

Prevalence of potentially inappropriate medications among elderly patients with diabetes – study based on STOPP/START criteria

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Abstract

Objective: The prevalence of drug-related problems in elderly patients is a concerning issue that can lead to elevated morbidity, mortality, and health care resource utilisation. This study focuses on the significance of addressing diabetes in the context of an ageing population, where elderly individuals face higher risks of comorbidities and mortality. The main objective of this study was to assess potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) among patients with diabetes in Bulgaria, using the explicit STOPP/START criteria, version 2. By evaluating the appropriateness of drug prescriptions in this specific patient population, this study aims to shed light on areas that require optimisation to enhance patient safety and treatment outcomes.

Materials and methods: A national prospective questionnaire study was conducted in Bulgaria among patients aged over 65 years. The research was conducted in 25 randomly selected pharmacies. The study supports the use of the STOPP/START criteria based on the clinical information provided. A total of 133 patients with T1DM or T2DM participated in the study. The evaluation of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) was performed in 131 patients. Statistical differences in demographics and medication numbers between patients with and without PIMs or PPOs were assessed using a Chi-square test, with a p-value of ≤ 0.05 considered statistically significant.

Results: The pharmacotherapy of 131 patients with diabetes was assessed, and it was found that 57% of them had polypharmacy. Among the study population, 90 PIMs were identified, indicating that 66% of the patients had inappropriate prescribing. Notably, inappropriate prescribing concerning diabetes was associated with the use of long-acting sulfonylureas (n=10) and beta-blockers (n=13). Applying the START criteria revealed 67 PPOs among 67 patients, representing a prevalence of 50% in the study population. However, no PPOs were detected in the context of diabetes pharmacotherapy. Furthermore, a significant relationship was observed between the number of medications and PIMs, as evidenced by the chi-square test result with a p-value close to zero, indicating statistical significance.

Conclusion: The study revealed a high prevalence of PIMs in elderly patients with diabetes in Bulgaria. Endocrine disorders contribute to 26% of PIMs. As Bulgaria's ageing population faces increasing diabetes challenges, effective management strategies are crucial. These findings underscore the significance of addressing prescribing practices to enhance disease control and prevent complications.

Keywords

STOPP/START criteria, diabetes, polypharmacy, inappropriate prescribing, elderly patients

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterised by elevated blood glucose levels. It encompasses various categories, such as type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes resulting from endocrinopathies or steroid usage. The primary subtypes of DM are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), which typically arise from impaired insulin secretion (T1DM) and/or reduced insulin action (T2DM) (Sapra and Bhandari 2023). According to the International Diabetes Federation, the global population of adults aged 20–79 years living with diabetes stands at 537 million. Projections indicate that this figure is expected to increase to 643 million by 2030 and further rise to 783 million by 2045. In Europe, the number of individuals affected by diabetes currently stands at 61 million and is estimated to grow to 69 million by 2045 (IDF 2023). In 2021, the average prevalence of diabetes among adults in European countries was 9.2%. In the European region, there is a notable annual incidence of diabetes, with approximately 31,000 new cases reported each year. Additionally, this region ranks second in terms of the average cost per person with diabetes, amounting to USD 3,086 for individuals aged between 20 and 79 years. These findings highlight the significant impact of diabetes on public health and health care costs in Europe (IDF Diabetes Atlas 2021). According to the data from the Institute of Health Metrics and Evaluation, as of 2019, Bulgaria had a total of 657,568 diagnosed cases of diabetes, with 28,693 individuals having T1DM and 628,874 individuals having T2DM (The Institute for Health and Metrics Evaluation 2023). Among the diabetes patient population, 294,576 individuals, constituting 45%, fall into the age category of 65 years and older (The Institute for Health and Metrics Evaluation 2023). The prevalence of diabetes is increasing in Europe and around the world. This is due to several factors, including an ageing population, changes in lifestyle (such as a lack of physical activity and unhealthy diets), and the increasing prevalence of obesity. Indeed, a comprehensive review of existing literature and statistical data consistently supports the notion that diabetes is more prevalent among elderly individuals and is accompanied by a higher incidence of comorbidities and mortality rates when compared with younger age groups. This robust evidence underscores the significance of addressing diabetes in the context of an ageing population and highlights the need for targeted interventions and health care strategies to effectively manage this condition in older adults.

