Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs

Matanović, Suzana Mimica; Vlahović-Palčevski, Vera

Eur J Clin Pharmacol (2014) 70:483–490
DOI 10.1007/s00228-014-1648-3

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs

Suzana Mimica Matanović · Vera Vlahović-Palčevski

Received: 17 October 2013 / Accepted: 10 January 2014 / Published online: 24 January 2014

Abstract
Purpose Screening tools for detecting potentially inappropriate medications (PIMs) represent an important way to assess drug prescribing in the elderly. Recently, we introduced a new comprehensive tool to detect both PIMs and clinically important drug-drug interactions (DDI). The aim of the study was to assess the applicability of the new tool.
Methods The new tool was used to detect PIMs and DDI and to assess their relation to morbidity and hospital admissions. It was also compared to the widely used Beers criteria. The study population included 454 consecutive patients aged ≥65 years who were acutely admitted to the Department of Internal Medicine of the University Hospital of Osijek. The Naranjo protocol was used to analyze the causal relationship between a drug and an adverse event.
Results According to the new protocol, 44 % patients were taking PIMs, while 33 % patients were taking drugs with potentially serious DDIs. In 11 % of the overall number of patients, the cause of admission was adverse drug reaction (ADR), and among contributing drugs, 44 % were potentially inappropriate according to our protocol. Gastrointestinal bleeding was the most common diagnosis causing ADR-associated admission, and in 72 % cases, either PIM or a potentially serious DDI was involved.
Conclusion The new Croatian tool detected a high number of patients taking PIMs and/or having potentially important drug-drug interactions. The tool also detected almost half of the drugs contributing to ADR-associated admission. We expect the tool to be useful in prescription evaluation for the elderly inpatient and outpatient population.

S. M. Matanović (✉)
University hospital Osijek, Huttlerova 4, 31000 Osijek, Croatia
e-mail: mimica-matanovic.suzana@kbo.hr

V. Vlahović-Palčevski
University Hospital Rijeka, Krešimirova 42, 51000 Rijeka, Croatia

Keywords Elderly patients · PIM screening tools · Potentially inappropriate medications · Drug–drug interactions · Adverse drug reactions

Introduction

In recent years, geriatric pharmacotherapy has come into focus because the elderly consume most of the health care resources due to their rapidly growing numbers, especially in developed countries [1, 2]. The elderly are at an increased risk of adverse drug reactions (ADRs) as a result of co-morbidities, polypharmacy, and age-related changes in the pharmacodynamics and pharmacokinetics of drugs [3–7].

Potentially inappropriate medications (PIMs) may pose more risks than benefits to a patient, particularly where safer alternative therapies exist for the same condition. Therefore, avoiding PIMs represents a strategy aimed at reducing drug-related mortality and morbidity [8–12].

Several screening tools for the detection of PIMs have been published, the most frequently cited being Beers criteria, developed in the United States. The first version of Beers criteria was published in 1991, with updates in 1993, 2003, and the recent update in April 2012 [13–17]. The recent update has brought major changes in the list of potentially inappropriate drugs. The applicability of Beers criteria to elderly patients in Europe is not straightforward, as many drugs from the Beers list are still unavailable in European countries. Also, some of the Beers criteria are controversial (e.g., amiodarone) and the duplication of treatments or drug-drug interactions are not addressed. Recently, we introduced a new comprehensive tool detecting both PIMs and clinically important drug-drug interactions [18]. The new tool detects PIMs by adapting previously adopted tools: the adjusted 2003 version of Beers criteria (2003 version was used because it was available when our protocol was developed in 2008), the

French consensus panel, McLeod's list, and Lindblad's list of clinically important drug-disease interactions [19–21]. We assumed that combining PIMs and potential drug-drug interactions in the same protocol would enable a more thorough assessment of drug prescribing in the elderly. Thus, we used Hanlon's and Malone's lists of drug-drug interactions in the elderly and expanded them with four more clinically relevant potential drug-drug interactions [18, 22, 23].

As the application of our tool in both detecting and assessing PIM- or drug interaction-related morbidity and hospital admissions had to be tested in a real-life environment, we compared our tool with the new Beers criteria and in relation to hospitalizations for ADRs. The study population included acutely ill elderly patients admitted to the department of internal medicine of a university hospital.

