Geographic variation in top-10 prescribed medication and potentially inappropriate prescription in Portugal: An ecological study of 2.2 million older adults

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Abstract

Background: The use of multiple medications by older adults is considered a Public Health concern since it is associated to a higher risk of adverse drug reactions and potentially inappropriate medication (PIM). This study aimed to describe the top-10 prescribed active substances in older adults considering geographical distribution and PIM prescription.

Methods: A retrospective ecological study was conducted using data on the prescribed active substances during 2020 to people with 65 years or older. Information on active substances and defined daily doses (DDD) by age group, sex and region were retrieved from a Portuguese health administrative database. The average number of prescribed packages and DDD per 1000 inhabitants per day of top-10 active substances were calculated.

Results: A total of 2228090 older adults (58% females) were included. The active substances with higher prescription rates (mean DDD/1000 inhabitants/day) in all ARS were furosemide and atorvastatin in both males and females, compared to the other active substances of the top-10. Geographic differences in prescription were observed (higher prescription in ARS North and Centre and lower in ARS Algarve). In females, 2/10 most prescribed active substances were PIM (benzodiazepines and opioids) with geographic disparities across regions.

Conclusions: Most prescribed active substances to older adults belong to the cardiovascular system. The prescription of benzodiazepines and opioids in females, classified as PIM, alert for the need of public health policies to reduce inappropriate prescribing. Geographic differences in the top-10 most prescribed active substances and in PIM highlighted the importance of medication optimisation across regions.

Introduction

The worldwide population is ageing fast and by 2050, one out of six people will be over the age of 65 (1). Portugal is among the top five countries with the highest percentage of older adults, showing an increase from 9.4% in 1970 to 22.3% in 2020 (2). As life expectancy increases, the prevalence of multimorbidity (3, 4) and medication use (5) also rises.

The use of multiple medications in older adults is considered a Public Health concern since it is commonly associated to a higher risk of adverse drug reactions due to the metabolic changes and decreased in drug clearance associated with ageing (5, 6). Moreover, older adults have been commonly excluded from clinical trials leading to a lack of evidence regarding the safety and efficacy of many used medications in this population (5, 7–9).

Medications are considered inappropriate when the risks of their use are greater than its potential benefits, or they are prescribed in inappropriate doses and/or for unsuitable durations (10, 11). Prior studies (12–14) reported that in older adults the potentially inappropriate medication (PIM) prevalence ranges from 21–79% according to the different healthcare contexts. Inappropriate drug treatment has also been associated to various adverse clinical outcomes, as for instance frailty, falls, renal failure, poor physical function, impaired health-related quality of life (5, 7–9), higher risk of hospitalization, and mortality (12–14). Thus, PIM leads to negative health consequences and substantial financial costs for individuals and society (5, 14, 15).

Literature also suggests an increasing concern on the geographic variation in health care utilisation and costs (16, 17); and although in Portugal medication cost accounts for 14.8% of all health spending (18), few studies have addressed the geographic differences in medication prescription in older adults yet (16, 19), in particular the PIM prescription (20).

Optimisation of medication prescription and improvements in therapeutic effectiveness across regions are therefore a worldwide priority to improve health and wellbeing of older adults and consequently reduce health costs (21). Thus, this study aimed to describe the top-10 prescribed medication in older adults considering geographical distribution, and PIM prescription in this population.

Methods

Study design and data source

A retrospective ecological study on the prescribed medication to people with 65 years or older from all Portuguese Health Administrative Regions (Administração Regional de Saúde - ARS) was conducted. Data on the prescribed medication from January 1st to December 31st, 2020 were retrieved between September 1st to November 31st, 2021 from the official System of Information and Monitoring of the Portuguese NHS (SIM@SNS) public-access platform (22), which was developed by the shared services of the Health Ministry (Serviços Partilhados do Ministério da Saúde—SPMS). Data retrieved included active substances and defined daily doses (DDD) by age group, sex and ARS.

Setting

Portugal has a population of around 10.3 million inhabitants with about 2.3 million of older adults (≥ 65 years old) (23).

