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Popović, Branislava; Quadranti Radošević, Nives; Matanović Mimica, Suzana; Diminić-Lisica, Ines; Ljubotina, Aleksandar; Duliba Pezelj, Dubravka; Vlahović-Palčevski, Vera

Eur J Clin Pharmacol (2014) 70:737–744
DOI 10.1007/s00228-014-1667-0

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Potentially inappropriate prescribing in elderly outpatients in Croatia

Branislava Popović · Nives Radošević Quadranti · Suzana Mimica Matanović · Ines Diminić Lisica · Aleksandar Ljubotina · Dubravka Pezelj Duliba · Vera Vlahović-Palčevski

Received: 6 December 2013 / Accepted: 2 March 2014 / Published online: 21 March 2014

Abstract
Purpose The purpose of this study was to determine the prevalence of inappropriate prescribing to the elderly and to identify possible gender-related differences in prescribing certain potentially inappropriate medications (PIMs) to outpatients by using large administrative prescription database.
Methods Medications prescribed for elderly outpatients (≥ 65 years) in Primorsko-Goranska County, Croatia, who received five or more different drugs simultaneously in 2010, were analyzed. The prevalence of potentially inappropriate drugs prescribed to the elderly was assessed using the new comprehensive protocol developed by authors Mimica Matanović and Vlahović-Palčevski.
Results A total of 62.4 % of patients received at least one medication with unfavorable benefit/risk ratio in the elderly. Female patients were given inappropriate medications in a significantly higher percentage than men (69.3 % vs. 50.5 %; $p<0.001$). The average number of prescriptions for PIMs that should have been avoided with certain diseases or conditions was 0.88 per patient in the survey. The most common drug combination potentially leading to serious drug–drug interactions (DDIs) included an angiotensin-converting enzyme (ACE) inhibitor and a potassium supplement.
Conclusions Our study has shown that every tenth medication prescribed to a patient >65 years and receiving five or more drugs was potentially inappropriate. Elderly women were prescribed PIMs more often than men. Drugs of concern in female patients were benzodiazepines, antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs). In male patients, there was a significantly higher proportion of possible interactions with warfarin, theophylline, and medications affecting the cardiovascular system, such as ACE inhibitors and amiodarone.

Keywords Inappropriate prescribing · Elderly · Outpatients · Polypharmacy · Gender

B. Popović · I. D. Lisica · A. Ljubotina
Department of Family Medicine, University of Rijeka Medical Faculty, Braće Branchetta 20, 51000 Rijeka, Croatia

N. R. Quadranti (✉) · V. Vlahović-Palčevski
Department of Pharmacology, University of Rijeka Medical Faculty, Braće Branchetta 20, 51000 Rijeka, Croatia
e-mail: nives051@gmail.com

S. M. Matanović
Clinical Pharmacology Unit, University Hospital Center Osijek, J. Huttlera 4, 31000 Osijek, Croatia

S. M. Matanović
Department of Pharmacology, Medical Faculty Osijek, University J.J. Strossmayer Osijek, J. Huttlera 4, 31000 Osijek, Croatia

D. P. Duliba
Croatian Health Insurance Fund, Margaretska 3, 10000 Zagreb, Croatia

V. Vlahović-Palčevski
Department of Clinical Pharmacology, University Hospital Center Rijeka, Krešimirova 42, 51000 Rijeka, Croatia

Introduction

Drug prescribing affects the health of the entire population, especially the elderly. Technology and better living standards have extended life expectancy, and consequently, the percentage of the elderly population has increased [1]. In the process of aging, physiological changes occur in all organ systems. These changes significantly alter drug pharmacokinetics and pharmacodynamics [2]. Many seniors suffer from chronic diseases that require multiple medications [3]. The use of five or more different drugs taken simultaneously is defined as polypharmacy. It is associated with a higher risk of adverse

events, proportionate to the number of prescribed drugs [4, 5], including higher risk of drug–drug interactions (DDIs) and drug–disease interactions. Inappropriate prescribing to the elderly results in increased morbidity, mortality, and health care costs [6, 7]. It is a duty of practicing physicians, especially general practitioners (GPs), to follow evidence-based guidelines and optimize drug treatment accordingly. Dealing with polypharmacy may sometimes be difficult due to lack of valid, applicable, simple, and comprehensive tools to detect potentially inappropriate medications (PIMs).

