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Original Research

# Potentially Inappropriate Medication Prescribing in Older Adults According to EU(7)-Potentially Inappropriate Medication List: A Nationwide Study in Portugal

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ABSTRACT

*Background:* Portugal has among the highest rates of dependency among older adults in Europe. Older adults with aging-related comorbidities are prone to the use of potentially inappropriate medication (PIM).
*Objective:* The aim of this study was to analyze PIM prescriptions in older Portuguese adults, as well as the change rate of PIM prescriptions over time, and assess the geographical variability between the different regions of mainland Portugal.
*Methods:* Using a national database, PIM prescriptions were analyzed for older adults (aged 65 years and older) between 2019 and 2021 from 2 perspectives: PIM-defined daily dose (DDD) frequency (%) and DDD per 1000 inhabitants per day (DID).
*Results:* Overall, mainland Portugal presented a PIM DDD frequency of 9.20%, which was relatively higher in Alentejo and Centro and lower in the North. Alprazolam, fluoxetine, and rivaroxaban were PIM with higher DDD frequency values. Over the years, the DID change rates for these three PIM were −3.80%, −14.86%, and +18.54%, respectively, depending on the geographic region. Alprazolam and fluoxetine were mostly prescribed to older women, whereas rivaroxaban was mostly prescribed to older men.
*Conclusions:* These results emphasize the need to implement initiatives and interventions to decrease PIM prescriptions in older adults.



## Introduction

Aging involves pharmacokinetic and pharmacodynamic changes.[1] Older adults have a reduced ability to adjust to external environmental changes, increased susceptibility to disease, and a reduced ability to recover, which leads to a modified drug response and greater vulnerability to adverse drug reactions.[2–4]

Beyond this, aging-related comorbidities lead older adults to multiple treatments, increasing the complexity of therapeutic management,[5] and the concomitant use of 5 or more medicines (ie, polypharmacy) can easily arise,[6] potentiating the occurrence of medication-related problems[7] and increasing the need for health resources. Overall, polypharmacy is associated with the use of potentially inappropriate medication (PIM), which can be defined as drugs that should be avoided in older adults because the risk of

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potential adverse events outweighs the clinical benefit, particularly when safer or more effective alternatives are recommended for use in this population.[8–10] PIM use is associated with an increased risk of hospitalization and poor clinical outcome.[11] Therefore, several tools have been developed to assess the appropriateness of medication and to reduce PIM use in older adults.[12] The EU(7)-PIM list is an explicit criteria tool developed in 2015 by experts from seven European countries (Germany, Finland, Estonia, Holland, France, Spain, and Sweden) that identified 282 PIMs.[8] Recently, our research team operationalized the EU(7)-PIM list for Portuguese reality, publishing a list with 184 PIMs, within 178 active principles and 6 drug classes.[13]

The world is facing a change in the distribution of older ages and it is expected that the European old-age dependency ratio will increase from about 34% in 2019 to 59% in 2070,[14] which will increase the demand for tools that promote the optimization of pharmacotherapy of older adults to optimize health resources. A recent study found that the worldwide prevalence of PIM in primary care settings was 19.1%.[15] Additionally, polypharmacy has been reported to be a statistically significant risk factor for PIM in community-dwelling older adults.[16,17] According to a recent systematic review, 24 studies were performed in European countries aiming to reduce PIM use in the older population[18]; however, no PIM intervention studies have been published in Portugal, reinforcing the need to develop studies in this field and to alert Portuguese health entities for PIM used by older adults and to guide the development and implementation plan to guarantee an appropriate medication use.