The Portuguese mainland ARS is divided in five areas: North (ARSN), Centre (ARSC), Lisbon and Tagus Valley (ARSLVT), Alentejo (ARSALE) and Algarve (ARSALG).

Medication

The list of 10 most prescribed active substances was extracted from the SIM@SNS platform and classified using the corresponding Anatomical Therapeutic Classification (ATC) code (24). Each active substance was considered PIM if listed on the European Union (7)-PIM list (25) adapted for the Portuguese population (26). Nevertheless, it was not possible to apply all the EU(7) PIM List criteria, due to the information available in the database. Therefore, the following drugs were excluded from the analysis: (a) drugs in which the classification of PIM was dependent on dose and/or duration of treatment and/or therapeutic scheme; (b) drugs classified as PIM that have lost their marketing holder in Portugal or that are not currently being marketed; (c) and PIM without a defined daily dose (DDD).

The active substances consumption was quantified in terms of number of prescribed packages and DDD per 1000 inhabitants per day. The concept of DDD was developed as a standard measure of drug utilisation which represents the average maintenance dose per day of a drug when used for its major indication in adults (27, 28). The DDD is a technical unit of comparison and overcomes difficulties in comparing prescriptions of different price, pack size, duration and dose (27, 28). The DDD per 1000 inhabitants per day also allowed us to compare between the different ARS, providing an approximate estimate of the proportion of the study population treated daily with a particular drug or group of drugs (29).

Data analysis

Descriptive statistics, using absolute and relative frequencies were performed to characterise the sample (age, sex and region).

The average number of prescribed packages and DDDs per 1000 inhabitants per day of top-10 ATCs level 5 were calculated using mean and standard deviation (SD) and results were illustrated by column charts. The study population used to calculate both estimates per 1000 inhabitants per day was the Portuguese population by administrative regions as illustrated in Table S2 (supplementary material).

Results

Sociodemographic data

A total of 2 228 090 older adults from the five Portuguese regions were analysed, 58% were females, about 51% were aged from 65 to 74 years and the remaining 75 years of age or older (Table S2, in supplementary material).

Top-10 prescribed active substances

The list of the 10 most prescribed active substances was ordered by dispensed packages (Table S1, in supplementary material) and corresponded to a median of 14.4% of all prescribed medicines, from a minimum of 1.0% in Algarve to a maximum of 39.1% in Alentejo.

The most prescribed active substances in both males and females from all age groups were the lipid modifying agents, such as atorvastatin, rosuvastatin and simvastatin with a mean DDD of 203.9 ± 40.8 , 126.4 and 124.7 ± 40.8 per 1000 inhabitants per day, respectively (Fig. 1). Medicines for thyroid therapy (levothyroxine sodium), analgesics (paracetamol and tramadol/paracetamol fixed-dose combination) and benzodiazepines (alprazolam) were mainly found among females, while antigout preparations (allopurinol) were found among males. In the top-10 prescribed active substances, diuretics (furosemide) were mainly prescribed in the age group ≥ 75 years in both males and females with a mean number of DDD of 261.0 ± 9.8 per 1000 inhabitants per day (Fig. 1).

Geographic variation in prescription

Figures 2 and 3 illustrate the mean DDD per 1000 inhabitants per day in top-10 ATCs level 5, by ARS, stratified by sex. In males, the active substances with higher mean DDD per 1000 inhabitants per day were furosemide and atorvastatin, compared to the other substances of the top-10. In both substances, a higher mean DDD was found in ARSC (furosemide: 422.8; atorvastatin: 403.7 ± 67.7) and ARSN (furosemide: 276.7; atorvastatin: 240.3 ± 10.5) compared to the other ARS. For instance, the mean DDD per 1000 inhabitants per day of these substances in ARSC was more than two-fold higher than the mean prescribed in ARSALG (furosemide: 197.4 and atorvastatin: 191.3 ± 1.3) (Fig. 2; Table S3).

