the relationship between clinical experience and quality in healthcare, found out that 52% of the evaluations reported a decrease in performance with years of practice, while other 21% stated that decreases in performance were noted for certain outcomes. The conclusion was that whoever practices longer "may be at risk of providing lower-quality care". (38) Before, in 2002, a review paper on the changes in Cognitive Processing in the ageing physician used a medical knowledge test to assess the performance of older physicians and it concluded that they also performed worse than younger physicians. The reason that was theorized by this study was that the findings were not necessarily due to neuropsychological impairment but more likely to have less" up-date knowledge bases". (39) Later, another review study focused on assessing the actual cognitive changes and implications of ageing for physicians. It reminded that because ageing is so heterogenous, the effects of performance with age cannot be generalized to all physicians, being even possible that for some the performance increases. However, the study concluded that due to the physical deterioration that compromises vision and hearing and due to the short-time memory decline, prevailing the long-term one, the errors might occur due to premature diagnosis and automation. Older physicians rely more on experience and so they are not so apt to respond to new and complex challenges. At last, the short memory and capacity to new skills and knowledge can also be affected which would be consistent with the previous study's theory: "the up-to-date knowledge bases" being compromised. (40)

If the recent findings in medicine are more difficult to be learned, one could assume that the higher prevalence of PIM prescriptions in older physicians can be due to the dynamic field that is one of the potentially inappropriate prescriptions among the elderly. The Beers criteria are updated every three years (41) while the EU(7)PIM-list was only released three years before the year of the study (2015 and 2018, respectively). The main differences in the 2019 AGS Beers Criteria compared the 2012 AGS Beers list were: the addition of atropine (excluding ophthalmic), that besides being already recognized as highly anticholinergic in 2012, was not included in the criteria; digoxin was included in the independent of diagnosis or condition list for doses above 0,125 mg/d in 2012, while in 2019 digoxin was included without a reference dose; in 2012 mainly tricyclic antidepressants were present in the independent of diagnose or condition list while in 2019 paroxetine and some tricyclic antidepressants were added to the same list

and the entire SNRIs and SSRIS chemical groups were put into the use with caution list; finally the proton-pump inhibitors were included in the independent of diagnose or condition list; before 2019, diuretics were included in the use with caution list while spironolactone was the only diuretic mentioned in 2012 as a drug to be avoided "independently of diagnose or condition"; in 2019, tramadol and glimepiride were also added to the use with caution list but, as the study is based on data from 2018, this cannot be included to this particular analysis. (42,43)

At last, there are limited studies that correlate the gender of the physician with the prevalence of prescribed PIM and so, it is difficult to approach this significant difference that was observed between the prescribing patterns per gender. There are, however, studies about the higher tendency for females to prescribe some chemical groups than males. Those studies and how they correlate to the current study will be mentioned later.

Older physicians tend to prescribe more Drugs for acid-related disorders than younger physicians. This can be explained by the recent changes in the recommendations for proton-pump inhibitors prescribing. Besides the risk of Clostridium difficile infection, bone loss, and fractures(43), it is known that these groups of medicines have also interactions with other medications metabolized by the cytochrome P-450 isoenzyme CYP2C19, which is inhibited by the proton pump inhibitors (PPIs). Older physicians also tend to prescribe more PIM from the Antidiarrheals, intestinal anti-inflammatory/anti-infective agents group, Beta blocking agents group, Calcium channel blockers group, Antibacterial drugs group, Antiparkinson drugs group, Psycholeptic drugs group, and Ophthalmological drugs group. There were no relevant studies to assess the prescription differences per age observed, except for antibacterial drugs, where another study related inappropriate Antimicrobial Prescribing with older physicians. (44).

On the contrary, younger physicians were more likely to prescribe more PIM for functional gastrointestinal disorders, antithrombotic agents, antianemic drugs, diuretic drugs, urological drugs, endocrine therapy drugs, psychoanaleptics, and obstructive airway diseases. The only studies found that observed a prescription prevalence among younger were related to the cardiovascular diseases therapy drugs, including antihypertensive, antiplatelet, glucose, and lipid-lowering medicines. According to one study, besides prescribing more medicines in the mentioned category, patients treated by younger physicians (less than 45 years old) had a higher prevalence of myocardial

infarction and stroke which lead to conclude that older physicians prescribe focused more on lifestyle changes, providing more efficient guidance to high-risk profiles. (45)

Unrelated to gender, cough and cold drugs PIM were also more prescribed by younger physicians.

