

## Original Research

# Prevalence of potentially inappropriate prescriptions in primary care and correlates with mild cognitive impairment

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### Abstract

**Background:** Potentially inappropriate prescribing is clearly associated with adverse health consequences among older people. Nevertheless, scarce evidence exists regarding the prevalence of potentially inappropriate prescriptions (PIP) in Albania, a Western Balkans country.

**Objective:** The aim of this study was to assess the prevalence of PIP among older Albanian patients in primary care and to determine the associated sociodemographic and medical factors, including the presence of mild cognitive impairment (MCI).

**Methods:** Cross-sectional study in two primary healthcare centers located in two different cities of Albania, a middle-income country in the Western Balkans. The Montreal Cognitive Assessment (MoCA) tool was applied to evaluate MCI. PIPs were assessed by two trained pharmacists using the Beers criteria 2019 update. Multivariate logistic regression analysis was conducted for possible risk factors predicting PIP in the study population.

**Results:** At least one PIP was identified among 40.23 % of the participants (174 older patients) and 10.35 % had more than one PIP. MCI was detected among 79.31 % of the patients. The most commonly represented drug groups in PIP were diuretics (24.71 %), benzodiazepines in the presence of MCI and antidepressants (both 8.62 %). The lack of electrolytes monitoring was the most common reason for PIP. According to the multivariate analysis, the only statistically significant association observed was between PIP and number of drugs prescribed [three to four drugs (OR 3.34; 95% CI 1.65:6.76), five or more than five drugs (OR 4.08; 95% CI 1.42:11.69)].

**Conclusions:** About four out of 10 older Albanian patients experience PIP in primary care. Further studies are needed for a comprehensive estimation of the prevalence and factors associated with PIP, particularly among elderly with mild cognitive impairment.

### Keywords

Inappropriate Prescribing; Potentially Inappropriate Medication List; Cognitive Dysfunction; Antidepressive Agents; Benzodiazepines; Aged; Risk Factors; Pharmacists; Cross-Sectional Studies; Multivariate Analysis; Albania

## INTRODUCTION

Drug prescribing is an important and necessary part of patients' treatment, however it can become a source of particularly hazardous and adverse effects, especially among vulnerable populations such as older people with or without cognitive impairment.<sup>1-3</sup> There is conflicting evidence among studies regarding the occurrence of potentially inappropriate prescriptions among people living with undetected dementia or MCI.<sup>1,3,4</sup> However, strong evidence shows that the use of drugs with anticholinergic properties has a negative impact on cognition and increases the risk of Alzheimer.<sup>5</sup> Several tools and approaches have been developed to support prescribers and researchers for PIP detection and prescribing optimization. Beers criteria, which were recently updated in 2019, represent the most applied tool for this purpose.<sup>6,7</sup>

There is scarce published research with regard to suboptimal prescribing in the Western Balkan countries,

either in hospital settings, nursing homes, or focused on specific drug groups like benzodiazepines and antibiotics.<sup>8-13</sup> Only few studies have reported inappropriate prescribing in primary care among older patients of the Western Balkans, and just one in Albania, a middle-income country.<sup>14-17</sup>

Obviously, in order to design and implement effective interventions to reduce improper prescribing, measuring the extent and factors related to this issue is essential.

The aim of our study is to assess the prevalence of PIP among older Albanian patients and its correlates with the presence of mild cognitive impairment, as well as with sociodemographic and medical factors.

## METHODS

### Study design

Cross-sectional study. We included in the study older patients (60 years old or more) attending the primary healthcare centers from two cities in Albania (Tirana and Shkodra, respectively capital and larger northern city of Albania). Patients were consecutively selected. Study period comprised three months (from 1 March to 31 May 2019). All patients gave their consent to participate in the study, by previously signing the document of informed consent. We excluded patients with no official diagnosis or who did not use any medication.