In females, the active substances with higher mean DDD per 1000 inhabitants per day were also furosemide and atorvastatin, compared to the other substances of the top-10, with a higher mean DDD found in ARSN (furosemide: 304.4; atorvastatin: 195.0 ± 3.5) and ARSC (furosemide: 300.2; atorvastatin: 202.2 ± 0.4), compared to the other ARS (Fig. 3; Table S4, in supplementary material). Also, in females two proton pump inhibitors (PPI) active substances were prescribed, pantoprazole and omeprazole, while in men only pantoprazole was prescribed, considering the top-10 classification (Figs. 2 and 3; Table S3 and S4, in supplementary material).

PIM prescription

In females, two of the 10 most prescribed medications were PIM (Fig. 4). Considering all regions, at ages 65 to 74, a mean DDD of 76.8 ± 19.3 of alprazolam and 7.7 ± 1.3 of tramadol/paracetamol per 1000 inhabitants per day were found. At 75 years of age or older, only one PIM was prescribed - tramadol/paracetamol fixed dose combination, with an increase to 11.3 ± 2.8 DDD/1000inhabitants/day, in comparison with the mean value at ages 65 to 74 (Fig. 4). Differences in prescription across regions were observed. Again, ARSC showed the higher mean DDD/1000inhabitants/day of alprazolam (96.0), which was almost two-fold higher than in ARSALG (51.1). Regarding the tramadol/paracetamol fixed-dose combination at ages 65 to 74 values were similar across regions, and at 75 years of age or older the higher mean DDD/1000inhabitants/day was found in ARSALE (14.0) which was two-fold higher than in ARSALG (7.1) (Fig. 4).

Discussion

This study described the top-10 prescribed active substances to older adults, by age groups and sex. The most prescribed active substances belong to the cardiovascular system, regardless of sex, specifically atorvastatin in individuals from 65

to 74 years old and furosemide in those of 75 years or older. These findings agreed with previous evidence showing that cardiovascular disease is the leading cause of disability and mortality in Portugal and worldwide (30–32). Nevertheless, the modifiable and preventable nature of the main risk factors for cardiovascular disease (i.e., high systolic blood pressure, dietary risks, high cholesterol, tobacco, high body mass index, among others) alert for the need of interventions to address these risk factors, namely changes in lifestyles together with investments to reduce pharmacological treatments with potential to diminish disease burden and health costs (30, 33, 34).

Geographic differences in prescription and specifically in PIM were found, with a higher mean DDD per 1000 inhabitants per day observed in Centre and North regions and a lower mean DDD in Algarve. Geographic variation in medicines prescription has been documented in the literature (19, 20, 35–37) however, few therapeutic classes have been explored, mainly cardiovascular, psychotropic, opioids and antibiotics, with many therapeutic classes remaining unexamined, despite the importance of this information to reduce inappropriate prescribing (37). Furthermore, prior studies addressing geographic differences in PIM reported that higher age and female gender were the main individual characteristics associated to an increased likelihood of PIM (20, 38). In fact, our sample is composed by older adults and we also found that the PIM prescription was mainly in females, with the prescription of benzodiazepines (39) and opioids (40), which fully agreed with this previous evidence (20, 38, 41, 42). Several factors have been pointed out to explain this trend, namely the increased demand for health care services by females than males (43), their tendency to live longer and have more physical or psychological health complaints, their higher report of chronic conditions including pain (44) or their higher tendency to be prescribed with psychotropic medication compared to men (45, 46).

Other factors related to the regions' characteristics were also associated to a higher PIM prescription, as the lower socioeconomic status, lower access to health services and lower access to general practitioners (GPs) (20). However, in contrast to this study (20), our findings suggest that Algarve, in which PIM prescription is lower compared to the other ARS, is a region characterised by a lower value of pensions either retirement or disability, and lower access to GPs (47–49). We may hypothesise that the lower socioeconomic status due to the lower pensions and the lower access to GPs of individuals from Algarve in 2020 (47, 48, 50) might explain their lower access to the PIM prescription associated with a lower purchasing power. Moreover, a previous study also conducted in Portugal showed that Algarve region presented the lowest values of cardiovascular risk factors, although they had higher levels of smoking (33), which support our results. Additional studies also reported that Centre regions presented the higher admission and mortality rates by ischaemic heart disease (34) and one of the highest ageing ratio in 2020 (51), which might further explain the higher prescription in Centre region. Nevertheless, more research is required to investigate geographic differences in prescription by regions since they might be associated to over or undertreatment and may require public health policies to reduce inappropriate prescribing (20, 37).