When it comes to the gender effect overprescribing patterns, males were observed to prescribe more PIM for the Antidiarrheals, intestinal anti-inflammatory/anti-infective agents group, Antithrombotic agents group, Cardiac therapy group, Antihypertensive drugs group, Diuretic drugs group, and for the Antiepileptic drugs group. On the other hand, females are more likely to prescribe PIM in the Drugs used for diabetes group, Mineral supplements group, Calcium channel blockers group, Antibacterial drugs group, Psycholeptics drugs group, and in the Psychoanaleptics group. Although there are still few studies, research on the influence of gender in prescription patterns is more frequent than age-related ones. Comparing with females, males tend to take more risks and follow newer therapies and medicines. Females, on the contrary, tend to be more cautious and conservative, and, as mentioned before, more focused on preventive medicine, which can be an explanation of the results observed for the Mineral supplements group (35–37). A recent study, mentioned before in this discussion, concludes from a literature review that females tend to prescribe more opioids and antidepressants as they tend to assess more the subject of mental well-being. (36) These results are consistent with our results where females tend to prescribe more PIM regarding the Psycholeptics and Psychoanaleptics groups. Another study mentioned before was also able to associate the female gender with more prescriptions for blood glucose which can also explain this research results, for PIM in Diabetes group. The same study also showed that males prescribed less antihypertensive, and for this case, the results in higher prevalence of PIM in the Antihypertensive group. (35) Focusing on the males' results for the Antithrombotic drugs group, a study concluded they were more likely to prescribe NOAC (novel oral anticoagulants) since they tend to follow newer therapies. However, many NOACs medicines are included in lists of inappropriate medicines for the elderly, which can explain why males show a higher number of prescriptions for these groups. (46) Due to the lack of research on the physicians' prescription patterns, no more studies were found to understand the results.

Drugs for Acid Related Disorders, Psycholeptics, Diuretic Drugs, Anti-inflammatory, and Antirheumatic Drugs, and Psychoanaleptics were associated with the most prescribed PIM for the physicians in general but also for each one of each demographic groups, while Pantoprazole, Furosemide, Zolpidem, Diclofenac, Indapamide, Naproxen, Alprazolam, Bromazepam, Esomeprazole, and Spironolactone were the tenth most prescribed medications.

Earlier in this discussion, adverse effects from the inappropriate use of proton-pump inhibitors were mentioned but it is important to notice that the medicines in this group are also extremely important to prescribe in certain conditions. Older adults tend to take several medications at the same time, some of them that can cause gastrointestinal bleeding and ulcers such as corticosteroids or NSAIDs. There are clear benefits in using PPIs for the prevention of ulcers in the patient that have a low dose regimen of acetylsalicylic acid for example. (47) It was mentioned before that circulatory system diseases were the most prevalent diseases among Slovenians, with death rates per ischaemic heart disease and stroke being the highest in the country. With this information, it is no surprise that prevalent regimens with antithrombotic medicines require a prevalent regimen of PPIs and acid-related drugs. This also explains while the most chemical substance taken by the Slovenian population is pantoprazole and the ninth from the same group, esomeprazole. To reduce the incidence of side effects, safer alternatives to prevent cardiovascular emergencies among older adults should be considered so the PPIs use can be diminished.

Among the psycholeptics group, the second most prescribed chemical group, several types of medication are included such as antipsychotics, anxiolytic drugs, and hypnotics. Antipsychotics are related to increased risk of stroke and cognitive decline and mortality in older adults suffering from dementia. Thus, the tendency to prescribe antipsychotics for behavioral problems of dementia or delirium such be avoided. (43) Anxiolytics and hypnotics are given to the elderly as an attempt to manage their anxiety and sleeping problems, like zolpidem, alprazolam, and bromazepam cases, which were few of the most prescribed drugs. Benzodiazepines, such as alprazolam and bromazepam, increase the risk of cognitive impairment, delirium, falls, and fractures in older adults. Nonbenzodiazepines, such as zolpidem, have similar side effects as benzodiazepines. (43) Efforts in recommending other therapies, referring older adults to psychologists for example, and implementing lifestyle changes can be a safer alternative for this population.