As in other European countries, Portugal has a high percentage of older adults (23.4%) and the dependency rate of the older population is higher than that of Europe (38.6%).[19] Although some studies have been carried out in Portugal that show a high percentage of PIMs, these studies were conducted in restricted settings (hospitalized, primary care, or institutionalized older patients)[20–23] and specific populations (with cerebrovascular and cardiovascular diseases).[24] To address this gap, this study analyses the Portuguese National Health System database prescribing medication data for the entire Portuguese-aged population using the EU(7)-PIM list. The aim of this study was to analyze PIM prescriptions to Portuguese older adults. It also intended to analyze the change rate of PIM prescriptions over time and assess the geographical variability between the different regions of mainland Portugal.

## Materials and Methods

### *Study design and study population*

A retrospective nationwide population-based study to evaluate PIM-prescribing according to the EU(7)-PIM list in primary health care between January 2019 and September 2021 for all persons aged 65 years and older in mainland Portugal, who were reported in the official System of Information and Monitoring of the Portuguese National Health System. This public-access platform was created by the shared services of the Health Ministry (Serviços Partilhados do Ministério da Saúde).[25] Data were collected from a national public database that provided aggregated and previously anonymized data without any reference to identifiable individuals; therefore, no ethics approval was required.[26]

### *Study medication*

The selection of PIM medicines included in this study was performed by applying the EU(7)-PIM list[8] adapted to Portuguese reality.[14] Given the information available from the database, it was not possible to apply all criteria of the EU(7)-PIM list. Therefore, the following drugs were excluded from the analysis: drugs in which the classification of PIM was dependent on the dose and/or duration of treatment and/or therapeutic scheme, drugs classified as PIM that have lost their marketing holder in Portugal, drugs classified as PIM that are not currently being marketed in Portugal,[27] and PIM medicines without defined daily dose (DDD).

### *Data source*

The database provides information that allows the characterization and monitoring of all functional units of primary health care through the consolidation and centralization of data from the clinical and administrative activities of most units providing care, according to the Portuguese National Health System.[25] It was accessed between September 1 and November 30, 2021, and information regarding PIM prescriptions was extracted. Data included: active substance, sex (female or male), age group (between 65-74 and ≥75 years), DDD and Regional Health Administration (Administração Regional de Saúde [ARS]) of Algarve (ARSALG), Alentejo (ARSALE), Centro (ARSC), Lisbon and Tagus Valley (ARSLVT), and the North (ARSN).

### *Statistical analysis*

Numerical and ordinal data were presented in terms of frequency. The prescription of PIM according to the EU(7)-PIM list was analyzed from 2 perspectives: PIM DDD frequency (%), calculated as the number of DDDs of each PIM divided by the total number of DDDs prescribed during the same period and ARS to older people, and DDD per 1000 inhabitants per day (DID) value, in which inhabitants were considered the number of the older population according to the National Institute for Statistics (Instituto Nacional de Estatística).[28] The change rate (%) was calculated as the difference between the DID values in 2021 and 2019 divided by the DID value in 2019. The cumulative DID value was calculated by considering the average number of older people during the 3 years of the study.

## Results

### *Selection of the medicines*

Among the 184 different PIM identified in the Portuguese version of EU(7)-PIM list, included in this study were a total of 140 PIMs, within 138 active substances and 2 drug classes, such as estrogens (G03C) and selective serotonin-5HT1-agonists (N02CC). The remaining PIMs were excluded because the classification as PIM is dose and/or duration of treatment, or drug regiment-dependent (n = 22 PIMs), the medicines lost their marketing holder in Portugal (n = 6 PIMs); they were not being marketed in Portugal (n = 12 PIMs) or there is a lack of DDD information (n = 4 PIMs) (see Supplemental Table 1 in the online version at doi:xxxxxxx).

### *Population*

The study population comprised 2.3 million older people aged 65 years and over, with approximately 58% being women. ARSLVT and ARSN together account for more than half of the older population in mainland Portugal, while ARSALG contains only 4.46% of the total older population in the country (see Supplemental Tables 2, 3, and 4 in the online version at doi:xxxxx).

### *Frequency of PIMs*

During the study period, 1.232 billion DDD of PIM were prescribed. Overall, the frequency of PIM DDD was 9.20% (Figure 1).