The PPI prescription in older adults was also found, pantoprazole in males and both pantoprazole and omeprazole in females. Evidence is consistent showing the associations between longer duration of PPI therapy and numerous adverse effects that are a concern in older adults such as, osteoporotic-related fractures, infections, community-acquired pneumonia, vitamin B12 deficiency, kidney disease, and dementia (52, 53). Although in our study we could not assess the inappropriate use of these active substances since we do not have information on the treatment duration, the high prescription of PPI and the presence of geographic differences alert for the need of periodically evaluations on the use of these active substances, considering the importance of investments for treatment discontinuation in this population.

Strengths and limitations

The national coverage of the prescribed active substances to the entire Portuguese older adults is the strong point of this study, as it provides a prescription profile alerting for the risks of inappropriate prescribing in this population. Some limitations should also be recognised. The main limitation of our study design is the ecological fallacy since individual data was not available and the study of the Portuguese regions might be subject to aggregation bias. Although not

available, data on the individuals' health conditions and socioeconomic indicators would strengthen our results. Another limitation of this study is associated with the data source, as our data on active substances prescription were only obtained from the outpatient care of the public health sector, and not from the private sector, and may thus not reflect the total prescription within the population. Finally, the cross-sectional nature of the study limits the ability to detect the inappropriate use of PPI by the application of all criteria of the EU(7) PIM List. Additional longitudinal studies might help to further elucidate this issue.

Conclusion

This study found that four of the 10 most prescribed active substances to older adults belong to the cardiovascular system group, regardless of sex, suggesting the high prevalence of cardiovascular diseases in this population. The prescription of benzodiazepines and opioids in females, classified as PIM, alert for the need of public health policies to reduce inappropriate prescribing. Geographic differences in the top-10 most prescribed active substances and in PIM highlighted the importance of medication optimisation across regions to improve health and wellbeing of older adults, and consequently reduce health costs.

Declarations

Conflicts of Interest:

The authors have no conflicts of interest to be disclosed.

Data availability statement:

Data included in this study are de-identified and are publicly available from the official System of Information and Monitoring of the Portuguese National Health System platform – section “how we do – como fazemos” [<https://bicsp.min-saude.pt/pt/biufs/Paginas/default.aspx>]

Authors' contributions:

FR, AF and MTH conceived the study. AP, DR and ABT performed data collection. VR performed data analysis and interpretation and drafted the manuscript. All authors critically revised the manuscript, ensured accuracy and integrity of the work, approved the final version to be published, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate:

not applicable – data from this study was obtained from a public-access database.

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Figures

Figure 1

Mean number of defined daily dose per 1000 inhabitants per day of top-10 ATCs level 5, stratified by sex and age in all Portuguese regions.

Figure 2

Defined daily dose (DDD) per 1000 inhabitants per day in top-10 ATCs level 5, by health administrative regions (ARS) in males. Legend: ARS - North (ARSN), Centre (ARSC), Lisbon-Tejo Valley (ARSLVT), Alentejo (ARSALE), Algarve (ARSALG).

Figure 3

Defined daily dose (DDD) per 1000 inhabitants per day in top-10 ATCs level 5, by health administrative regions (ARS) in females. Legend: ARS - North (ARSN), Centre (ARSC), Lisbon-Tejo Valley (ARSLVT), Alentejo (ARSALE), Algarve (ARSALG).

Figure 4

Defined daily dose (DDD) per 1000 inhabitants per day of potentially inappropriate medication (PIM), by health administrative regions (ARS). Legend: ARS - North (ARSN), Centre (ARSC), Lisbon-Tejo Valley (ARSLVT), Alentejo (ARSALE), Algarve (ARSALG).

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