Several different screening tools exist for detecting inappropriate prescribing. They are generally classified into two main groups: implicit criteria, which are judgment based; and explicit criteria, which are based on expert consensus. Explicit criteria are more suitable for use on large prescribing databases but are usually country specific and can only partially be used internationally [8]. A set of explicit criteria developed by Beers et al. [9, 10] and updated by Fick et al. in 2003 [11] are often used in research and clinical practice and for many years have been considered the gold standard for detecting PIMs in the elderly. However, those criteria have some limitations and cannot be applied uniformly to all settings [3]. The latest version of Beers criteria was published in 2012, offering some advantages over the former version [12]. However, as they are too broad [e.g., all benzodiazepines, antipsychotics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are considered inappropriate], those criteria are difficult to compare with other explicit criteria. Gallagher et al. developed a screening tool for identifying PIMs in older patients called Screening Tool of Older People's Potentially Inappropriate Prescriptions (STOPP) that proved to be more sensitive than Beers criteria in identifying patients with PIMs [13]. Prescribing habits, national drug policies, and availability of certain drugs vary between countries, and a majority of screening tools are country specific and not applicable to all settings.

A new and comprehensive protocol for detecting PIMs in the elderly has been published [14]. It consists of four parts: drugs with unfavorable benefit/risk ratio, drugs with questionable efficacy, drugs to be avoided with certain diseases/conditions, and potentially serious DDIs. In addition to the listed PIMs and potentially serious DDIs, the protocol gives alternative therapeutic solutions. It was developed in 2008 by combining four existing PIM screening tools with the addition of several new drugs (Beers 2003 criteria, the French consensus panel, McLeod's list, and Lindblad's list of clinically important drug–disease interactions were combined). As every PIM screening tool has advantages and disadvantages, we chose the clinically most useful parts of these criteria and included them in one protocol. A list of potentially clinically important DDIs was compiled by combining and modifying Malone's and Hanlon's lists with the addition of four new DDIs. Detecting PIMs and clinically important DDIs within the same protocol gives a simple overview of drug-prescribing patterns in the elderly and enables prediction of possible adverse outcomes. Our protocol is not country specific, and we assume that it can be used internationally by prescribers and pharmacists in ambulatory and clinical settings. The tool has been tested in the population of acutely hospitalized elderly [15]. Sensitivity of this new protocol has not been tested on a large administrative database and in an ambulatory setting. According to statistical information provided by the Croatian Bureau of Statistics, in 2011, 17.3 % of the population in Croatia was >65 years, and Croatia is classified in the group of countries with an aging population [16].

The purpose of this study was to determine the prevalence of inappropriate prescribing to the elderly and identify possible gender-related differences in prescribing certain PIMs to outpatients in Primorsko-Goranska County, Croatia, by using a large administrative prescription database and the new comprehensive protocol [14].

Methods

This study is a part of large pharmacoepidemiological survey of inappropriate prescribing in the elderly in Croatia. It concerns outpatients in Primorsko-Goranska County, located in the northwestern part of Croatia, along the Adriatic coast, with a population of 303,491 inhabitants, of which 57,816 (19.05 %) are >65 years (58.5 % female) [15]. Information on prescribed drugs for 2010 was retrieved from the electronic database of the Croatian Health Insurance Fund, which contains data on all reimbursed drugs prescribed to outpatients. The insurance coverage is nearly 100 % of the population. In Croatia, only GPs may prescribe reimbursable drugs, which often occurs upon the recommendation of hospital specialists. Thus, data on prescribed drugs are complete, and exclude medications for hospitalized patients and over-the-counter" (OTC) medications. We analyzed medications prescribed by GPs to elderly patients (≥ 65 years) who receive five or more different drugs simultaneously. Simultaneous drug prescribing was considered if drugs were prescribed within the same month. Each patient's personal data were coded, so that for each anonymized patient, year of birth, gender, prescribed drugs coded by the Anatomical Therapeutic Chemical Classification (ATC), dose, amount, diagnosis by the *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision (ICD-10), prescription date, date of dispensing the drug, and the prescriber's code were noted.