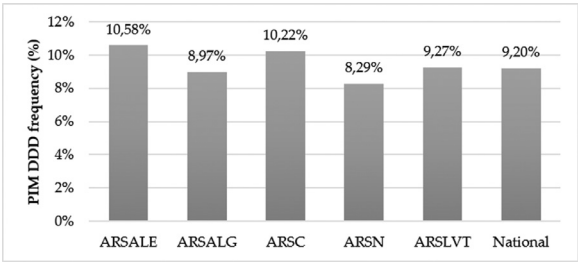


**Figure 1.** Potentially inappropriate medication (PIM) defined daily dose (DDD) frequency (%) by Regional Health Administration. ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

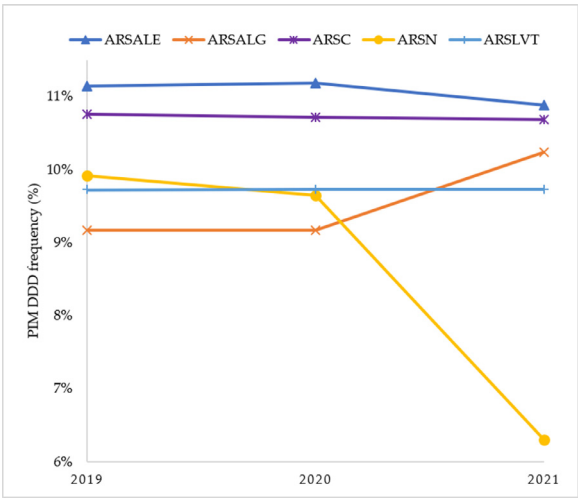


**Figure 2.** Potentially inappropriate medication (PIM) defined daily dose (DDD) frequency (%) by Regional Health Administration. ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

Of the 5 ARSs, ARSALE and ARSC had the highest PIM DDD frequencies (10.58% and 10.22%, respectively). This observation suggests that PIM with higher DDD was prescribed in these ARS, in contrast to ARSN and ARSALG with a PIM DDD frequency of 8.29% and 8.97%, respectively.

Although the extracted data do not include the full year 2021, Figure 2 suggests a trend toward an increase in the PIM DDD frequency values in ARSALG (9.74%). In contrast, in the ARSN, there was a tendency for a decrease in the PIM DDD frequency in 2021 (5.80%). In the remaining ARSs, the PIM DDD frequency values remained stable over time.

The analysis of PIM DDD frequencies revealed that alprazolam, fluoxetine, rivaroxaban, venlafaxine, and apixaban were the 5 PIMs with the highest prescription values. Figure 3 shows that the PIM DDD frequency was higher for alprazolam, particularly in ARSC (1.34%). Similarly, fluoxetine had a higher DDD frequency in ARSC (0.53%), although very similar frequencies were observed throughout the country. In contrast, the DDD frequency of venlafaxine was higher in ARSALE (0.68%). For the remaining PIM, the differences between each ARS were minor. These results suggest similar prescription patterns at the national level.

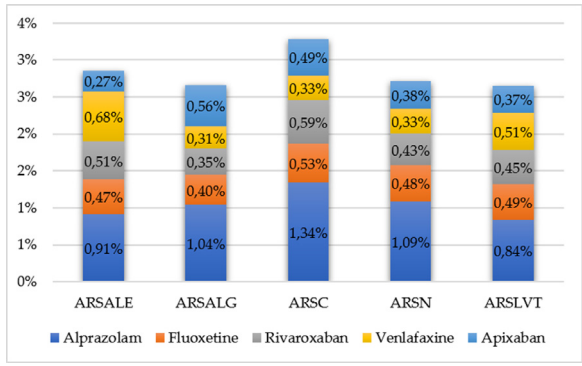


**Figure 3.** Potentially inappropriate medication (PIM) defined daily dose (DDD) frequencies of alprazolam, fluoxetine, rivaroxaban, venlafaxine, and apixaban by Regional Health Administration. ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