Methods

We prospectively analyzed 454 consecutive patients aged 65 years or more who were acutely admitted to the Department of Internal Medicine of the University Hospital of Osijek during two periods: August–October 2009 and January–April 2010. For each patient, we collected data on drug consumption before admission and during hospital stay: data on types and dosages of all drugs, including OTC drugs and herbal supplements were collected. Drug consumption before admission was referred to all medications that the patient was taking regularly for at least 2 weeks before admission to the hospital, but long-term use of NSAIDs or stimulant laxatives was defined as at least 3 months of continuous use. Data on drugs were obtained by interviewing the patient and were retrieved from medical records and the patient's family physician. Data on the condition or disease causing hospital admission, co-morbidities, serum creatinine values, body weight and history of ADRs were also recorded. Estimation of glomerular filtration rate was calculated using the Cockroft-Gault formula. Patients that were electively admitted (i.e., patients that were admitted for diagnostic evaluation of their condition, where the date of admission was known in advance) were not included.

Potentially inappropriate medicines were analyzed using both our new screening tool and the 2012 Beers criteria [15, 16, 18]. According to our screening tool, we also assessed potentially serious drug-drug interactions.

Among causes of hospital admission, we evaluated those that were likely to be caused by ADRs. The causal relationship between a drug and an adverse event was analyzed using the Naranjo protocol [24]. A trained specialist in clinical pharmacology performed all the Naranjo scoring. As defined by the Naranjo protocol, with scores in the range of 5–8, the relationship was considered probable, while with a score of 9 or more, it was considered definite. Co-morbidity was calculated using both the basic and age-adjusted Charlson co-morbidity index [25].

The aim of the study was to determine: (1) the number of PIMs using two different tools, (2) the frequency of prescribing drugs with potentially serious drug-drug interactions (two drugs in a possible interaction were calculated as a case of one interaction), (3) the frequency of hospital admission caused by ADRs, and (4) the the importance of PIMs in those ADRs. We also assessed the difference in the number of drugs in female and male patients, and also in the number of drugs in groups of patients with or without PIMs. Differences regarding age, sex, co-morbidity, renal function (as a percentage of patients with estimated GF <60 ml/min), history of ADRs, and the number of drugs in groups of patients that were admitted for ADRs or other causes were assessed. In NSAIDs users with or without GI bleeding, the consumption of proton pump inhibitors (PPI) was analyzed.

The study received approval by both ethics committees of the University Hospital of Osijek and the Medical Faculty of Osijek.

Statistical analysis

IBM SPSS Statistics 19 software was used to analyze the data. Comparison of the categorical variables was performed using the χ^2 test or Fisher's exact test, and a comparison of the continuous variables was performed using the *t*-test or the Mann–Whitney test, depending whether the data were normally distributed or not. The Kolmogorov-Smirnov test was used to test the normality of data distribution. While comparing continuous variables in the same patients before and during hospitalization, we used the *t*-test for dependent samples and the Wilcoxon rank-sum test.

Sample size was calculated using GPower software: with 0.05 significance level, 99 % power and large effect size, we calculated that the minimum number of subjects would be 238 (we included more than the minimum number of subjects).

$P<0.05$ was selected as level of statistical significance.

Results

Characteristics of the study population are shown in Table 1. Sociodemographic data, data on drug consumption, and clinical data are included.

The mean number of drugs (SD) before admission and during hospital stay was 5.3 (2.9) and 6.1 (2.9), respectively ($p<0.001$). Women were found to be taking significantly more drugs compared to men (5.6 (2.8)) and 4.8 (3.0), respectively, $p=0.0053$).

Table 1 Study population characteristics

	Number of patients (percentage of all patients)
Sociodemographic characteristics	
Female sex	262 (57.7)
Male sex	192 (42.3)
Age, y	
65–74	232 (51.1)
75–84	198 (43.6)
≥85	24 (5.3)
Drug-related characteristics	
Number of drugs used before admission	
≤4	193 (42.5)
≥5	262 (57.5)
≥9	70 (15.4)
Use of cardiovascular system drugs (ATC class C)	378 (83.3)
Use of ACE inhibitors or ATII blockers	264 (58.2)
Use of nervous system drugs (ATC class N)	243 (53.5)
Use of benzodiazepines	144 (31.7)
Use of NSAIDs	103 (22.7)
Clinical characteristics	
Diagnoses leading to admission	
Ischaemic heart disease	106 (23.3)
Congestive heart failure	79 (17.4)
Acute upper gastrointestinal bleeding	52 (11.5)
Heart conduction disorder	44 (9.7)
Poorly controlled diabetes mellitus	27 (6.0)
Co-morbidities	
Hypertension	220 (48.5)
Ischaemic heart disease	168 (37.0)
Congestive heart failure	137 (30.2)
Diabetes mellitus	131 (28.8)
Peptic ulcer disease	40 (8.8)

