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Research Article

Evaluating potentially inappropriate medications in elderly patients in a pharmacy setting in Bulgaria: A pilot study utilizing the EU (7)-PIM List

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Abstract

Objective: The primary aim of this study was to evaluate, for the first time, the use of the EU-7 PIM List in identifying potentially inappropriate medications among older patients. Researchers have firmly established the connection between drug-related problems, which include increased morbidity and mortality rates and the heightened utilization of healthcare services. While previous studies have focused on methodologies for identifying potentially inappropriate medications in Bulgaria, further research is warranted to explore the applicability of the widely recognized EU(7)- PIM List.

Materials and methods: A prospective review was conducted on patient prescriptions aligned with the National Health and Insurance Fund, explicitly focusing on patients aged over 65 years from a single pharmacy in Veliko Turnovo City, Bulgaria. The review spanned from November 2022 to April 2023. The prescriptions analyzed in this study exclusively comprised medications covered by the insurance fund. The pharmacy manager provided patient prescription data in a coded form, which included information on the patients' age, corresponding medications, and accompanying ICD codes.

Results: The study analyzed a sample of 255 patients. Healthcare providers prescribed 2,623 medications, and 61.96% of the patients had polypharmacy, taking more than five medications daily. Among the study population, 67% with polypharmacy had at least one PIM based on the EU (7)-PIM List criteria. In total, 173 potentially inappropriate medications (PIMs) were identified. The main PIMs were categorized into four groups: alimentary tract and metabolism, blood and blood-forming organs, cardiovascular system (CVS), and nervous system. Most PIMs (75.72%) were in the ATC cardiovascular system. Within the CVS category, 11 PIMs were associated with digoxin intake and 11 with antiarrhythmics such as propafenone, flecainide, and amiodarone. In addition, trimetazidine was linked to 9 PIMs, and centrally acting antiadrenergic agents had 22 PIMs, with moxonidine being the most prevalent (n=16). Peripherally acting agents were linked to 22 PIMs, primarily doxazosin. The study identified 24 PIMs related to diuretics, specifically spironolactone, and 18 PIMs related to selective calcium channel blockers such as verapamil. The antithrombotic agent category had the highest share, with 30 identified PIMs, including acenocoumarol, dabigatran, rivaroxaban, and apixaban. Furthermore, the examination of ICD codes confirmed that most PIMs occurred within CVS, with patients having ICD I11.0 and ICD I11.9 being associated with 40 and 47 PIMs, respectively.

Conclusion: This study highlights many PIMs among patients with cardiovascular diseases. Using the EU (7)-PIM List as a pilot study demonstrates its effectiveness in managing adult patients' conditions. Given the significant role of PIMs in deprescribing strategies for older patients with polypharmacy, there is a need for prescribers, educators, and drug regulatory institutions to show increased interest in regulatory measures and specific aspects related to PIM use. This is important because the demographic trend of population ageing continues, and organizations increasingly focus on the elderly population.

Keywords

cardiovascular diseases, elderly patients, EU-7 PIM List, inappropriate prescribing, polypharmacy

Introduction

According to a recent World Health Organization (WHO) report, polypharmacy is the concurrent use of multiple medications. Although there is no standard definition, polypharmacy is often defined as the routine use of five or more medications. This includes over-the-counter, prescription and traditional and complementary medicines a patient uses (World Health Organization 2019).

The clinical necessity of prescribing multiple medications (appropriate polypharmacy) is frequently observed. According to WHO, appropriate polypharmacy is present when multiple drugs are prescribed to achieve the purpose of specific therapeutic objectives with the agreement of the patient; when therapeutic objectives are achieved nowadays or in the future; when the drug therapy is oriented to minimal risk of adverse drug reactions; and when the patient is compliant and concordant with medication therapy (World Health Organization 2019). Nevertheless, exposure to multiple medications can result in harm or the continued use of no longer necessary medications (inappropriate polypharmacy). Inappropriate polypharmacy has been linked to various adverse health outcomes, particularly in older adults with multiple chronic conditions, including an elevated risk of mortality, falls, drug interactions, non-adherence, and hospitalization. Polypharmacy has emerged as a significant burden on healthcare systems and represents a significant phenomenon within the elderly population (Davies et al. 2020).