The prevalence of potentially inappropriate drugs prescribed to the elderly was assessed using a new comprehensive protocol published in 2012 by Mimica Matanović and Vlahović-Palčevski [14]. This PIMs screening protocol consists of drugs with unfavorable benefit/risk ratio (33 criteria of individual drugs), drugs with questionable efficacy (six

individual drugs), drugs to be avoided with certain diseases/conditions (71 individual drug–disease interactions involving 28 diseases or conditions), and potentially serious DDIs (70 DDIs). Identifying drugs with an unfavorable benefit/risk ratio is based on a combination of adjusted Beers list and the French consensus panel. Identifying drugs to be avoided with certain diseases/conditions is based on adjusted Beers list, McLeod's list, and Lindblad's list of clinically important drug–disease interactions. List of potentially serious DDIs was developed by combining adjusted Malone's list of clinically important DDIs in the general population with Hanlon's adjunct to the list, which contains 34 pharmacokinetic and nine pharmacodynamic DDIs in the elderly population; we included six more potentially serious DDIs.

Prescribing drugs with questionable efficacy, which is part of the protocol, could not be evaluated because the administrative database used contains only data on reimbursed medications. Potentially serious DDIs were determined if two potentially interacting drugs were prescribed at an interval of 30 days or less. Statistical evaluation of data was performed using Statistica v.8.0 software (StatSoft Inc., Tulsa, OK, USA). Comparisons were made using chi-square test, with a significance level at $p<0.05$.

Results

The study included 29,418 patients aged ≥65 years (63.2 % women), and mean age was 77 (range 65–103) years. A total of 62.4 % of patients received at least one medication with unfavorable benefit/risk ratio in the elderly. Female patients were given inappropriate medications in a significantly higher percentage than men (69.33 % women, 50.5 % men; $p<0.001$)

Total number of medications prescribed to elderly patients (≥ 65 years) who received five or more different drugs simultaneously in 2010 was 1,315,624, of which 8.56 % was for drugs potentially inappropriate for use by the elderly because of their unfavorable benefit/risk ratio, and 1.96 % for drugs that should be avoided with certain diseases or conditions (Tables 1 and 2). The average number of prescriptions for PIMs with unfavorable benefit/risk ratio among all patients was 3.83 per patient, and 6.13 per patient among patients who were prescribed PIMs. More female patients received PIMs (69 % vs. 51 %), but the average number of PIM prescriptions was higher in men than in women (7.13 vs. 5.71). The most frequently prescribed inappropriate medications with unfavorable benefit/risk ratio were short-acting benzodiazepines (more than half the dose in younger adults: lorazepam>3 mg, alprazolam>2 mg, oxazepam>60 mg) with a supply of >30 days (37.93 % of all inappropriate prescriptions), followed by long-acting benzodiazepines (17.14 %), methyl digoxin>0.125 mg (8.62 %), and doxazosin (8.32 %) (Table 1). Doxazosin, amiodarone, indomethacin, and ticlopidine were more frequently inappropriately prescribed to men, whereas benzodiazepines, antidepressants, piroxicam, methyl digoxin, and nitrofurantoin were significantly more often registered in female patients.

Long-term use of NSAIDs managing osteoarthritis was registered in 10.6 % of patients. Long-term benzodiazepines were used in patients diagnosed with depression in 8.55 % of cases (Table 2). These combinations of drugs/diseases were significantly more often registered in women. NSAIDs in hypertensive senior women were prescribed almost twice as often as in men. Prescribing nonselective beta-blockers to patients with chronic obstructive lung disease was significantly more frequent in men (Table 2). The average number of prescriptions for PIMs that should have been avoided with certain diseases or conditions was 0.88 per patient in the survey. Proportion of these PIM prescriptions in the total prescription number was almost two fold among women (2.39 % women, 1.23 % men; $p<0.001$). Total number of drug combinations potentially leading to serious DDIs was 33,231 (Table 3). Nearly half included a combination of an ACE inhibitor and a potassium supplement (49.1 %). This interaction was significantly more often observed in male patients ($p<0.001$). The second most common DDI was a combination of NSAID with a diuretic (20.73 %), followed by concomitant prescribing of a statin and amiodarone (6.26 %). In male patients, drug combinations with potential for developing DDIs more frequently involved ACE inhibitors, theophylline, warfarin, and amiodarone; in women, it was combinations of antidepressants and NSAIDs.