Potentially inappropriate medications

As identified by the new protocol, 200 patients (44,1 %) were exposed to a total of 274 PIMs. Among those, 141 patients (31.1 %) were taking one PIM, 44 (9.7 %) patients were taking two PIMs, and 15 patients (3.3 %) had been prescribed three PIMs. The mean number of drugs (SD) in the group of patients taking PIMs was significantly higher as compared to patients not taking PIMs (6.3 (2.7) and 4.5 (2.8), respectively ($p<0.001$)).

The most common PIMs detected by the new protocol were: inappropriate use of NSAIDs (63 times); long-acting benzodiazepines (63 times); amiodarone (47 times), cerebral vasodilators (25 times), and drugs with anticholinergic properties (22 times). All identified PIMs are presented in Table 2.

The new 2012 version of Beers criteria identified a total of 409 PIMs, taken by 263 patients (57,9 %). The most common of them were: non-COX-selective NSAIDs (103), short- and intermediate-acting benzodiazepines (99), and amiodarone (47) (see Table 2.).

Adverse drug reaction-related hospitalizations

ADRs were considered to be cause of admission only in patients meeting a Naranjo score ≥5, i.e., the relationship between the drug and reactions was concluded as probable or definite in those cases. The mean (SD) Naranjo score was 6.9 (0.9) and the highest score was 8 (i.e., there was no case of definite relationship, as there were no re-challenge cases).

Among the 454 patients, in 50 of these ADRs were identified as a cause of admission (11.0 %) (Table 3). PIMs identified by the new protocol contributed to 44 % cases of ADR-related admissions, whereas those identified by 2012 Beers list contributed to 54 % cases of such admissions, respectively.

Half of all ADR-related hospital admissions (25 patients) were attributed to drug-induced upper gastrointestinal (GI) bleeding. Among them, five cases of bleeding were caused by aspirin and 20 cases by NSAIDs. The new protocol identified 64 % of all drug-induced cases of upper GI bleeding, whereas the Beers list identified 88 % of such cases. In our study, NSAID users without upper GI bleeding did not take significantly more proton pump inhibitors (PPIs), as compared to NSAIDs users that were admitted for upper GI bleeding (10.0 % vs 10.8 %, respectively, $p=1.000$).

"Appropriate drugs"were also involved in admission. All admissions caused by warfarine overdose, bradycardia, and hypotension were associated with the use of appropriate drugs (i.e., warfarine, beta blockers (bisoprolol and carvedilol) and ACE inhibitors (lisinopril+hydrochlorothiazide)). Among six patients who were admitted for hypoglycaemia, three of them were using potentially inappropriate glibenclamide, while the other three (appropriate) drugs included insulin, glimepiride, and gliclazide.

Patients that presented with ADRs were more likely to be prescribed inappropriate medications compared to patients without ADRs (64.0 % vs 40.4 % respectively). They were also more likely to be prescribed NSAIDs (46.0 % vs 20.8 % respectively) and warfarine (26.0 % vs 6.9 % respectively).

Patients admitted for ADRs, when compared to those admitted for other diagnoses, did not differ statistically in terms of age (75.6±6.1 vs 74.0.6±5.9, respectively), sex (58.0 % vs. 57.7 %, respectively), number of drugs taken before admission (4.7±2.3 vs. 5.4±3.0, respectively), co-morbidity (expressed as basic or age-adjusted Charlson co-morbidity index: 2.0±1.5 and 2.1±1.5, respectively, and 5.2±1.8 and 5.0±1.6, respectively), renal function impairment (50.0 % vs. 51.2 %, respectively, expressed as the percentage of patients

Table 2 Potentially inappropriate medications identified by the new protocol and the 2012 Beers criteria