Population ageing began several decades ago and has been a long-term trend across Europe. The population of the EU is estimated to be 446.7 million as of 1 January 2022. The proportion of the population aged 65 and over in Europe is 21.1% of the total population. Another aspect of population ageing is the progressive ageing within the older population itself, as the relative importance of the elderly increases faster than any other age group within the EU population. The EU population's share of individuals aged 80 and over is projected to double between 2022 and 2100, increasing from 6.1% to 14.6% (Eurostat 2023). The data for Bulgaria is not different from that of Europe as a whole, as indicated by the reference from the National Statistical Institute, which states that individuals aged 65 and over comprise 22% of the population (National Statistical Institute in Bulgaria, https://www.nsi.bg/bg/content/2994). Considering the trend of ageing populations and the fact that polypharmacy is particularly prevalent in this patient population, healthcare systems have an increasing focus on implementing methodologies and principles to prevent and control polypharmacy. Efforts are being made to develop and implement strategies to prevent, identify, and manage inappropriate polypharmacy.

Pharmacist-involved medication review procedures have been proposed to identify, resolve, and prevent drug-related issues, ultimately leading to improved outcomes in patients' drug therapy. A cross-sectional online survey was conducted in 2011 across all 28 European Union countries and four additional European countries (total n=32). The survey aimed to assess medication review practices regarding prescription, adherence and clinical medication reviews. The findings revealed that, out of all the countries surveyed, 64% had implemented some form of medication review procedures. However, it was noted that Bulgaria did not incorporate the evaluation of adherence as part of its medication review process (Bulajeva et al. 2014). Another approach to address inappropriate polypharmacy and optimize medication use is implementing deprescribing mechanisms. Deprescribing, which refers to the supervised withdrawal of medications that may no longer provide benefit or may be causing harm, is recognized as a critical strategy for addressing the complex problem of polypharmacy. It is considered a crucial approach in tackling this significant public health concern on a global scale (Reeve et al. 2015). A growing global emphasis on deprescribing has led to the establishment of various networks facilitating multidisciplinary collaboration among professionals. In Europe, notable networks include the English Deprescribing Network (EDeN) and the Network of European Researchers in Deprescribing (NERD). These networks serve as platforms for professionals to exchange knowledge, conduct research, and promote best practices in deprescribing. Nevertheless, a shared consensus regarding the optimal practices and approaches for deprescribing interventions in diverse cultures, healthcare systems, and clinical environments still needs to be improved.

Potentially inappropriate prescribing (PIP) is a consequence of polypharmacy. It encompasses various suboptimal prescribing practices, such as inappropriate dosage or duration of medication, drug interactions, drug-disease interactions, and the use of medications associated with a high risk of adverse drug events (Clyne et al. 2016). Numerous internationally available tools and frameworks are designed to identify inappropriate prescribing practices and support deprescribing efforts, especially in the elderly population. In recent years, efforts have been made to develop and refine these methodologies, aligning them with European countries' specific needs and healthcare systems. These tools aim to enhance medication review processes, promote deprescribing practices, and improve patient safety by reducing the use of potentially inappropriate medications.

The EU (7)-PIM list is a screening tool developed with experts from seven European countries. It facilitates

identifying and comparing potentially inappropriate medication (PIM) prescribing patterns for older individuals across different European countries. The list was developed with experts from different European regions – Scandinavia, Southern, Eastern and Central Europe. The complete EU(7)-PIM list comprises 275 chemical substances, including two combinations of two chemical substances, plus seven drug classes, belonging to 55 therapeutic classes and 34 therapeutic groups (Renom-Guiteras et al. 2015).

The successful application of the EU(7)-PIM list in various studies conducted across all European regions demonstrates its efficacy in identifying potentially inappropriate medications (PIMs) in diverse healthcare and prescribing settings (Grina and Briedis 2017; Stojanović et al. 2021). Considering that the EU(7)-PIM List was developed through a broad consensus among European experts from diverse regions, this pilot study aims to evaluate the suitability and applicability of this tool within the prescribing practices in Bulgaria.