Discussion

In this study, we used a new screening protocol for inappropriate drug prescribing in the elderly in general practice. According to the results, every tenth medication prescribed to a patient >65 years and receiving five or more drugs was potentially inappropriate. This is the first study that assessed drug prescribing in the ambulatory setting in which a new protocol was applied to a large electronic database of the elderly. The new protocol was previously tested in 454 acutely hospitalized elderly and compared with the 2012 Beers criteria, with focus on ADR-related hospitalizations [15]. PIMs of main concern were the same in both studies: benzodiazepines and NSAIDs. Also, in both studies, the combination of an ACE inhibitor and a potassium supplement was the most common potentially serious DDI. Future research in other elderly populations (e.g., inpatients, long-term-care facilities), with comparison to other explicit tools, is necessary to further prove applicability of our protocol.

A study using computerized pharmacy records of 78,000 patients aged≥70 years was conducted in 2002 in the city of

Table 1 Inappropriate medications prescribed to elderly patients (drugs with unfavorable benefit/risk ratio)

Drug	No. patients with PIMs (% all patients)	Male patients (%)[b]	Female patients (%)[b]	*P* value	OR (95 % CI)	No. Rx for PIMs (%all Rx)
Indomethacin	665 (2.26)	346 (3.20)	319 (1.72)	< 0.001	1.9 (1.6–2.2)	1,698 (0.13)
Piroxicam	1,075 (3.65)	280 (2.59)	795 (4.28)	< 0.001	0.6 (0.5–0.7)	2,706 (0.21)
Antidepressants: amitriptyline, maprotiline	491 (1.67)	112 (1.03)	379 (2.04)	< 0.001	0.5 (0.4–0.6)	2,605 (0.20)
Antipsychotics: fluphenazine, levopromazine	173 (0.59)	57 (0.53)	116 (0.62)	0.331	0.8 (0.6–1.1)	1,155 (0.09)
Long-acting benzodiazepines	4,892 (16.63)	1,597 (14.57)	3,295 (17.72)	< 0.001	0.8 (0.7–0.9)	19,301 (1.47)
Short-acting benzodiazepines	16,041 (54.53)	4,328 (39.99)	11,713 (62.99)	< 0.001	0.4 (0.3–0.41)	42,702 (3.25)
Meprobamate	26 (0.09)	12 (0.11)	14 (0.08)	0.432	1.4 (0.6–3.2)	102 (0.01)
Moxonidine	696 (2.37)	242 (2.24)	454 (2.44)	0.280	0.9 (0.7–1.1)	5,000 (0.38)
Short-acting nifedipine	846 (2.88)	310 (2.86)	536 (2.88)	0.960	0.9 (0.8–1.1)	6,419 (0.49)
Doxazosin	1,300 (4.42)	929 (8.58)	371 (2.00)	< 0.001	4.6 (4.0–5.2)	9,365 (0.71)
Amiodarone	1,669 (5.67)	988 (9.13)	681 (3.66)	< 0.001	2.6 (2.4–2.9)	6,047 (0.46)
Methyl digoxin>0.125 mg	2,028 (6.89)	663 (6.13)	1,365 (7.34)	< 0.001	0.8 (0.7–0.9)	9,709 (0.74)
Ticlopidine	204 (0.69)	101 (0.93)	103 (0.55)	< 0.001	1.6 (1.2–2.2)	1,423 (0.11)
Glibenclamide	168 (0.57)	50 (0.46)	118 (0.63)	0.070	0.7 (0.5–1.0)	889 (0.07)
Baclofen	40 (0.14)	17 (0.16)	23 (0.12)	0.559	1.2 (0.6–2.3)	211 (0.02)
Ferrous sulfate>325 mg/day	104 (0.35)	40 (0.37)	64 (0.34)	0.802	1.0 (0.7–1.5)	318 (0.02)
Nitrofurantoin	1,310 (4.45)	200 (1.85)	1,110 (5.97)	< 0.001	0.2 (0.1–0.3)	2,054 (0.16)
Fluoxetine	153 (0.52)	28 (0.26)	125 (0.67)	< 0.001	0.3 (0.2–0.5)	891 (0.07)
Total	**18,358[a] (62.40)**	**5,467 (50.50)**	**12,891 (69.33)**	< 0.001		**112,595 (8.56)**