New protocol		2012 Beers criteria	
Type of medication	Number of drugs, *N*=274 (percentage of all PIMs)	Type of medication	Number of drugs, *N*=409 (percentage of all PIMs)
Drugs with unfavourable benefit/risk ratio		Drugs to be avoided independent of diagnoses or conditions	
Analgesics		Pain	
Indomethacin	5 (1.8)	Indomethacin	5 (1.2)
Concomitant use of two or more NSAIDs	4 (1.5)	Non-COX-selective NSAIDs, oral	103 (25.2)
Long-term use of full-dosage, longer half-life NSAIDs: piroxicam[a]	12 (4.3)		
Drugs with anticholinergic properties		Central nervous system	
Amitriptyline	4 (1.5)	Tertiary TCAs - amitriptyline	4 (1.0)
Maprotiline	1 (0.4)	Antipsychotics – first and second generation	17 (4.2)
Fluphenazine	2 (0.7)		
Promazine	10 (3.6)		
Biperiden	3 (1.1)		
Sedative or hypnotic drugs			
Long-acting benzodiazepines		Benzodiazepines	
Diazepam	44 (16.1)	Long-acting (diazepam, flurazepam)	45 (11.0)
Nitrazepam	12 (4.4)		
Flurazepam	1 (0.4)		
Bromazepam	6 (2.2)	Short- and intermediate-acting	99 (24.2)
Meprobamat	4 (1.5)	Meprobamat	4 (1.0)
		Nonbenzodiazepine hypnotics	26 (6.4)
Antihypertensives			
Centrally-acting: moxonidine	16 (5.8)		
Nifedipine, short-acting	2 (0.7)	Cardiovascular	
Doxazosine	1 (0.4)	Alpha$_1$ blockers – doxazosin	1 (0.2)
Antiarrhythmics		Antiarrhythmic drugs	
Amiodarone	47 (17.2)	amiodarone	47 (11.5)
		propafenone	7 (1.7)
Drugs used to treat gastrointestinal disorders		Anticholinergics (excludes TCAs)	
Scopolamine	2 (0.7)	Antispasmodics - scopolamine	2 (0.5)
Long-term use of stimulant laxatives: bisacodyl[b]	2 (0.7)	Gastrointestinal	
		Metoclopramide	8 (2.0)
Long-acting sulfonylureas		Endocrine	
Glibenclamide	7 (2.6)	Sulphonylureas, long duration - glibenclamide	7 (1.7)
Other		Anti-infective	
Nitrofurantoin	2 (0.7)	Nitrofurantoin	2 (0.5)
Drugs to be avoided with certain diseases/conditions		Drugs to be avoided considering disease or syndrome	
Heart failure – long-term prescription of NSAIDs[a]	7 (2.6)	Heart failure – NSAIDs	7 (1.7)
Hypertension – long-term prescription of NSAIDs[a]	16 (5.8)		
Chronic renal failure – long-term prescription of NSAIDs[a]	5 (1.8)	Chronic kidney disease (stage IV,V) - NSAIDs	5 (1.2)
Gastric or duodenal ulcers – NSAIDs	6 (2.2)	History of gastric or duodenal ulcers – NSAIDs	6 (1.5)
Gastric or duodenal ulcers – aspirin	2 (0.7)	History of gastric or duodenal ulcers – aspirin	2 (0.5)
Patients receiving anticoagulant therapy - NSAIDs	1 (0.4)		
Patients receiving anticoagulant therapy – aspirin	1 (0.4)		
COPD - long-acting benzodiazepines	5 (1.8)		
Osteoarthritis - long-term prescription of NSAIDs[a]	7 (2.6)		
Dementia - benzodiazepines	7 (2.6)	Dementia or cognitive impairment -benzodiazepines	7 (1.7)

Table 2 (continued)

New protocol		2012 Beers criteria	
Type of medication	Number of drugs, *N*=274 (percentage of all PIMs)	Type of medication	Number of drugs, *N*=409 (percentage of all PIMs)
Dementia – conventional neuroleptics	5 (1.8)	Dementia or cognitive impairment - antipsychotics	5 (1.2)
Drugs with questionable efficacy			
Gingko-biloba	9 (3.3)		
Pentoxifylline	4 (1.5)		
Betahistine	8 (2.9)		
Cinnarizine	4 (1.5)		

[a] long-term use of NSAIDs defined as continuous every day use for ≥3 months

[b] long-term use of stimulant laxatives defined as continuous every-day use for ≥3 months

with estimated glomerular filtration rate <60 ml/min), or a positive history of adverse drug reactions (24.0 % vs. 14.9 %, respectively).