Materials and methods

Study design

In this pilot study, a prospective review was conducted to analyze patient prescriptions obtained in Veliko Turnovo City, Bulgaria, explicitly focusing on individuals aged 65 years or older; the review period extended from November 2022 to April 2023. The prescriptions under investigation exclusively consisted of medications the National Health and Insurance Fund covered. To ensure privacy and confidentiality, the pharmacy manager provided the patient prescription data in a coded format, which included details on patients aged 65 years and above, the medications prescribed, and accompanying ICD codes.

Inclusion and exclusion criteria

The study included individuals aged 65 years and older who received their medications from the designated pharmacy. The sole inclusion criterion was the age of the patients, with no additional specific limitations or constraints outlined. For clinical data, the study did not have access to specific patient health records and instead relied on medication intake, confirmed by ICD codes signifying the patients' diagnoses.

Ethics

The pharmacy manager, who also serves as the privacy administrator, protected personal data by providing the research data in a coded format that did not include identifiable information. Before the data transfer, the pharmacy manager provided informed consent, demonstrating their understanding of the research objectives and willingness to contribute to the study. Only the prescriptions of patients who agreed to participate were included in the analysis.

Results

Medication profile and identification of PIMs

The analysis of the sample encompassed 255 patients. Among the participants, 54% fell within the age range of 70 to 79 years, indicating a significant representation of this demographic. Additionally, 11% of the patients were aged 85 or older (Table 1).

Table 1. Age groups of the study population.

Age (years)	Nr of patients
65–69	44 (17.25%)
70–74	70 (27.45%)
75–79	68 (26.67%)
80–84	44 (17.25%)
>85	29 (11.37%)

During this timeframe, 2 623 medications were prescribed, encompassing 1 328 prescriptions (Table 2).

Table 2. Medications and prescriptions among the study population.

Characteristics:	Nr
Total nr of patients with PIM	170
Total Nr of medications	2623
Total Nr of prescriptions	1328
Total Nr of PIM	173

The findings revealed that 61.96% of the patients had polypharmacy, defined as the daily intake of more than five reimbursed medications. In contrast, 38.13% of the patients took fewer than five medications per day, as shown in Table 3.

Table 3. Distribution of patients based on medication intake.

Number of medications	Nr (%)
1–2	27 (10.59%)
3–4	70 (27.45%)
5–6	67 (26.28%)
7–8	48 (18.82%)
9–10	25 (9.80%)
>10	18 (7.06%)

A total of 173 PIMs in 170 patients with polypharmacy were identified when applying EU (7)-PIM List criteria. This accounted for 67% of the study population having at least one PIM.

Based on the ATC-1st level classification, the main PIMs fall into four groups: The alimentary tract and metabolism, blood and blood-forming organs, cardiovascular system (CVS), and Nervous system (Table 4).

Table 4. Number of PIMs based on ATC classification.

ATC-1st level		Nr of PIMs identified (%)
A	Alimentary tract and metabolism	10 (5.78%)
B	Blood and blood-forming organs	30 (17.34%)
C	Cardiovascular system	131 (75.72%)
N	Nervous system	2 (1.16%)

The majority of PIMs were in the ATC Cardiovascular system – 75.72%. Out of the identified CVS PIMs, 11 were associated with Digoxin intake, while 11 others were linked to the intake of antiarrhythmics, including propafenone (n=7), flecainide (n=2), and amiodarone (n=2). Trimetazidine was associated with 9 PIMs. Many PIMs were attributed to antiadrenergic agents, with centrally acting agents accounting for 22 cases. Most PIMs were linked to moxonidine (n=16) among the centrally acting agents. On the other hand, peripherally acting agents were connected to 22 PIMs, particularly associated with doxazosin. The significant number of PIMs related to diuretics is worth discussing, with 24 associated with spironolactone intake. Additionally, the Selective calcium channel blockers group merits examination, with 18 PIMs related to verapamil, which raises essential considerations regarding its usage and safety profile. Among other ATC groups, the Antithrombotic agent's category represents the highest share, with 30 identified PIMs. This group includes specific drugs such as acenocoumarol (n=11), dabigatran (n=1), rivaroxaban (n=8), and apixaban (n=10), which call for scrutiny and evaluation in terms of their appropriateness and potential risks in clinical practice (Table 5).