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Variable	N (%)
Gender	
Female	75 (43.1)
Male	99 (56.9)
Age (years old)	
60-65	49 (28.2)
66-70	53 (30.5)
71-75	50 (28.7)
≥ 76	22 (12.6)
Median (IQR)	73.5 (8)
Years of formal education	
0 (illiterate)	19 (10.9)
1 – 7	18 (10.3)
8 – 12	101 (58.1)
13 – 17	36 (20.7)
Median (IQR)	12 (4)
Number of drugs prescribed	
1 – 2	105 (60.3)
3 – 4	51 (29.3)
≥ 5	18 (10.3)
Median (IQR)	2 (2)
Number of diagnoses	
1 – 2	154 (88.5)
3 – 5	20 (11.5)
Median (IQR)	1 (1)
MoCA score	
≥23	36 (20.7)
<23	138 (79.3)
Median (IQR)	19 (4)

The study was performed in accordance with the ethical standards as displayed in the 1964 Declaration of Helsinki, as revised in Brazil 2013. It was approved by the University of Medicine of Tirana (no. 154).

#### Collected data

Data were extracted by two trained pharmacists from patients' medical records, interviews with patients and answers to the MoCA tool. All data were assigned an alpha-numeric code, in accordance with The General Data Protection Regulation (EU) 2016/679. Study variables were sex, age, years of formal education, number of drugs prescribed, number of diagnoses, MoCA score, number and type of potentially inappropriate prescriptions according to Beers criteria (2019 update).

To evaluate potential mild cognitive impairment (MCI) we applied the MoCA tool (Montreal Cognitive Assessment). It is a simple, relatively short (time of administration about 10 minutes, one page length) and validated instrument for detecting MCI. The MoCA assesses several domains which are often impaired among people with cognitive and behavioural deterioration, namely, short-term memory; visual, spatial and orientation abilities; executive functions and language skills; attentiveness and dealing with numbers. To each of these domains there are corresponding specific questions and respective scores with a maximum of 30 points. For illiterate patients or those with low-level of education, MoCA Basic was applied

	Number (%)	Reason	Recommendation (Strength of recommendation)	Quality of evidence
<b>Drugs potentially inappropriate in most older people</b>				
Paroxetine (Antidepressants)	5 (2.9)	Highly anticholinergic, sedating, and cause orthostatic hypotension	Avoid (Strong)	High
Glimepiride (Sulfonylureas, long acting)	4 (2.3)	Higher risk of severe prolonged hypoglycemia	Avoid (Strong)	High
Insulin, sliding scale	3 (1.7)	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting. It does not apply to regimens that contain basal or long-acting insulin.	Avoid (Strong)	Moderate
Methyldopa (Central alpha-agonists)	2 (1.2)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid (Strong)	Low
Benzodiazepines	15	Risk of delirium, falls, fractures, cognitive impairment	Avoid (Moderate)	Strong
Antipsychotics	3	Higher risk of stroke	Avoid, except schizophrenia, bipolar disorder, or antiemetic in chemotherapy (Strong)	Moderate
Zolpidem (Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics, Z-drugs)	1 (0.6)	Adverse events similar to those of benzodiazepines in older adults (eg. delirium, falls, fractures); increased emergency room visits/ hospitalizations: motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid (Strong)	Moderate
Amiodarone	1 (0.6)	Greater toxicities than other antiarrhythmics used in atrial fibrillation.	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial leftventricular hypertrophy (Strong)	High
Ibuprofen	1 (0.6)	Increased risk of GI bleeding or peptic ulcer disease in high-risk groups, can increase blood pressure and induce kidney injury. Risks are dose related.	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (Strong)	Moderate