Individual drugs (as defined by the new protocol) that caused PIM-related hospital admissions are presented in Table 3. Diclofenac was associated with five cases of upper GI bleeding caused by PIMs.

Drug-drug interactions

A total of 149 patients (32.8 %) were found to be taking drugs with potentially serious drug-drug interactions, as defined by our protocol. Among those, 115 patients (25.3 %) had one potential drug-drug interaction, 21 (4.6 %) patients had two, 11 patients (2.4 %) had three and two patients (0.4 %) had four potentially serious drug-drug interactions. The most common potential drug-drug interactions were: interactions possibly resulting in hyperkalaemia, involving ACE inhibitors, ATII blockers, potassium-sparing diuretics or potassium supplements (56 times); interactions involving the inhibiting effects of amiodarone on other drugs, e.g., warfarine, atorvastatin/simvastatin or methyldigoxin (36 times); interactions between two drugs with CNS depressing properties, e.g., benzodiazepines and opiate analgesics (31 times); and interactions invoving two drugs with anticoagulant/antiplatelet activity (28 times).

Drug-drug interactions possibly contributed to two hospital admissions caused by warfarine overdose and seven caused by upper GI bleeding. Among the latter seven interactions, two were the sole reason for GI bleeding-related admission (interactions of aspirin with diclofenac or ibuprofen), while in the other five cases both PIMs and drug-drug interactions were present. By evaluating both PIMs and drug-drug interactions, our protocol was able to detect 18 among 25 cases of ADR-related GI bleeding.

Discussion

Our protocol identified PIMs in 44.1 % patients and the 2012 Beers criteria identified them in 57.9 % patients. The Beers list identifies entire classes of drugs as potentially inappropriate: all benzodiazepines (short- and long-acting), all new and older antipsychotics, and all non-selective NSAIDs. Our patients were taking those drug classes commonly (31.7 %, 22.7 %, and 5.0 % were taking benzodiazepines, non-selective NSAIDs, and antipsychotics, respectively), which resulted in high percentage of patients with PIMs, as measured by the new Beers criteria. Each drug listed as inappropriate according to the 2012 Beers criteria is not absolutely, but is relatively inappropriate in predefined conditions, which in turn makes straightforward comparison between the 2012 Beers and other explicit criteria difficult.

Including NSAIDs in the PIMs list is appreciated, and we advocated for that when developed our protocol. As confirmed by many studies, NSAIDs are commonly used by the elderly, mostly for chronic musculoskeletal pain [26, 27]. In our study, almost one-quarter of all patients reported taking NSAIDs regularly prior to hospital admission. Chronic pain syndromes in the elderly often necessitate permanent analgesics use, while this age group is particularly at a high risk for NSAID-related ADRs. Advanced age is an independent risk factor for NSAID-related GI toxicity, and when such toxicity occurs, the elderly are at a higher risk for serious complications, e.g., bleeding or perforation [28, 29]. Also, numerous studies have demonstrated theunderutilization of gastroprotective drugs in elderly patients taking NSAIDs [30].

Now that high cardiovascular risk has been recognized as a consequence of selective cyclooxygenase-2 (COX-2) inhibitors use, non-selective NSAIDs have also come into focus for assumed prothrombotic effects and CV toxicity. It appears that NSAID-induced fluid retention and hypertension also contribute to CV adverse effects. There are meta-analyses showing an

Table 3 Hospital admissions caused by adverse drug reactions (ADRs) and the role of PIMs