Furthermore, the examination of the ICD Codes validates that the PIMs predominantly occur within CVS. Specifically, patients with ICD I11.0 (Hypertensive heart disease with (congestive) heart failure) and ICD I11.9 (Hypertensive heart disease without (congestive) heart failure) were found to have 40 and 47 identified PIMs, respectively. The cumulative count of PIMs identified within the Cardiovascular Disease ICD Codes amounts to 161 (Table 6).

Discussion

This is the first study assessing the potential inappropriate prescribing in elderly patients using the EU (7)-PIM List in the secondary healthcare setting in Bulgaria, aiming to assess potential inappropriate medication patterns among elderly patients who receive their medications in line with the health insurance fund.

The results of the current study partially validate a prior analysis conducted in Bulgaria using the STOPP START methodology in patients with cardiovascular diseases (Krustev et al. 2022). As an example, digoxin is frequently prescribed in Bulgaria to treat heart failure and atrial fibrillation, according to currently performed studies. However, in geriatric patients, altered pharmacokinetics can increase digoxin toxicity risk (Hanratty et al. 2000). Another illustration pertains to centrally-acting antihypertensives like clonidine, moxonidine and aldosterone antagonists like spironolactone. These INNs are commonly included in various tools for evaluating inappropriate prescribing due to their propensity for drug interactions, risk of orthostatic hypotension, bradycardia, and an increased likelihood of hyperkalemia and hyponatremia (in the case of spironolactone) (Renom-Guiteras et al. 2015).

The results unequivocally demonstrate that the predominant occurrence of PIMs was observed within the CVDs

Table 5. Identified PIMs based on EU (7)-PIM List.

ATC-Code	Potentially inappropriate drugs	Nr of PIMs identified
A	**Alimentary tract and metabolism**	
A10B	***Blood glucose lowering drugs, excl. insulins***	
A10BB12	Glimepiride	5
A10BF01	Acarbose	5
B	**Blood and blood-forming organs**	
B01A	***Antithrombotic agents***	
B01AA07	Acenocoumarol	11
B01AE07	Dabigatran	1
B01AF01	Rivaroxaban	8
B01AF02[i]	Apixaban	10
C	**Cardiovascular system**	
C01A	***Cardiac glycosides***	
C01AA05	Digoxin	11
C01B	***Antiarrhythmics, Class I and III***	
C01BC03	Propafenone	7
C01BC04	Flecainide	2
C01BD01	Amiodarone	2
C01E	***Other cardiac preparations***	
C01EB15	Trimetazidine	9
C02A	***Antiadrenergic agents, centrally acting***	
C02AC01	Clonidine	3
C02AC05	Moxonidine	16
C02AC06	Rilmenidine	3
C02C	***Antiadrenergic agents, peripherally acting***	
C02CA04	Doxazosin	22
C03D	***Potassium-sparing agent***	
C03DA01	Spironolactone (>25 mg/d)	24
C04A	***Peripheral vasodilators***	
C04AD03	Pentoxifylline	2
C04AE02	Nicergoline	9
C08C	***Selective calcium channel blockers with mainly vascular effects***	
C08CA05	Nifedipine (non- sustained-release)	3
C08D	***Selective calcium channel blockers with direct cardiac effects***	
C08DA01	Verapamil	18
N	**Nervous system**	
N06B	***Psychostimulants, agents used for ADHD and nootropics.***	
N06BX03	Piracetam	2

Table 6. ICD Codes with PIMs.