Table 2 (cont.). Drugs involved in potentially inappropriately prescribed (PIP) and PIP-qualifying criteria according to Beers 2019				
	Number (%)	Reason	Recommendation (Strength of recommendation)	Quality of evidence
<b>Drugs potentially inappropriate in older people with certain conditions</b>				
Dementia or cognitive impairment				
Benzodiazepines	15 (8.6)	Avoid because of adverse CNS effects, behavioural problems	Avoid (Strong)	Moderate
Anticholinergics	6 (3.5)			
Zolpidem	1 (0.6)			
<b>Drugs to be used with caution in older people</b>				
Hydrochlorothiazide (Diuretics)	34 (19.5)	May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults	Use with caution (Strong)	Moderate
Escitalopram (Antidepressants)	10 (5.7)			
Furosemide (Diuretics)	8 (4.6)			
Carbamazepine (Antiepileptics)	2 (1.2)			
Risperidon (Antipsychotics)	2 (1.2)			
Olanzapine (Antipsychotics)	1 (0.6)			
Spironolactone (Diuretics)	1 (0.6)			
<b>Potentially clinically significant drug-drug interactions to be avoided in older people</b>				
Escitalopram	1 (0.6)	Any combination of three or more of these CNS-active drugs (Antidepressants, Antipsychotics, benzodiazepines)		
Olanzapine				
Mexazolam				
<b>Drugs with strong anticholinergic properties</b>				
Paroxetine (Antidepressants)	5 (2.9)			
Olanzapine (Antipsychotics)	1 (0.6)			

instead. A score of less than 23 points obtained in the MoCA was considered to indicate MCI.<sup>18</sup>

To assess potentially inappropriate prescriptions two trained pharmacists independently applied the Beers criteria (2019 update). Due to the unavailability of information on renal function, we did not include those criteria on drugs to be avoided or used with reduced dosage because of varying levels of kidney function.

#### Data analysis

STATA/SE software version 12 was used for data analysis. Firstly, a bivariate analysis was applied to identify which variables were associated with PIP; the statistical tests applied were the Chi-Square test or Fisher's exact test, as appropriate. Also, the odds ratio (OR) and 95% confidence interval (95%CI) for every independent variable was estimated. Finally, we conducted a multivariate logistic regression analysis to assess possible risk factors predicting PIP in the study population. The variables that initially entered in the multivariate model were those with p-value < 0.2 in the bivariate analysis. The final models were derived by backward stepwise logistic regressions based on likelihood ratio test statistic G.<sup>19</sup>

## RESULTS

After initial assessment of 206 patients, we excluded 32 patients who were not prescribed any medication or had no official diagnosis. Final sample consisted of 174 patients (56.9% male), 50.00% from Tirana, with a mean age of 69.49 (SD=19.09) years old. Most of the participants (88.5%) had one or two official diagnoses and the most

frequent was arterial hypertension among 71.3% of the participants, followed by diabetes mellitus among 17.4% of them. Mean number of drugs was found 2.56 (SD=1.53), ranging from one to eight drugs simultaneously prescribed. Polypharmacy defined as five or more than five drugs prescribed was present among 10.34% of the participants. Anticholinergic drugs were prescribed to 6 patients (4.0%). MCI was detected among 79.3% of the participants who obtained less than 23 points after applying the MoCA tool (Table 1).

In approximately four out of ten patients was identified at least one PIP (70 patients; 40.2%) and 10.4% of them had more than one PIP according to the applied criteria (two PIP among 16 patients and three PIP among 2 patients). The overall number of PIP found among the study sample was 90 (42.9% of all drugs prescribed), accounting for 18 different PIP. The average number of PIP per patient was calculated 0.53. With reference to the Beers 2019 tool, only 11 different PIP-qualifying criteria contributed to the detected PIP. The most commonly represented drug groups among PIP were diuretics (hydrochlorothiazide, furosemide, and spironolactone), benzodiazepines (mexazolam, lorazepam, diazepam, and alprazolam), and antidepressants (escitalopram, paroxetine). Diuretics on the one hand are the drugs of choice in many indications, on the other hand they are among the drugs to be used with caution in older people due to the risk of SIADH (syndrome of inappropriate antidiuretic hormone secretion) and hyponatremia. We identified 43 cases (24.7% of patients) with diuretics prescriptions without sodium level monitoring when starting or changing doses, most frequently hydrochlorothiazide (34 patients). Benzodiazepines are listed in Beers criteria as PIP in the