PIM potentially inappropriate medications, *OR* odds ratio, *CI* confidence interval, *Rx* prescription

[a] Some patients received multiple PIMs

[b] % of all male/female patients

Rijeka, Croatia. Beers 1997 criteria were applied to detect PIMs, and the most common inappropriate drug prescribed to the elderly was the long-acting benzodiazepine, diazepam, comprising 56 % of all inappropriate drugs, with an overall prevalence of 1.2 % [17]. In our study, long-acting benzodiazepines were the second most frequently prescribed inappropriate medication, with a frequency of 17.14 % of all inappropriate prescriptions, with an overall prevalence of 1.47 %. Although the previous study used a different protocol, long-acting benzodiazepines remain the drugs of concern in the elderly.

In a prevalence study of PIMs prescribed by family physicians to patients ≥65 conducted in southern Ontario, Canada, Howard et al. reported that 16.3 % of seniors received at least one potentially inappropriate medication, with short-acting benzodiazepine prescriptions for >30 days prescribed most frequently (6.4 % of elderly patients) [18]. From data retrieved from computer-based patient records of a group of 150 GPs in The Netherlands between 1997 and 2001, Van der Hooft et al. found that the most frequently prescribed drugs inappropriate for the elderly according to Beers criteria were nitrofurantoin, long-acting benzodiazepines, amitriptyline, promethazine, and cimetidine. NSAIDs in patients with a history of gastric or duodenal ulcer were the most frequently prescribed contraindicated drugs [19]. In our study, long-acting benzodiazepines were the second most frequently prescribed drugs with unfavorable benefit/risk ratio (16.6 %). Nitrofurantoin was prescribed to <5 % of patients. NSAIDs were prescribed to patients with gastric or duodenal ulcers to <0.1 % of patients, but it should be noted that we have taken into account only patients who received NSAIDs for an extended period. According to Cahir et al. one third of the Irish population aged ≥70 years was prescribed at least one PIM in 2007 based on STOPP criteria. The main prescribed drugs were proton-pump inhibitors (PPIs) at maximum therapeutic dose for>8 weeks, NSAIDs for>3 months, and long-acting benzodiazepines for>1 month. Those authors emphasized the association between potentially inappropriate prescribing and polypharmacy [20]. In a large, retrospective, cross-sectional study using combined Beers 1997 and 2002 and McLeod's 1997 criteria, in eight European countries, the prevalence of inappropriate prescribing differed in eastern (41.4 % in Czech Republic) and western Europe (mean 15.8 %, ranging from 5.8 % in Denmark to 26.5 % in Italy). The most frequently prescribed drugs were pentoxifylline, long-acting benzodiazepine (diazepam), amiodarone, and amitriptyline [21].

Osteoarthritis often affects older patients and may lead to substantial disability [22]. Our study shows that patients