Ageing is associated with alterations in various aspects, including biological, physiological, psychological, behavioural, and social processes. The characteristics of elderly people are changes in the pharmacokinetics and pharmacodynamics of medications, leading to variations in the safety and efficacy profiles of medicinal products. Coupled with the presence of multiple chronic diseases and comorbidities, this significantly contributes to polypharmacy. The study by Massoud et al. (2017) focuses on reviewing

the pharmacokinetic and pharmacodynamics changes in elderly individuals. This research offers prescription recommendations for key therapeutic classes, along with potential clinical implications of inappropriate prescribing. The recommendations emphasise the need for personalised prescribing in the elderly population, including dose adjustments based on individual responses to medications (Massoud et al. 2017). In both Chinese and Canadian studies (Gagnon et al. 2020; Lu et al. 2022), a notable correlation has been established between PIMs and comorbidities among elderly patients with diabetes. The prevalence of elderly patients receiving at least one PIM was found to be approximately 50% (43.2%, 44.88%, and 42.40% in China over a three-year period and 56% in Canada). Furthermore, the risk of PIM usage increased with the rise in both comorbidities and the number of medications prescribed to these individuals. In a nationwide study conducted in France, it was observed that diabetes mellitus ranked as the most prevalent long-term disease in both older adults (aged 65 years and over) and middle-aged adults (aged 45 to 65 years). Among older adults with chronic polypharmacy, a substantial proportion (64.8%) had at least one chronic PIM, whereas among middle-aged adults with chronic polypharmacy, 46.2% had at least one chronic PIM (Guillot et al. 2020). These findings emphasize the significant correlation between PIMs and comorbidities, particularly in elderly patients with diabetes. Health care providers must exercise heightened vigilance in closely monitoring and optimizing medication regimens, especially for individuals with multiple comorbidities and polypharmacy, to mitigate the risks associated with PIM usage. It is essential to focus on interventions and strategies aimed at reducing PIM usage and improving the quality of care for elderly patients with comorbidities, particularly those with diabetes.

In response to the demographic trend of population aging and the increasing demand for optimizing prescribing practices in this specific group, various tools have been developed to identify PIMs. One of the extensively used tools in Europe for identifying PIMs is the STOPP/START criteria, which serves as an explicit method for identifying both PIMs (STOPP) and PPOs. In 2014, the methodology was updated, and versions two was validated through the involvement of 19 experts from 13 European countries. The final list of 114 criteria was established after two Delphi validation rounds, comprising 80 STOPP criteria and 34 START criteria (O'Mahony et al. 2015). Given the existence of a prior study in Bulgaria that demonstrated the successful application of the STOPP/START criteria within the context of Bulgarian prescribing practice among patients with cardiovascular diseases (Krustev et al. 2022), our objective is to extend the investigation and assess the applicability of these criteria in a distinct patient population affected by primary diseases T1DM and T2DM. By expanding the scope of the criteria to include patients with T1DM and T2DM, we aim to gain insights into the appropriateness of drug prescriptions and identify any areas that may require optimization to ensure patient safety and improve overall treatment outcomes.

Materials and methods

Study design

A national representative, the prospective questionnaire study was conducted among patients over 65 years of age in Bulgaria. The study was conducted in 25 randomly selected pharmacies throughout the country, where pharmacy managers expressed their willingness to participate. Graduating pharmacy students conducted the data collection during patients' visits to the pharmacy. The questionnaire used in this study was developed as part of the EUROAG-EISM project, funded under the Horizon 2020 program. It encompassed various aspects, including demographic characteristics, lifestyle, physical activity, laboratory test results, health status, health care utilisation, existing medical conditions, disease symptoms, pain and depression levels, medications used, and patient satisfaction with therapy. The clinical information provided in this study supports the utilisation of the STOPP/START criteria.

A total of 133 patients with either T1DM or T2DM were recruited for the study. However, because of insufficient or inaccurate information regarding medication treatment for two patients, the evaluation of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) was performed for 131 patients. A Chi-square test was employed to assess the statistical variations in demographics and the number of medications among older patients with and without PIMs or PPOs. A *p*-value of ≤ 0.05 was considered statistically significant.

Inclusion and exclusion criteria

No specific limitations were imposed on the participants. The survey included all patients aged 65 years and above who obtained their medications from the respective pharmacy and consented to participate. The inclusion criteria were age, willingness to participate, and responsiveness to the survey questions.

Ethics

All patients were provided with comprehensive information about the study objectives, and informed consent was obtained. The research protocol was approved by the ethics committees of the Medical Universities in Sofia, Plovdiv, and Varna.