presence of dementia or cognitive impairment with a strong recommendation to avoid in older people with this condition. Fifteen patients were prescribed benzodiazepines and all of them had MCI according to MoCA. The improperly used antidepressants were escitalopram (10 patients; 5.7%) and paroxetine (5 patients; 2.9%). We identified one potentially clinically significant drug-drug interaction, the combined prescription of three drugs acting in the central nervous system – escitalopram, olanzapine, and mexazolam. Only two types of drugs with strong anticholinergic properties were prescribed, the antidepressant paroxetine and the antipsychotic olanzapine (Table 2). The mean MoCA score of the six patients taking drugs with strong anticholinergic properties was 18.17 (SD=1.94).

With regard to the results obtained in the bivariate analysis, it was found that PIP were more common among females, however this was not statistically significant (OR 1.32; 95%CI 0.71:2.43). Age, years of formal education, and number of diagnosed diseases were not significantly associated with PIP. Increasing number of prescribed drugs was a significant risk factor for PIP, as shown in Table 3.

The candidate variables to enter into the multivariate model were age, number of prescribed drugs and MoCA score (p-value < 0.20). According to the likelihood test, only the number of prescribed drugs and MoCA score finally contributed to the multivariate model. Patients with a MoCA score of less than 23 (cut-off for MCI), had increased odds for PIP (OR 2.11; 95%CI 0.91:4.89), although results did not achieve statistical significance. Higher number of prescribed drugs remained a significant risk factor for PIP even according to the multivariate model. Patients who were prescribed five or more than five drugs (OR 4.08; 95%CI 1.42:11.69), as well as those with 3 to 4 drugs prescribed (OR 3.34; 95%CI 1.65:6.76), showed significantly higher risk for PIP compared to patients with two or less drugs prescribed.

## DISCUSSION

To our knowledge, this is the first study reporting PIP identified by Beers criteria in primary care in Albania, a Western Balkan country. We applied the most recent version of Beers criteria (2019 update) as a detection tool for PIP among older patients in two primary healthcare settings located in two Albanian cities. The prevalence of PIP calculated as percentage of patients with at least one PIP was 40.2% and about one tenth of the participants had two or three potentially inappropriately prescribed drugs. These figures are consistent with the recent published literature on PIP measured by Beers criteria in populations with and without cognitive impairment. A systematic review by Redston *et al.* in 2018 found a wide variation of potentially inappropriate medications according to Beers criteria among 35 studies in patients with cognitive impairment, ranging from 20.6 % to 80.5%.<sup>1</sup> Another systematic review by Johnell included 11 studies that identified PIP applying former versions of Beers criteria and reported an inappropriate drug use ranging from 10.2% to 56.4%.<sup>4</sup> In our study, the most frequent drug categories involved in PIP were diuretics, benzodiazepines and antidepressants. These groups of drugs are included in the 2019 AGS Beers Criteria with a strong recommendation to be used with caution in older people (certain diuretics and antidepressants) or to be avoided in the presence of cognitive impairment (benzodiazepines). However, clinicians as well as other health professionals and patients should bear in mind that potentially inappropriate prescriptions (PIP) are not necessarily always inappropriate. The lack of electrolytes monitoring was the most common reason for potential inappropriateness of drugs in our study. It is imperative to understand the rationale behind each recommendation and adjust treatment accordingly. For instance, in order to reduce the risk of SIADH or hyponatremia, sodium levels should be strictly monitored when hydrochlorothiazide and escitalopram are prescribed. As already commented by Steinmann & Fick, Beers criteria