Table 2 Drugs to be avoided with certain diseases/conditions

Disease or condition /drug	No. patients with PIMs (% all patients)	Male patients (%)[a]	Female patients (%)[a]	*P* value	OR (95 % CI)	No. Rx for PIMs (% Rx)
Heart failure						
Disopyramide	75 (0.25)	19 (0.18)	56 (0.30)	0.074	0.6 (0.3–0.9)	176 (0.01)
Calcium-channel blockers, except dihydropyridines	160 (0.54)	36 (0.33)	124 (0.67)	< 0.001	0.5 (0.3–0.7)	762 (0.06)
Long term use of NSAIDs	99 (0.34)	36 (0.33)	63 (0.34)	0.988	0.9 (0.5–1.5)	193 (0.01)
Hypertension						
Long term use of NSAIDs	648 (2.20)	160 (1.48)	488 (2.62)	< 0.001	0.5 (0.4–0.6)	1,223 (0.09)
Gastric or duodenal ulcers						
Long term use of NSAIDs	24 (0.08)	7 (0.06)	17 (0.09)	0.573	0.7 (0.2–1.7)	51 (< 0.01)
Renal failure						
Long term use of NSAIDs	9 (0.03)	2 (0.02)	7 (0.04)	0.575	0.5 (0.1–2.3)	16 (< 0.01)
Stress incontinence						
Anticholinergics	52 (0.18)	13 (0.12)	39 (0.21)	0.105	0.6 (0.3–1.0)	173 (0.01)
Arrhythmias						
Tricyclic antidepressants	4 (0.01)	1 (0.01)	3 (0.02)	0.977	0.6 (0.1–5.5)	5 (< 0.01)
AV block						
Digoxin	11 (0.04)	6 (0.06)	5 (0.03)	0.364	2.0 (0.6–6.7)	28 (< 0.01)
Insomnia						
Theophylline	140 (0.48)	51 (0.47)	89 (0.48)	0.998	0.9 (0.6–1.4)	330 (0.03)
Depression						
Long term benzodiazepines	2,514 (8.55)	610 (5.64)	1,904 (10.24)	< 0.001	0.5 (0.4–0.6)	12,754 (0.97)
COPD, asthma						
Long term benzodiazepines	13 (0.04)	5 (0.05)	8 (0.04)	0.871	1.0 (0.3–3.2)	26 (< 0.01)
Beta blockers-nonselective	68 (0.23)	38 (0.35)	30 (0.16)	0.002	2.1 (1.5–3.5)	157 (0.01)
Constipation						
Calcium channel blockers	54 (0.18)	14 (0.13)	40 (0.22)	0.13	2.3 (1.5–3.5)	132 (0.01)
Diabetes						
Corticosteroids	2 (0.01)	2 (0.02)	0	0.263	N/A	12 (< 0.01)
Osteoarthritis						
Long term use of NSAIDs	3,111 (10.58)	733 (6.77)	2,378 (12.79)	< 0.001	2.7 (2.5–2.9)	9,183 (0.70)
Gout						
Thiazide diuretics	10 (0.03)	5 (0.05)	5 (0.03)	0.59	3.4 (1.1–10.0)	16 (< 0.01)
Dementia						
Barbiturates	25 (0.08)	10 (0.09)	15 (0.08)	0.9	2.8 (1.5–5.4)	111 (0.01)
Anticholinergics	73 (0.25)	11 (0.10)	62 (0.33)	< 0.001	2.0 (1.4–2.8)	299 (0.02)
Raynaud syndrome						
Beta blockers	4 (0.01)	1 (0.01)	3 (0.02)	0.977	2.3 (0.5–10.2)	13 (< 0.01)
Hyperplastic prostate						
Anticholinergics	40 (0.14)	40 (0.37)	0	< 0.001	N/A	126 (0.01)
Total						**25,786 (1.96)**

PIM potentially inappropriate medications, *OR* odds ratio, *CI* confidence interval, *Rx* prescription, *AV* atrioventricular, *COPD* chronic obstructive pulmonary disease

[a] % all male/female patients

diagnosed with osteoarthritis are often prescribed NSAIDs for a longer period (10.6 % of patients). It is well known that prolonged use of these drugs may cause gastropathy, bleeding, and salt and water retention [23]. Because of the latter, long-term use of NSAIDs should also be avoided in hypertensive elderly patients. We noted this combination in 2.2 % of patients. Long-term benzodiazepine use should be avoided in elderly patients with depression because it presents a

Table 3 Potentially serious drug–drug interactions (DDIs)