Results

Table 1 presents the characteristics of the study participants, including gender distribution, age groups, and the number of medications prescribed. The study comprised 133 participants, with no available pharmacotherapy information for 2 of them. Women constituted the majority, accounting for approximately 63%, whereas men represented 33% of the participants. The largest proportion of

Table 1. Distribution of sociodemographic and number of medications.

Characteristic	Number (frequency)
Gender	
Male	44 (33.08%)
Female	85 (63.91%)
No information	4 (3.01%)
Age (years)	
65–69	43 (32.33 %)
70–74	44 (33.08%)
75–79	22 (16.54%)
80–84	14 (10.53%)
>85	10 (7.52%)
Number of medications	
1–2	27 (20.61%)
3–4	30 (22.91%)
5–6	38 (29%)
7–8	28 (21.38%)
9–10	6 (4.58%)
>10	2 (1.52%)

Table 2. Prevalence of self-reported diseases in the study population.

Reported diseases	Number
CVD	227
Musculoskeletal	66
Endocrine and metabolic	221
Respiratory system	17
Digestive system	73
Genitourinary system	41
Blood and blood-forming organs	11
Nervous system	7
Mental disorders	126
Infectious diseases	19
Malignant diseases	4
ENT	122
Skin diseases	9

participants (65%) fell into the age group of 65–74 years, and only 7% were above 85 years. Notably, 57% of the elderly participants were classified under polypharmacy, taking five or more medications daily, whereas 43% were taking fewer than five medications per day, as per their age category.

In the study population, participants reported several diseases, and data analysis revealed significant patterns. The most commonly reported diseases were associated with the cardiovascular system (CVD), with 227 cases observed. Following CVD, endocrine and metabolic diseases were the second most prevalent, with 221 reported cases (Table 2). The overall number of reported diseases reached 943, highlighting the substantial burden of multimorbidity among the elderly population.

Upon reviewing the reported endocrine disorders, it becomes evident that patients with diabetes not only suffer from comorbidities but also experience diabetic complications. Among them, 40 patients reported the presence of diabetic neuropathy, and 12 patients reported diabetic nephropathy (Table 3).

Table 3. Endocrine and metabolic disorders.

Diabetes melitus	133
Diabetic neuropathy	40
Diabetic nephropathy	12
Hyperthyroidism	1
Hypothyroidism	8
Dyslipidemia	25
Others	2

A total of 90 PIMs were identified among 88 patients, indicating that 66% of our study population were taking inappropriate medications (Table 4). The highest proportion of PIMs was detected in CVD with a count of 42, followed by the endocrine system with 23 instances. Within the CVD category, most of PIMs were related to aspirin intake without proton pump inhibitors (PPI) when there was a history of peptic ulcer (n=13), digoxin intake (n=8), combination of aldosterone antagonists with concurrent potassium-conserving drugs (n=8), and centrally acting antihypertensives such as moxonidine and clonidine (n=6). Inappropriate prescribing concerning diabetes was to the intake of long-acting sulfonylureas (n=10) and beta-blockers intake (n=13).

Upon applying the START criteria, we identified 67 PPOs among 67 patients, representing a prevalence of 50% within the study population. The CVD category exhibited the highest number of PPOs, notably associated with antiplatelet therapy (n=14). Moreover, the gastrointestinal system displayed significant PPOs, particularly concerning the absence of proton pump inhibitors (PPI) in cases of severe gastroesophageal reflux (n=9) and the lack of fiber supplements in the presence of constipation (n=10). Additionally, 10 PPOs were linked to the musculoskeletal system, predominantly concerning the omission of xanthine-oxidase inhibitors in the presence of gout (n=6). No PPOs were detected in diabetes pharmacotherapy.

In addition a chi-square test was conducted at a significance level of alpha = 0.05 to analyse various associations (Table 6). The results showed significant associations between certain variables. Specifically, there was a significant relationship between gender and PPOs, with a p-value of 0.00001 (< 0.05). Similarly, a significant association was observed between the age distribution of patients and PIMs, with a p-value of 0.00035 (< 0.05). Additionally, the age of the patients exhibited a significant association with PPOs,

Table 4. Number of potentially inappropriate medications identified according to the STOPP criteria, version 2 (n=90).