Type of ADRs causing admission	No. of patients with ADRs causing admission, *N*=50 (percentage of patients with ADRs causing admission)	PIMs causing ADRs, identified by the new protocol (*N*=22)			No. of patients with PIMs causing ADRs, identified by 2012 Beers list *N*=27 (percentage of patients with ADRs causing admission)
		Type of potentially inappropriate medication		No. of patients (percentage of patients with ADRs causing admission)	
Upper gastrointestinal bleeding	25 (50)	indomethacin		1 (2)	22 (44)
		piroxicam		2 (4)	
		NSAIDs with PUD	meloxicam	2 (4)	
			ketoprofen	1 (2)	
		aspirin with PUD	aspirin	1 (2)	
		long-term NSAIDs in osteoarthritis	diclofenac	1 (2)	
		long-term NSAIDs in hypertension	diclofenac	2 (4)	
		long-term NSAIDs in heart failure	ibuprofen	1 (2)	
			diclofenac	1 (2)	
		long-term NSAIDs in renal failure	diclofenac	1 (2)	
		NSAIDs in patients taking warfarin	diclofenac	1 (2)	
		aspirin in patients taking warfarin	aspirin	1 (2)	
		concomitant 2 NSAIDs	piroxicam + meloxicam	1 (2)	
Warfarine overdose	10 (20)	/		0	0
Hypoglycemia	6 (12)	glibenclamide		3 (6)	3 (6)
Bradycardia	3 (6)	/		0	0
Anaphylactic shock	2 (4)	amiodarone		1 (2)	1 (2)
Hypotension	2 (4)	/		0	0
Bowel dysfunction	1 (2)	bisacodyl		1 (2)	0
Hyperthyreosis	1 (2)	amiodarone		1 (2)	1 (2)

increased risk for myocardial infarction and stroke with individual non-selective NSAID use. Risks for NSAID-related CV side effects include established CV disease or an estimated 10-year risk >20 % [31].

While some authors opt for the evaluation of GI and CV risk prior to NSAID use in the elderly, regulatory agencies, including the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) recommend using NSAIDs "in minimum effective dose[s] for the shortest possible duration“. In October 2012, the EMA finished its new review on the cardiovascular risks of non-selective NSAIDs, concluding that "the overall benefit-risk balance of these medicines remained positive, but that a small increased cardiovascular risk could not be excluded"[32]. However, the guidelines of the American Geriatrics Society (AGS) for the management of persistent pain in older persons (published in 2009) are in concordance with our recommendations for appropriate analgesics use in the elderly [33]. According to the AGS guidelines, acetaminophen is recommended as an initial and ongoing pharmacotherapy in the treatment of persistent mild to moderate pain in the elderly, while all patients with moderate to severe pain should be considered for opioid therapy. Nonselective NSAIDs and COX-2 selective inhibitors "may be considered rarely, and with extreme caution, in highly selected individuals".

Most studies show that ADRs cause approximately 5 % of hospital admission in general population, but the percentage rises to 10 % in the elderly, which is in concordance with our results [34–38]. In a similar Swedish retrospective study of 154 elderly patients admitted to the emergency department of a university hospital, the admission was drug-related in 14 % patients [39].

The only Croatian study on ADR-related admissions analyzed adult patients (regardless of their age) admitted to the department of internal medicine of a university hospital. The result show that 2.5 % of admissions were caused by ADRs. The difference between results in our two studies (i.e., 2.5 % vs 11 % of ADR-caused admissions) could be explained by the difference in age of the studied population and by different inclusion criteria for acute admission. The main cause for admission in both studies was upper gastrointestinal tract bleeding (64.6 % and 50 %). In the other study, the second cause was cardiac rhythm disturbances caused by methyldigoxin, while in our study the second cause was

warfarine overdose, indicating that digitalis was commonly used 20 years ago. An increasing number of elderly patients are prescribed warfarine today, notably for chronic atrial fibrillation [40].

An Italian study involving 1,756 elderly patients admitted to a geriatric unit showed that 5.8 % of patients had an ADR-related hospitalization. Gastrointestinal disorders, platelet, bleeding, and clotting disorders and cardiovascular disorders were the most frequent ADRs in this study, which is in concordance with our results [41]. Similar results in our study and in studies from other European countries show that we share the same consequences of adverse drugs effects in our elderly patients.

Geriatrics is not recognized as a separate medical specialty in Croatia, nor does a separate geriatric ward exist in our hospitals. This study evaluated patients admitted to the Department of Internal Medicine, and drugs causing ADR-related hospital admissions differ when compared to drugs responsible for admissions to geriatric wards (e.g., side effects of psychotropic drugs are often involved in such cases). Although 53.5 % of the patients were taking at least one ATC class N drug (nervous system), we didn't detect any CNS adverse effects as a cause of admission (e.g., falls or syncope), as those patients would be admitted to a neurology or psychiatry ward instead.

In our study, patients taking PIMs were taking significantly higher numbers of drugs (6.3±2.7 vs. 4.5±2.8), confirming an increased risk for PIMs in patients with polypharmacy. Similar to other studies, a significant number of eldely patients were taking benzodiazepines (31.7 %) or NSAIDs (22.7 %).