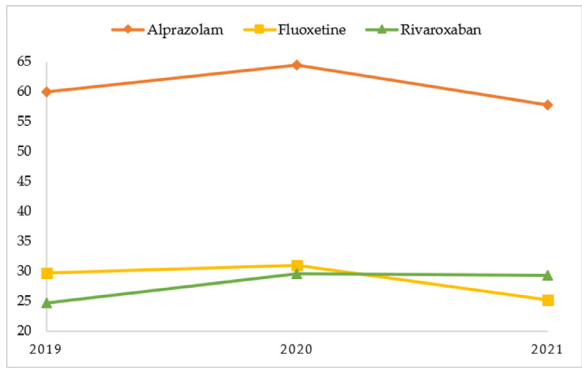


**Figure 4.** Prescriptions of alprazolam, fluoxetine, and rivaroxaban during 2019-2021 expressed in defined daily dose (DDD) per 1000 inhabitants per day (DID).

### *Trends and change rate of PIM prescriptions*

Regarding the top-5 PIMs with the highest DDD frequencies, alprazolam belongs to the anxiolytics group (N05B), fluoxetine and venlafaxine are antidepressants (N06A), and apixaban and rivaroxaban are both antithrombotic agents (B01A). Among these, alprazolam, fluoxetine, and rivaroxaban presented higher DDD frequency values and so more extensive analyses were performed.

Prescription over the years for alprazolam, fluoxetine, and rivaroxaban at a national level and according to each ARS level is represented in Figures 4 and 5, respectively, and in more detail in Supplemental Tables 5 and 6 (in the online version at doi:xxxxx). Between 2019 and 2021, the DID of alprazolam decreased from 60.01 in 2019 to 57.73 in 2021, with a change rate of 3.80%. Although this slight trend was verified at the national level, the regional analysis revealed that the decrease was more evident in the ARSN (28.16%). The ARSLVT registered the largest increase in alprazolam prescription (11.75%). The prescription of fluoxetine registered the greatest decrease from 29.68 DID in 2019 to 25.27 DID in 2021, with a 14.86% change rate. A greater decrease occurred in ARSN (41.11%), whereas the only increase occurred in ARSLVT (5.79%). Nevertheless, rivaroxaban showed the greatest increase between 2019 and 2021, from 24.74 DID to 29.33 DID (18.54%). ARSLVT showed the largest increase (41.92%), followed by ARSALE (31.22%), ARSALG (20.79%), and ARSC (10.86%). Only ARSN showed a decrease in rivaroxaban prescription (4.20%).

Regarding sex and age group differences, ARSC, ARSLVT, and ARSALE often presented the highest DID values for the three PIM an-

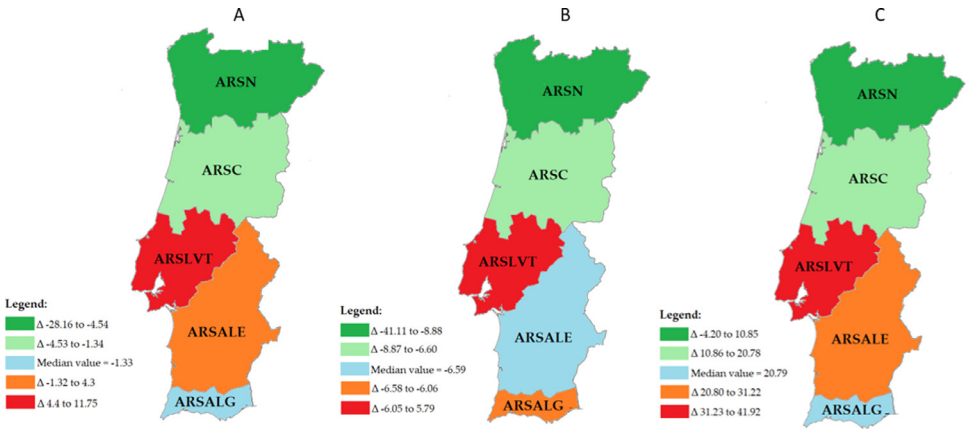


**Figure 5.** Change rate of alprazolam (A), fluoxetine (B), and rivaroxaban (C) prescriptions in Portugal between 2019 and 2021. ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