ICD Code	Disease	PIM
E11.4	Non-insulin-dependent diabetes mellitus with neurological complications	9
E11.5	Non-insulin-dependent diabetes mellitus with peripheral vascular complications	1
G63.2	Diabetic polyneuropathy	2
I10	Essential (primary) hypertension	2
I11.0	Hypertensive heart disease with (congestive) heart failure	40
I11.9	Hypertensive heart disease without (congestive) heart failure	37
I12.9	Hypertensive kidney disease without renal failure	3
I20.8	Other types of angina pectoris	17
I48	Atrial flutter and fibrillation	24
I50.0	Congestive heart failure	23
I50.1	Left ventricular failure	3
I69.3	Consequences of subarachnoid hemorrhage	11
I80.2	Phlebitis and thrombophlebitis of other deep vessels of the lower extremities	1

category. The elevated prevalence of CVD in elderly patients can be attributed to their life-long exposure to cardiovascular risk factors and age-related comorbidities. The complexity of CVD in this population necessitates a multifactorial approach to manage and address the associated complications effectively. Research conducted in the USA indicates that approximately 70% of individuals aged over 70 years are projected to develop CVD. Moreover, more than two-thirds of this population will also have CVD-related noncardiovascular comorbidities (Dunlay and Chamberlain 2016). CVD is the leading cause of mortality in Europe, responsible for over 3.9 million deaths a year, or 45% of all deaths. Within the EU, the proportion of all deaths due to CVD ranges from 23% in France to 60% in Bulgaria among men, while in women, the burden ranges from 25% in Denmark to 70% in Bulgaria (Wilkins et al. 2017).

Nonetheless, the risk of CVDs, encompassing heart failure, atrial fibrillation-related stroke, heart valve disease, or coronary heart disease, escalates with age. Projections indicate that by 2040, the European population over 65 will reach 155 million (Eurostat 2023). With Europe's population continuing to age, the incidence of CVDs is expected to surge significantly.

Few studies have detected PIMs in patients with CVD. A retrospective chart review conducted in a tertiary care centre in the USA shows that the prevalence of PIMs accounted for 20% of all reported medications, with an average of 2.4 PIMs per patient. Additionally, 87.4% of the patients were found to be receiving at least one PIM. Notably, a significant association was observed between the use of PIMs and the number of home medications, female gender, and the number and types of comorbidities (Sheikh-Taha and Dimassi 2017).

In another study conducted in Portugal, the primary focus was evaluating the risk prevalence of PIMs associated with cardiac and cerebrovascular adverse events (CCVAEs), preeminent adverse cardiac and cerebrovascular events (MACCE), using the PIM-MACCE list. The study identified a total of 682 PIMs; remarkably, more than half of these (n=378) were linked to the risk of MACCE. The prevalence of PIMs with a risk of CCVAEs was found to be 59.4% (n=404), and it was noted that 47.4% (n=322) of the patients had a previous history of cardiovascular disease (Aguiar et al. 2019). A recent study conducted in Turkey aimed to identify, for the first time, the characteristics and rates of inappropriate prescriptions of cardiovascular system medications using the Beers Criteria. Among 65 million prescriptions analyzed, the rate of PIMs, including "drugs to be used with caution," was 11.56%. Notably, the most frequently prescribed potentially inappropriate drugs were doxazosin for diagnosing hypertension and methyldopa, irrespective of the indication (Kitapçı et al. 2023).

The methodologies for assessing potentially inappropriate prescribing have been extended to patient populations with various diseases. In a cross-sectional study of the Danish population aged ≥65, patients with dementia were evaluated using the red-yellow-green list from the Danish Institute for Rational Pharmacotherapy and the German PRISCUS list to define PIMs. The findings revealed that individuals with dementia were more commonly exposed to polypharmacy and, similarly to PIMs, which could have adverse implications for patient safety. These results emphasize the necessity for interventions to enhance drug therapy for people with dementia (Kristensen et al. 2018). A recent study conducted in a medical ward at a hospital in Northern Sweden aimed to compare the prevalence of potentially inappropriate medication (PIM) among elderly patients using two different criteria: the EU (7)-PIM list and the Swedish quality indicators. The study included 93 patients, and the results indicated that 18.3% of them had at least one PIM, according to the Swedish quality indicators. Among the identified PIMs, the most common class was non-steroidal anti-inflammatory drugs, with diclofenac being one of the most frequently prescribed PIMs. When assessing the same patient population using the EU (7)-PIM list, the study found that 45.2% of elderly patients were prescribed one or more PIMs. In this case, the most prevalent PIM class was hypnotic and sedative drugs, and the most frequently prescribed specific PIM was apixaban (Wamil et al. 2019). These findings suggest the importance of utilizing PIM assessment criteria to comprehensively evaluate and address inappropriate medication use in elderly patients, emphasizing the need for tailored interventions to optimize drug therapy in this vulnerable population.