Interactions	No. patients with interactions (% all patients)	Male patients (%[a])	Female patients (%[a])	*P* value	OR (95 % CI)
Antiepileptics					
Carbamazepine, macrolides	6 (0.02)	4 (0.04)	2 (0.01)	0.274	3.4 (0.6–18.2)
Carbamazepine, theophylline	78 (0.27)	39 (0.36)	39 (0.21)	0.021	1.7 (1.1–2.6)
Other drugs with low therapeutic index					
Digoxin, amiodarone	329 (1.12)	147 (1.36)	182 (0.98)	0.003	1.4 (1.1–1.7)
Digoxin, propafenone	141 (0.48)	48 (0.44)	93 (0.50)	0.554	0.8 (0.6–1.2)
Digoxin, verapamil	568 (1.93)	155 (1.43)	413 (2.22)	< 0.001	0.6 (0.5–0.7)
Digoxin, clarithromycin	73 (0.25)	33 (0.30)	40 (0.22)	0.171	1.4 (0.9–2.2)
Lithium, ACE inhibitors	34 (0.12)	12 (0.11)	22 (0.12)	0.997	0.9 (0.4–1.9)
Lithium, NSAIDs	3 (0.01)	2 (0.02)	1 (0.01)	0.635	3.4 (0.3–37.4)
Theophylline, clarithromycin	245 (0.83)	129 (1.19)	116 (0.62)	< 0.001	1.9 (1.5–2.5)
Warfarin, quinolones	18 (0.06)	7 (0.06)	11 (0.06)	0.952	1.1 (0.4–2.8)
Warfarin, allopurinol	347 (1.18)	261 (2.41)	86 (0.46)	< 0.001	5.3 (4.1–6.7)
Warfarin, macrolides	1 404 (4.77)	745 (6.88)	659 (3.54)	< 0.001	2.0 (1.8–2.2)
Great clinical importance					
Benzodiazepines, azole, antifungal agents	27 (0.09)	6 (0.06)	21 (0.11)	0.116	0.5 (0.2–1.2)
Methotrexate, trimethoprim	10 (0.03)	1 (0.01)	9 (0.05)	0.153	0.2 (0.1–1.5)
Theophylline, fluvoxamine	96 (0.33)	25 (0.23)	71 (0.38)	0.037	0.6 (0.4–0.9)
Theophylline, quinolones	105 (0.36)	71 (0.66)	34 (0.18)	< 0.001	3.6 (2.4–5.4)
Warfarin, barbiturates	13 (0.04)	5 (0.05)	8 (0.04)	0.871	1.0 (0.3–3.2)
Warfarin, thyroid hormones	201 (0.68)	68 (0.63)	133 (0.72)	0.382	0.8 (0.6–1.2)
Other clinically important					
Atorvastatin/simvastatin, amiodarone	2 079 (7.07)	1 008 (9.31)	1 071 (5.76)	< 0.001	1.7 (1.5–1.8)
Clopidogrel, PPIs	100 (0.34)	71 (0.66)	29 (0.16)	< 0.001	4.2 (2.7–6.5)
Potassium, potassium- sparing diuretics	211 (0.72)	92 (0.85)	119 (0.64)	0.047	1.3 (1.0–1.7)
SSRIs, metoclopramide	355 (1.21)	63 (0.58)	292 (1.57)	< 0.001	0.4 (0.2–0.5)
SSRIs, tramadol	438 (1.49)	18 (0.17)	420 (2.26)	< 0.001	0.07 (0.05–0.1)
Atorvastatin/simvastatin, macrolides	576 (1.97)	208 (1.92)	368 (1.98)	0.765	0.9 (0.8–1.1)
Clinically significant pharmacodynamic interactions					
ACE inhibitors, potassium- sparing diuretics	1,065 (3.62)	478 (4.42)	587 (3.16)	< 0.001	1.4 (1.2–1.6)
ACE inhibitors, potassium supplements	16,316 (55.46)	6,456 (59.65)	9,860 (53.03)	< 0.001	1.3 (1.2–1.4)
NSAIDs, diuretics	6,888 (23.41)	2,223 (20.54)	4,665 (25.09)	< 0.001	0.8 (0.7–0.8)
NSAIDs, corticosteroids	1,357 (4.61)	306 (2.83)	1051 (5.65)		0.5 (0.4–0.5)
Verapamil, beta blockers	130 (0.44)	29 (0.27)	101 (0.54)	< 0.001	0.5 (0.3–0.7)
Warfarin, antiplatelet agents	18 (0.06)	13 (0.12)	5 (0.03)	0.002	4.5 (1.6–12.5)
Total	**33,231**	**12,723**	**20,508**		

SSRI selective serotonin reuptake inhibitors, *ACE* angiotensin-converting enzyme, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PPIs* proton pump inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *OR* odds ratio, *CI* confidence interval

[a] % of all male/female patients

potential risk of worsening depression [11]. Nevertheless, this drug–disease combination was observed in 8.55 % of patients in our study.

Based on our findings, the main concern is prescribing NSAIDs and long-acting benzodiazepines to the elderly. On the other hand, insomnia and pain are common complaints in the elderly, and adequate therapy should be provided. Benzodiazepines should be prescribed for limited amounts of time because tolerance develops. Almost one quarter of all patients was using a combination of a NSAID and a diuretic. It is surprising that almost 1,000 patients were still using piroxicam, although European Medicines Agency recommended its limited use due to its potential to cause gastrointestinal adverse drug reactions (ADRs) in the elderly. It is essential to educate prescribers regarding PIMs and drugs with potentially serious DDIs, and a software solution that would

warn prescribers regarding those drugs could make significant contribution to better prescribing practices.