The diuretic drugs group belongs to the top three most prescribed drugs. It is expected that, along with the European Union, hypertension is a prevalent problem for Slovenia, especially due to its high rates of smoking and alcohol consumption. Hypertension is also an important determinant of cardiac dysfunction and atherosclerosis, which are the main causes of death mentioned above. Managing older adults' blood pressure is therefore crucial, however, the diuretic drugs are defined by the 2019 AGS Beers criteria as to be used with caution since they are related to hyperkalemia and/or hyponatremia in the elderly, which is the case for both furosemide and indapamide. (43,48,49) Once again, lifestyle changes, such as quitting smoking and ceasing alcohol consumption, exercise, and healthy nutrition should be highly encouraged from the youngest to the oldest so this disease can be attenuated in population, preventing the need to use multiple medicines, some of them not so safe for the elderly.

Anti-inflammatory and Antirheumatic Drugs groups, which include diclofenac and naproxen, are usually prescribed to deal with manage the incapacitant pain that strikes older adults routine. The ageing body loses bone mass and cartilage, being more susceptible to inflammation processes, better known as arthritis. (15) These medications, however, besides compromising the gastrointestinal system as described before, increase blood pressure and induce kidney injury. (43) Exercise and movement are extremely important, as it stimulates the production of synovial fluid, reducing inflammatory modulators (50) Other findings are related with the intake of fatty acids through a diet with low omega-6/omega 3 than can successfully diminish inflammatory processes while decreasing the incidence of several chronic diseases. (51)

At last, psycoanaleptics were the fifth most prescribed chemical group and include dementia drugs and antidepressants, both targeting prominent diseases in older adults. In opposition to dementia drugs, antidepressants are highly anticholinergic, sedative, and lead to orthostatic hypotension, problems that the ageing physiology is frailer to. Although depression is a major incapacitant disorder, alternatives to certain medicines in this category, such as the ones belonging to the tricyclic antidepressants group or paroxetine, such be replaced with other alternatives and the patient referred to a psychologist.

Overall, these results present a basis from which important insight can be derived for the development of educational programs and training for physicians. The influence of certain demographic dimensions on performance presents a case for providing

specifically tailored and targeted education and training for physicians based on their demographics. As various demographic groups seems to face different challenges in regards to their performance as a physician, the effectiveness of education and training to safeguard the quality of this performance can likely be improved by tailoring these to match the relevant demographics.

5 Conclusion

The current research shows the potential of studying the patterns of inappropriate prescriptions among physicians as a strategy to target groups of physicians, therapeutic groups or specialties and invest in personalized and extensive scientific programs in order to finally achieve significant and noticeable results in the prescribing practice among healthcare professionals, and older adults' health and quality of life. However, the lack of information available regarding prescribed dosages, indication, patient profile, and medical specialty of the physician greatly limited the analysis of this study as this information is crucial to have a critical perspective over the results. Future researches in this field should take account all the determinants to ensure the quality of their findings.

Although there are many studies about inappropriate prescription patterns among older adults, the prevalence of these prescriptions continues to be significantly high for many different contexts and countries. With the coming challenge of the ageing population in Europe and the burden of pharmaceuticals expenditure, of adverse drug reactions related to polypharmacy, the difficulty to adhere and manage a complex therapy, and the morbidity related to ageing, it is crucial that studies that target the healthcare community help to optimize and implement efficient therapies in the older patients.

There is still a lack of knowledge about the appropriateness of medicines in older people. The reason why this happens is due to the challenge of including older adults in clinical trials. Older adults show diverse health statuses and heterogenous compromises, and they are more vulnerable so they can have unexpected reactions to certain medicines. There are also limited studies that focus on the physician's performance on prescribing potentially inappropriate medicines, which determinants might lead to variations observed, which clinical and economic consequences may occur from these differences, and what can be done to harmonize the medical community. There is also a lack of consensus and criteria to manage multimorbidity since medicines prescribed are multiplied by different guidelines for different diseases. Guidelines focusing on multiple diseases could be helpful for physicians to be able to critically prescribe in an optimized strategy.

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