In the contemporary digital era, there is a growing emphasis on developing digital solutions that facilitate the identification of at-risk patients and the prevention of inappropriate prescriptions. A machine learning-based risk warning platform for potentially inappropriate prescriptions for elderly patients with cardiovascular disease in China has the potential to efficiently notify clinicians about the risk of potentially inappropriate prescribing (PIP), which is crucial for the development of effective and personalized treatment strategies (Maaroufi et al. 2021).

Another digital facilitation is a mobile app developeded based on the 2023 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. This app assists clinicians in implementing prescribing recommendations by providing a compendium of medications that should be avoided or used with caution in older adults. (GeriatricsOnlineCare 2023: https://geriatricscareonline.org/ProductAbstract/ags-beers-criteria-for-potentially-inappropriate-medications-for-older-adults-mobile-app/B067).

A continuous evaluation of the medications prescribed to this population is crucial to enhance medication management in older patients and reduce adverse drug effects. In this regard, using reliable tools and criteria to assess the appropriateness of medications becomes essential, particularly in detecting PIMs. The application of lists of potentially inappropriate medications would not negate the importance of personalized approaches and healthcare professionals' expertise, as these methodologies have limitations.

The present study demonstrates the applicability of the EU(7)-PIM List within the Bulgarian prescribing practice and its potential to detect potentially inappropriate

medications. The identified PIMs are presented based on ATC and ICD codes, facilitating experts to identify areas where potentially inappropriate prescribing occurs. This comprehensive approach enables a better understanding of the patterns and areas of concern related to potentially inappropriate medication prescribing. The study has certain limitations. Firstly, it focused solely on medications prescribed through health insurance, which excluded non-prescription medications like aspirin or NSAIDs.

Consequently, our findings may be conservative, and more individuals are likely exposed to PIMs than observed in this study. Secondly, this study is a pilot study, and the limited size of the study population could have influenced the results. Therefore, further investigations involving a larger cohort of patients are essential to validate the findings.

Our study possesses several limitations. The first one is its narrow coverage of the territory of Veliko Turnovo. This study serves as a pilot investigation, and the sample size is constrained to patients exclusively visiting a single pharmacy within the city. Within the municipality of Veliko Turnovo, as of 2022, the population encompasses 34,331 individuals aged 65 and older (NSI 2022). Upon applying a sample size calculation to assess the representativeness of the study, it becomes apparent that the current sample size warrants reconsideration to ensure its comprehensive and accurate reflection within the broader urban community. However, we did not want to analyze all probable prescriptions to test the applicability of the EU (7)-PIM List in the local settings. The second major limitation is that we focused only on reimbursable prescriptions and needed to collect information on OTC and dietary supplement intake. It might increase the number of patients with polypharmacy.

Conclusion

This study reveals a significant number of PIM among patients with cardiovascular diseases. As a pilot study using the EU(7)-PIM List, it demonstrates the usefulness of this tool in managing adult patient conditions. In Bulgaria, there is no official methodology for assessing potentially inappropriate medications, and our recent analyses emphasize the need for a consensus among medical specialists to implement an assessment tool for prescriptions in this population. This is particularly important given the ongoing demographic trend of population ageing and the focus of many organizations on the elderly population. Given the significance of PIMs in deprescribing strategies for older patients with polypharmacy, prescribers, educators, and drug-regulatory institutions must show increased interest in regulatory measures and specific aspects related to PIM use.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

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