**Table 1**
Sex and age group differences in alprazolam, fluoxetine, and rivaroxaban prescription according to each Regional Health Administration over the years.

| | Defined daily dose/1000 inhabitants*/d | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2019-2021 | | | | | | | | | |
| | Female | | | | | Male | | | | |
| | ARSN | ARSC | ARSLVT | ARSALE | ARSALG | ARSN | ARSC | ARSLVT | ARSALE | ARSALG |
| Alprazolam (N05BA12) | 77.46 | 96.77 | 67.13 | 77.20 | 47.92 | 39.56 | 46.90 | 33.48 | 31.94 | 24.28 |
| Fluoxetine (N06AB03) | 39.46 | 42.09 | 43.72 | 42.42 | 27.34 | 10.80 | 13.02 | 12.75 | 12.50 | 10.51 |
| Rivaroxaban (B01AF01) | 21.98 | 29.22 | 25.11 | 29.48 | 15.19 | 27.03 | 38.21 | 33.52 | 36.84 | 20.31 |
| | 2019-2020† 65-74 y | | | | | | | | | |
| | ARSN | ARSC | ARSLVT | ARSALE | ARSALG | ARSN | ARSC | ARSLVT | ARSALE | ARSALG |
| Alprazolam (N05BA12) | 89.11 | 95.67 | 63.07 | 75.35 | 49.38 | 43.75 | 44.36 | 30.36 | 28.37 | 24.20 |
| Fluoxetine (N06AB03) | 58.51 | 55.99 | 54.00 | 58.66 | 32.94 | 12.58 | 13.95 | 11.87 | 12.01 | 10.00 |
| Rivaroxaban (B01AF01) | 13.80 | 16.82 | 13.63 | 17.64 | 9.05 | 19.22 | 25.53 | 21.54 | 25.13 | 15.83 |
| | 2019-2020† ≥75 y | | | | | | | | | |
| | ARSN | ARSC | ARSLVT | ARSALE | ARSALG | ARSN | ARSC | ARSLVT | ARSALE | ARSALG |
| Alprazolam (N05BA12) | 79.83 | 99.91 | 67.65 | 77.71 | 47.31 | 45.50 | 53.36 | 35.91 | 35.50 | 26.38 |
| Fluoxetine (N06AB03) | 31.14 | 32.19 | 32.57 | 31.21 | 23.17 | 11.81 | 13.52 | 13.68 | 14.27 | 12.41 |
| Rivaroxaban (B01AF01) | 32.50 | 38.66 | 32.28 | 35.28 | 19.85 | 40.41 | 52.81 | 42.43 | 46.20 | 25.24 |

ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

* Inhabitant is defined as the number of the older population (aged 65 years and older) according to each region in Portugal.

† Defined daily dose per 1000 inhabitants per day stratified by age was calculated only between 2019 and 2020 because the official data for the older population in 2021 are grouped only in the "over 65 years" group.

alyzed (Table 1 and the Supplemental Figure in the online version at doi:xxxx). Alprazolam was most commonly prescribed to older women aged 75 years or older in ARSC (99.91 DID), whereas fluoxetine was prescribed to older women aged between 65 and 74 years in ARSALE (58.66 DID). Rivaroxaban was most commonly prescribed in older men aged 75 years or older in the ARSC group (52.81 DID). The lowest prescriptions were recorded in the ARSALG for all sex and age groups for the 3 PIM analyzed. Alprazolam and fluoxetine were less prescribed in older men aged between 65 and 74 years (24.20 and 10.00 DID, respectively). Rivaroxaban presented the lowest value in older women aged between 65 and 74 years (9.05 DID).