STOPP criteria. Screening Tool of Older People's potentially inappropriate Prescriptions	Number
Indication of the medication	
Any duplicate drug class prescription e.g. two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent)	5
Cardiovascular system	
Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)	8
Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available)	5
Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence)	2
Centrally-acting antihypertensives (e.g. methyl dopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of 2 antihypertensives (centrally-active antihypertensives are generally less well tolerated by older people than younger people).	6
Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g. ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. > 6.0 mmol/l – serum K should be monitored regularly, i.e. at least every 6 months)	8
Antiplatelet/Anticoagulant Drugs	
Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer).	13
Central Nervous System and Psychotropic Drugs	
Benzodiazepines for ≥ 4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly).	9
Renal System (The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR)	
Gastrointestinal System	
Drugs likely to cause constipation (e.g. antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminium antacids) in patients with chronic constipation where nonconstipating alternatives are available (risk of exacerbation of constipation)	1
Musculoskeletal System	
COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke).	4
Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease i.e. dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture).	1
Endocrine System	
Sulphonylureas with a long duration of action (e.g. glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)	10
Beta-blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms).	13
Drugs that predictably increase the risk of falls in older people	
Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia)	5

Table 5. Number of potentially prescribing omissions identified according to START criteria (n=67).

START criteria, version 2 . Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatment	Number
Cardiovascular System	
Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease.	14
Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease	4
Beta-blocker with ischaemic heart disease	8
Appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) with stable systolic heart failure.	6
Respiratory System	
Regular inhaled b2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) for mild to moderate asthma or COPD	4
Gastrointestinal System	
Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation	9
Fibre supplements (e.g. bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation	10
Musculoskeletal System	
Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (Bone Mineral Density T-scores more than -2.5 in multiple sites).	4
Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (Bone Mineral Density T-score is > -1.0 but < -2.5 in multiple sites).	2
Xanthine-oxidase inhibitors (e.g. allopurinol, febuxostat) with a history of recurrent episodes of gout	6

Table 6. Association of PIMs and PPOs with demographic characteristics and medication distribution in older patients (n=133).

Association	p value
Gender and PIM	0.421
Gender and PPO	0.00001
Age distribution and PIM	0.00035
Age distribution and PPO	0.023
Number of medications and PIM	0
Number of medications and PPO	0.1028

with a p-value of 0.023 (< 0.05). Furthermore, a notable relationship was detected between the number of medications and PIMs, with the chi-square test showing a p-value close to zero, indicating a statistically significant correlation.

If we extrapolate these findings to the broader national population, which comprises 294,576 individuals above 65 years with diabetes, we can anticipate that 199,337 elderly individuals with both type 1 and type 2 diabetes or an average of 67% may exhibit PIM.

Discussion

Diabetes mellitus is a socially significant disease that affects all age groups. A retrospective study conducted in Bulgaria from 2012 to 2016 assessed the frequency and complications of diabetes. The findings revealed a notable increase in the number of patients with T2DM, reaching a total of 452,490 individuals, whereas the number of patients with T1DM decreased to 25,426. The average age of patients with T2DM was approximately 65 years, indicating a higher prevalence in older adults. However, it is concerning to note that only 30% of the patients with T2DM exhibited good disease control (Mitov et al. 2019) significant. Simultaneously, there is a lack of sufficient data regarding prescribers and the presence of potentially inappropriate prescriptions within this population.

Our research on potentially inappropriate medications (PIMs) in the context of diabetes aligns with the findings of other similar studies conducted among geriatric patients. Notably, the prescription of long-acting sulphonylureas has been identified as a prominent PIM in several studies (Akande-Sholabi et al. 2020; Alturki et al. 2020; Khader et al. 2021; Lu et al. 2022). The prevalence of PIMs associated with sulphonylureas exhibits variability across different regions. Studies have reported PIM prevalence rates of 20.5% in Jordan (Khader et al. 2021), 26.8% in Saudi Arabia (Alturki et al. 2020), 11.2% in Nigeria (Akande-Sholabi et al. 2020), and 13.1% in China (Lu et al. 2022). These findings highlight the importance of considering regional variations when assessing the appropriateness of medication prescriptions and emphasise the need for targeted interventions to optimise medication regimens for patients. Various factors, including the study's methodology and the availability of clinical data, can indeed influence the identification of PIMs. The selection of criteria, the specific definitions used to identify PIMs, and the setting (hospital, ambulatory) can affect the prevalence rates. Additionally, the extent and quality of clinical information accessible for analysis can affect the accuracy and completeness of PIM identification. Therefore, it is crucial to consider these aspects when interpreting and comparing PIM prevalence rates across different studies and health care settings.