Other drugs that should be avoided with certain diseases or conditions were noted in <1 % of patients (Table 2). ICD-10 codes of diagnoses registered in prescriptions in the database were the only source of information about patients' diagnoses and conditions. If we had access to medical records, the proportion of patients receiving drugs that should be avoided with certain diseases or conditions would have probably been somewhat different. However, our study shows that elderly women are prescribed PIMs more often than are men. A French study conducted among 9,294 community-dwelling elderly showed that 15.6 % of male and 25.7 % female individuals used at least one PIM. Those authors concluded that female gender reduced the chances of receiving optimal pharmacotherapy [24]. Drugs of concern in female patients in our study were benzodiazepines, antidepressants, and NSAIDs. In male patients, there was a significantly higher proportion of possible interactions with warfarin, theophylline, and medications that affect cardiovascular system, such as ACE inhibitors and amiodarone. Tragni et al. identified 27 pairs of potentially negatively interacting drugs in Italy: 45.3 % of their study population was exposed to at least one of the drugs/classes of these 27 pairs. Exposure was higher for patients aged≥65 years, men, and those with a large number of drugs (> 10). Combination of ACE inhibitors and NSAIDs were the most concomitant prescriptions [25]. The review by Opondo et al. in 2013 (including19 studies, 14 of which used Beers criteria) found that 20.0 % of prescriptions to elderly persons in primary care is inappropriate. The four most commonly inappropriate medications were propoxyphene, doxazosin, diphenhydramine, and amitriptilyne [26].

The number of prescribed drugs is associated with a high risk of inappropriate prescribing in the elderly [27, 28]. However, managing polypharmacy in general practice is a complex issue, and avoiding PIMs is only one part of the solution. It is essential to prescribe drugs with a clear indication, proven efficacy, and favorable risk-to-benefit profile. If many different specialists are involved in prescribing medications to a patient, GPs should play the central role in balancing and rationalizing the overall number of drugs, taking into account that underuse of drugs with proven efficacy also represents inappropriate prescribing.

Quality assessment of prescribing for older people is an imperative, due to their needs, comorbidities, and cognitive impairment. It can reduce the risk of harm and total health care costs [3]. Spinewine et al. emphasize that choosing the measure to quantify misprescribing in the elderly should depend on study objectives and available data [8].

The main limitation of our study is the lack of access to clinical data and the unavailability of information about clinical outcomes of inappropriate prescribing. The advantage of the study is the availability of a large database of medications prescribed to nearly 100 % of population studied. A new screening protocol using a large administrative database to identify inappropriate drug prescribing in the elderly, developed by Mimica Matanović and Vlahović-Palčevski [14], represents a useful tool for quickly assessing the quality of prescribing to elderly outpatients. The protocol is simple to use and widely applicable to clinical practice because it offers an alternative treatment to a potentially inappropriate one. Future research should include comparison of this tool with other explicit criteria (e.g., STOPP and/or Beers criteria) in the ambulatory setting. Also, it is essential to focus on implementation of this comprehensive protocol in the daily work of general practitioners.

Conflict of interest None.

Contributions of Authors Dr. Branislava Popović: Conception and design of the study, analysis and interpretation of data, drafting and revising the article, and final approval of the manuscript.

Dr. Nives Radošević Quadranti: Conception and design of the study, analysis and interpretation of data, drafting and revising the article, and final approval of the manuscript.

Dr. Suzana Mimica Matanović: Conception and design of the study, interpretation of data, critically revising the manuscript, and final approval of the manuscript.

Dr. Ines Diminić Lisica: Interpretation of data, drafting and revising the article, and final approval of the manuscript.

Dr. Aleksandar Ljubotina: Interpretation of data, drafting and revising the article, and final approval of the manuscript.

Dr. Dubravka Pezelj Duliba: Acquisition and interpretation of data, drafting and revising the article, and final approval of the manuscript.

Dr. Vera Vlahović-Palčevski: Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting and critically revising the article, and final approval of the manuscript.

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