The distribution of DID in the 5 ARSs from mainland Portugal was analyzed in relation to the prescription of alprazolam, fluoxetine, and rivaroxaban according to age group. Regarding alprazolam (Figure 6A), ARSALE and ARSLVT are notable because of their similar levels of use and different age ranges. The same was true for fluoxetine and rivaroxaban (Figures 6B and 6C, respectively); however, in addition to ARSALE and ARSLVT, ARSC was also noted for different age ranges but similar levels of use.

## Discussion

This study analyzed PIM prescriptions for the entire Portuguese population older than age 65 years between 2019 and 2021. A PIM DDD frequency of 9.20% was observed during the study period. However, there was a high geographic variability regarding PIM frequency, and the data suggest a trend toward an increase in ARSALG, whereas in ARSN there was a tendency to decrease. The results indicated that, for the applied criteria, alprazolam was the PIM with the higher DID value followed by fluoxetine and rivaroxaban. For alprazolam and fluoxetine, the DID values showed a slight tendency to decrease over time, whereas an inverse trend was observed for rivaroxaban. It is important to note that the use of these criteria does not replace the clinical judgment made by the clinical practitioner according to each patient's health condition.

In line with our findings, PIM belonging to the central nervous system medications (alprazolam and fluoxetine) were the most prescribed in studies worldwide, regardless of the PIM criteria used. A cross-sectional study performed on 193 nursing home residents in the district of Viseu in Portugal found that 79.3% of older

**Table 2**
Definitions of abbreviations used.

| Abbreviation | Definition | Explanation |
|---|---|---|
| ACSS | Central Administration of the Health System | Public institute with administrative and financial autonomy that ensures the management of financial and human resources, facilities, and equipment of the Portuguese National Health Service, as well as the implementation of policies, standardization, regulation, and planning in health* |
| ADR | Adverse drug reaction | A response to a medicinal product that is noxious and unintended# |
| ARS | Regional Health Administration | Public institute integrated into the indirect administration of the Portuguese State, with administrative and financial autonomy and its own patrimony£ |
| ATC | Anatomical Therapeutic Chemical Classification System | A unique code assigned to a medicine according to the organ or system it works on and how it works. The classification system is maintained by the World Health Organization§ |
| DDD | Defined daily dose | The assumed average maintenance dose per day for a drug used for its main indication in adults† |
| PIM | Potentially inappropriate medication | Drugs that should be avoided in older adults because the risk of potential adverse events outweigh the clinical benefit, particularly when there are safer or more effective alternatives available that are recommended to be used in this population[8–10] |

* Ministério da Saúde. ADMINISTRAÇÃO CENTRAL DO SISTEMA DE SAÚDE. https://www.acss.min-saude.pt/ (acessed on 8 January 2022)
# Medicines Agency E. Guideline on Good Pharmacovigilance Practices (GVP)-Module VICollection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products (Rev 2). 2017. Available online: "http://www.ema.europa.eu" (accessed on 8 january 2022)
£ Serviço Nacional de SAúde; SNS. Available online: https://www.sns.gov.pt/institucional/ministerio-da-saude/
§ European Medicines Agency. ATC code. Glossary. Available online: https://www.ema.europa.eu/en/glossary/atc-code (accessed on 8 january 2022)
† "World Health Organization. Defined Daily Dose (DDD). Definition and general considerations. Available online: https://www.who.int/tools/atc-ddd-toolkit/about-ddd. (acessed on 7 january 2022)


**Figure 6.** Distribution of Regional Health Administration in relation to prescription (defined daily dose per 1000 inhabitants per day [DID]) of (A) alprazolam, (B) fluoxetine, and (C) rivaroxaban. ARSALG = Administração Regional de Saúde of Algarve; ARSALE = Administração Regional de Saúde of Alentejo; ARSC = Administração Regional de Saúde of Centro; ARSLVT = Administração Regional de Saúde of Lisbon and Tagus Valley; ARSN = Administração Regional de Saúde of the North.