A study in Poland compared patient-oriented tools (STOPP/START and Amsterdam tool) and drug-oriented tools (EU (7)-PIM List and Beers criteria) in a sample of 50 elderly patients at a daily care facility. All the tools demonstrated the ability to detect potentially inappropriate medications (PIMs) in this population. Notably, when clinical data were available, the STOPP/START methodology emerged as the most comprehensive approach for assessing pharmacotherapy appropriateness in geriatric patients (Lisowska et al. 2022). Another study focussing on hospitalised elderly patients using different criteria also confirmed the effectiveness of STOPP/START in de-

tecting more PIMs than other tools (Wickop et al. 2016). Furthermore, the use of the STOPP/START criteria in various health care settings in Serbia, including community pharmacies, nursing homes, and outpatient facilities, revealed a substantial rate of potentially inappropriate prescribing (Jovanović et al. 2023).

The STOPP/START criteria were initially developed as a user-friendly and efficient tool intended for physicians to assess the appropriateness of prescription drugs in older patients based on their specific diagnoses. Its primary purpose is not to serve as a diagnostic tool but rather as a practical aid for clinicians in their daily practice (Gallagher et al. 2008). The literature review indicates that the specificity of detecting potentially inappropriate medications (PIMs) is notably higher when using national lists of PIMs. Multicentric tools may have limitations, as they may include medications that are not approved at the national level. This indicates that national lists of PIMs are more effective in accurately identifying inappropriate medications in specific regions or countries. Several European countries have taken a pioneering approach in addressing potentially inappropriate medications (PIMs) among their elderly population. These countries have developed and implemented national lists and guidelines for the identification of PIMs. Examples include the Laroche list in France (Laroche et al. 2007), NORGEP (Rognstad et al. 2009) and NORGEP-NH (Nyborg et al. 2015) in Norway, National Quality indicators for good drug therapy in the elderly in Sweden (Fastbom and Johnell 2015), and the PRISCUS List in Germany (Holt et al. 2010). In Bulgaria, there is currently no consensus on the implementation and adoption of a national PIM list. Our present study highlights this concern, and the findings demonstrate a prevalence of 66% for PIMs despite the study's limited population size. Multimorbidity is strongly associated with advancing age, and research indicates that at least 50% of individuals aged 65 years and older experience multimorbidity (Nguyen et al. 2019). The diverse array of coexisting chronic conditions within our diabetic study population underscores the necessity of adopting a multidisciplinary approach in pharmacotherapy. Assessing and addressing preventable potentially inappropriate medications (PIMs) could be advantageous for the well-being of these patients.

When we extrapolate the findings from our study to a broader population of adult diabetic patients, we observe that, on average, 67% of them have been prescribed potentially inappropriate medications. The implementation of a PIM list in this population would serve as a preventive

measure against inappropriate prescriptions. In this context, it would enhance the quality of pharmacotherapy for the ageing population.

Our study presents several limitations that should be considered. First the study was conducted solely among pharmacy visitors, potentially representing a relatively independent subgroup, which may limit the generalizability of our findings to individuals in nursing homes or hospitalised patients with higher rates of polypharmacy and multimorbidity. Second, the patient population with diabetes in our study was limited, and therefore, caution is needed when extrapolating our results to a broader diabetic population. Finally, while we used the STOPP/START criteria for assessing potentially inappropriate medications, it is essential to acknowledge that different methodologies might yield varying PIM rates, suggesting the need for further research and comparison of assessment tools.

Conclusion

To our knowledge, this study represents the first investigation into the prevalence of PIMs among elderly patients with diabetes mellitus. The findings underscore the significant burden of multimorbidity and diabetes complications in this population, with 66% of elderly individuals with diabetes experiencing potentially inappropriate prescribing. Notably, endocrine disorders, including diabetes, accounted for 26% of the identified PIMs. Regarding potentially prescribing omissions (PPOs), 50% of the study population exhibited exposure to such omissions, although none were related to endocrine diseases. This study highlights the increasing challenges posed by diabetes in Bulgaria, compounded by an ageing population, necessitating effective management strategies to enhance disease control and prevent complications. Policymakers should focus on implementing actionable measures to address common and preventable inappropriate prescribing in all health care settings. This study sheds light on the importance of addressing appropriate prescribing practises to ensure optimal care and outcomes for elderly patients with diabetes in Bulgaria.

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