Table 3. Bivariate and multivariate logistic regression analysis on factors associated with potentially inappropriate prescribed drugs (n=70; 40.2%)

Variable	Bivariate			Multivariate	
	N	(%)	OR (95%CI)	OR (95%CI)	
Sex	Male	37	37.4	(ref)	
	Female	33	44.0	<b>1.32</b> (0.71-2.43)	
Age (years old)	60-65	22	40.9	(ref)	
	66-75	16	30.2	0.53 (0.24-1.20)	
	71-75	21	42.0	0.89 (0.40-1.97)	
	>76	11	50.0	<b>1.22</b> (0.45-3.36)	
Years of education	0	10	52.6	(ref)	
	1-7	10	55.6	<b>1.13</b> (0.31-4.14)	
	8-12	40	36.1	0.59 (0.22-1.58)	
	13-17	10	27.8	0.35 (0.11-1.10)	
Nº of prescribed drugs	1-2	30	28.6	(ref)	
	3-4	29	58.9	<b>3.30</b> (1.64-6.62)	<b>3.34</b> (1.65-6.76)
	>4	11	61.1	<b>3.93</b> (1.39-11.09)	<b>4.08</b> (1.42-11.69)
Nº of diagnosed diseases	1-2	60	39.0	(ref)	
	>2	10	50.0	1.57 (0.62-4.00)	
MoCA score	≥23	10	27.8	(ref)	
	<23	60	43.5	<b>2</b> (0.90-4.47)	<b>2.11</b> (0.91-4.89)



become a valuable support tool if applied wisely.<sup>20</sup>

The only significant factor associated with PIPs resulted the number of prescribed drugs. Two studies conducted in Serbia detecting PIP with the STOPP-START tool also identified benzodiazepines as frequent inappropriately prescribed drugs and higher number of medications as risk factor for PIP.<sup>14,15</sup> Indeed, polypharmacy was a strong predictor for PIP in most published research worldwide.<sup>21,22</sup>

We chose to identify potential MCI by applying the MoCA tool because several studies have shown that it is more appropriate than other screening tools (such as the Mini Mental State Examination) for the detection of MCI among patients over 60 years old.<sup>23,24</sup> Despite the absence of an official diagnosis of MCI, this condition was present in almost 80% of the participants of our study according to the MoCA tool. Undetected MCI contributed to more PIP among this population, although this was not statistically significant. This is in line with the findings by Johnell, who did not find an association between inappropriate drug use and cognitive impairment or dementia, probably explained by increased awareness among physicians when prescribing for this vulnerable group.<sup>4</sup> Nevertheless, this explanation does not seem plausible for our study, as MCI was undetected and not considered by prescribers in this population. Additional multicenter studies are needed to elucidate the prescribing patterns in older people with cognitive decline. This research was limited to one country (Albania) and two primary healthcare centers of the cities of Tirana and Shkodra. Therefore, findings cannot be extrapolated to the entire older population receiving primary care. Limitations of this study include the non-random selection of patients, the unavailability of clinical data and lack of patient assessment which might have

influenced the results obtained. Furthermore, these results should be interpreted with caution in the context of limitations related to the accuracy and sensitivity of the employed tools to detect PIP and MCI, respectively, Beers criteria 2019 update and MoCA tool.<sup>7,25</sup>

## CONCLUSIONS

Potentially inappropriate prescribing affects approximately four out of 10 older patients in primary care and three or more than three drugs prescribed is the most significant factor associated with it. The improper use of diuretics, antidepressants and benzodiazepines needs to be addressed. Cautious and tailored prescribing for patients with cognitive impairment should be encouraged, taking into account all patients' conditions and specific needs. Explicit tools such as Beers criteria aiming to optimize prescribing might help in careful decision-making regarding pharmacological treatment selection. Further studies are needed entailing larger populations and complete patient assessment for a comprehensive estimation of the prevalence and factors associated with PIP.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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