people took PIMs, with short-acting benzodiazepines (alprazolam) as the major pharmacological group.[20] We performed a study on polymedicated older patients from 38 primary care units in central Portugal, and 35.9% were taking at least 1 benzodiazepine included in the EU(7)-PIM list.[13] A cross-sectional study conducted in primary care in Thailand found that the prevalence of PIM prescriptions was 65.9%, and the most frequent ones were antidepressants and benzodiazepines.[29] In Switzerland, 76.7% of older patients followed by private family medicine practices had at least 1 PIM, and benzodiazepines (21.5%) were among the most frequently prescribed medications.[30] Similar results were observed in a study performed in a primary health care unit in southern Brazil, in which benzodiazepines stood out among other PIM.[31] Additionally, another study showed that for active drivers aged 65 to 79 years, PIM prevalence was 18.5%, and the most frequently used PIM drug class was benzodiazepines, accounting for 16.6% of the total PIMs identified.[32]

The most prescribed PIM belongs to the anxiolytics group, which is in accordance with the Organization for Economic Cooperation and Development (OECD) database, which reports that Portugal is among the OECD countries with the highest consumption of this pharmacological group.[33] According to the European Monitoring Center for Drugs and Drug Addiction, benzodiazepines are widely prescribed, particularly alprazolam because it presents a more rapid onset of action with a half-life of 6 to 24 hours.[34] In addition, alprazolam is frequently associated with drug-related deaths.[34] According to the EU(7)-PIM list, alprazolam is defined as a PIM because it causes a risk of falls resulting in hip fracture, prolonged reaction times, psychiatric reactions (can also be paradoxical; for example, agitation, irritability, hallucinations, and psychosis), cognitive impairment, and depression. It is recommended to use the lowest possible dose in the older population and for the shortest possible period.[8]

Regarding the use of antidepressants, according to the OECD, Portugal had the second highest antidepressant DID value in 2020 (131.1), surpassed only by Iceland (153.4).[33] This is in line with a previous study that reported that the estimated prevalence of anxiety and depression among Portuguese older adults is 9.6% and 11.8%, respectively.[35] According to the EU(7)-PIM list, fluoxetine causes central nervous system side effects (such as nausea, insomnia, dizziness, and confusion), and hyponatremia.[8]

As reported elsewhere, the use of fluoxetine is prevalent among older adults, increasing annually, particularly in those who report anxiety disorders, loneliness, and a lack of familiarity and social support.[36] Reducing the dose and avoiding the administration of fluoxetine at bedtime are specific recommendations for their use in older people.[8]

The prescriptions of alprazolam and fluoxetine were higher in older women. These results could be associated with the higher prevalence of anxiety and stress disorders in women.[37,38] Portugal is among the European countries with the highest share of the population reporting chronic depression in 2019 (12.2%), with higher values in women than in men.[39] Additionally, women are more prone to depression than men,[40] and psychiatric impairment is considerably more severe in women.[37,41,42] Furthermore, older women may be more likely to have benzodiazepine and antidepressant prescriptions because there is an increased risk of depression in postmenopausal women.[43,44]

The increased prevalence and incidence of blood-related disorders in older adults, such as venous thromboembolism and deep-vein thrombosis,[45,46] could explain why rivaroxaban presents with high DID values and shows a tendency to increase. This trend could be related to rivaroxaban prescription as an alternative to warfarin because it does not require regular monitoring and has few drug and food interactions.[47–49] However, according to the EU(7)-PIM list, there is limited information on rivaroxaban use in older adults, risk of bleeding events, and no reversal agent available in case of overdose.[8] The risk of bleeding may be higher in cases of severe renal failure.[8]

A study performed in England observed that the prescription of direct oral anticoagulants, such as rivaroxaban, increased from 9% in 2014 to 74% in 2019, whereas warfarin declined accordingly.[50] In Chinese hospitals, rivaroxaban was among the top-5 medications sold in 2014.[51] The recommendation is to reduce the dose for adults aged 65 years and older and avoid its use when creatinine clearance values are $>30$ mL/min.[8]

Unlike alprazolam and fluoxetine, rivaroxaban was prescribed more to older men. This result could be related to the higher incidence of atrial fibrillation in men than in women.[52,53] Moreover, according to previous studies, anticoagulant treatment is underused in women.[54,55] Other authors also reported that women are less likely to receive oral anticoagulation therapy than men because the risk for heart disease among women is not fully appreciated, and clinicians could minimize the risk.[56]

Although Portugal is a small country, it has many sociodemographic differences, especially in ARSALE and ARSC, which have high old-age rates (207.5 and 205.2, respectively), above the national average (165.1).[57] In this study, it was observed that there were some asymmetries in alprazolam, fluoxetine, and rivaroxaban use between regions in mainland Portugal, revealing that PIM prescriptions may be influenced by geographical context.

After the beginning of the COVID-19 pandemic, 1 study reported an immediate decrease in anxiolytic prescriptions in older adults.[58] Besides, the effective response of the Portuguese National Health System ensures the continuity of access to medicines for patients with chronic needs, through the automatic renewal of their prescriptions.[59]

The trend of decreasing alprazolam prescriptions until 2020 could be the result of the predicted goals of the National Program for Mental Health for benzodiazepine prescriptions.[60] In addition, the ARSLVT has developed guidelines to review good practice recommendations for the use of benzodiazepines, providing the most effective strategies to promote their gradual discontinuation.[61] Additionally, the Central Administration of the Health System in collaboration with the Faculty of Medicine of Lisbon created a protocol for the chronic use of benzodiazepines, aiming to evaluate interventions to discontinue their use in primary health care.[62] However, prescribing doctors reported that the resignation to stop taking a medication that they have been taking for 25 or 30 years and not understanding that it was causing more harm than good, often made the de-prescription process difficult.[63]

This study has some limitations. First, it only includes PIM prescribed in outpatient care, excluding possible PIM administered during hospital stays. In addition, this analysis excluded dose- and duration-of-treatment-dependent PIM such as proton pump inhibitors. Recent studies have shown that proton pump inhibitors are overused (between 25% and 70% of prescriptions have no indication of use).[64] Similar results were observed in a recent Portuguese study that applied the operationalized EU(7)-PIM list and found that 43.9% of the polymedicated older adults included in the study took at least 1 proton pump inhibitor.[13] However, because this pharmacological group is dependent on the duration of treatment, it was excluded from this analysis. The same methodology has been applied to some widely prescribed benzodiazepines[65] that are dose-dependent PIM, suggesting that the results presented here may have been underestimated and there is a chance that the number of PIMs prescribed to older adults could be larger than reported in this study. Another limitation is related to the fact that the data available in this database do not allow for the correlation of the possibility of the use of PIMs being associated with a certain pathology or with the occurrence of a certain adverse drug reactions. The major strength of this study is the use of national real-world data and coverage of the entire older population of mainland Portugal, independent of their actual health status, allowing the obtaining of a representative sample of the population. In addition, this study provides valuable data to facilitate the development of prescribing quality indicators useful for the electronic monitoring of the quality of prescribing in European older people.

## Conclusions

The data obtained from this study highlight the worrying consumption in older adults of PIM in the anxiolytics and antidepressants group. Despite the implementation of national prescription measures, alprazolam prescription remains high. The tendency to prescribe alprazolam and fluoxetine was higher in older women, whereas rivaroxaban was prescribed more frequently in older men.

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## Conflicts of Interest

The authors have indicated that there are no conflicts of interest regarding the content of this article.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2022.100681.

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