The average number of drugs taken by the patients was high both before admission and during hospital stay. This result is also similar to other studies showing polypharmacy in outpatient and inpatient elderly population [42–44]. Most authors agree, however, that we can't define polypharmacy simply as prescribing more than five or nine drugs, but instead, as prescribing "at least one potentially inappropriate drug", because in patients with several chronic conditions the underuse of drugs should also be avoided.

We plan to further test this tool against other similar and widely used tools, such as STOP/START and the Priscus list, in both ambulatory and clinical settings [45–47].

Conclusion

Eleven percent of the study population was acutely hospitalized due to probable ADRs. In this population, the new Croatian tool detected a high number of patients taking PIMs and/or having potentially important drug-drug interactions. The number of detected PIMs was lower compared to the 2012 Beers list.

The tool revealed almost half of the drugs contributing to ADR-associated admission, as well as three-quarters of drugs causing admission due to GI bleeding. We expect this tool to be useful in the evaluation of prescription patterns in the elderly inpatient and outpatient population, and will continue to test the tool in various settings, comparing it to other explicit tools.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Chrischilles EA, Foley DJ, Wallace RB, Lemke JH, Semla TP, Hanlon JT (1992) Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. J Gerontol 47(5):M137–M144
2. Barry M (2002) Drug expenditure in Ireland 1991–2001. Ir Med J 95(10):294–295
3. Mannesse CK, Derkx FH, de Ridder MA, Man in't Veld AJ, van der Cammen TJ (2000) Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 29(1):35–39
4. Simonson W, Feinberg JL (2005) Medication-related problems in the elderly: defining the issues and identifying solutions. Drugs Aging 22(7):559–569
5. Hohl CM, Dankoff J, Colacone A, Afilalo M (2001) Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med 38(6):666–671
6. Veehof LJ, Stewart RE, Meyboom-de Jong B, Haaijer-Ruskamp FM (1999) Adverse drug reactions and polypharmacy in the elderly in general practice. Eur J Clin Pharmacol 55(7):533–536
7. Routledge PA, O'Mahony MS, Woodhouse KW (2004) Adverse drug reactions in elderly patients. Br J Clin Pharmacol 57(2):121–126
8. Gallagher P, Barry P, O'Mahony D (2007) Inappropriate prescribing in the elderly. J Clin Pharm Ther 32(2):113–121
9. Hamilton HJ, Gallagher PF, O'Mahony D (2009) Inappropriate prescribing and adverse drug events in older people. BMC Geriatr 9:5
10. Laroche ML, Charmes JP, Bouthier F, Merle L (2009) Inappropriate medications in the elderly. Clin Pharmacol Ther 85(1):94–97
11. Passarelli MC, Jacob-Filho W, Figueras A (2005) Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. Drugs Aging 22(9):767–777
12. Page RL 2nd, Linnebur SA, Bryant LL, Ruscin JM (2010) Inappropriate prescribing in the hospitalized elderly patient: defining the problem, evaluation tools, and possible solutions. Clin Interv Aging 5:75–87
13. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC (1991) Explicit criteria for determinig inappropriate medication use in nursing home residents. Arch Intern Med 151:1825–1832
14. Beers MH (1997) Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch Intern Med 57(14):1531–1536
15. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH (2003) Updating the beers criteria. Arch Intern Med 63(22):2716–2724
16. American Geriatrics Society 2012 Beers criteria update expert panel (2012) American Geriatrics Society updated Beers criteria for

potentially inappropriate medication use in older adults. J Am Geriatr Soc 60(4):616–631
17. Marcum ZA, Hanlon JT (2012) Commentary on the new American geriatric society beers criteria for potentially inappropriate medication use in older adults. Am J Geriatr Pharmacother 10(2):151–159
18. Mimica Matanović S, Vlahovic-Palcevski V (2012) Potentially inappropriate medications in the elderly: a comprehensive protocol. Eur J Clin Pharmacol 68(8):1123–1138
19. McLeod PJ, Huang AR, Tamblyn RM, Gayton DC (1997) Defining inappropriate practice in prescribing for elderly people: a national consensus panel. CMAJ 156(3):385–391
20. Laroche ML, Charmes JP, Merie L (2007) Potentially inappropriate medications in the elderly. A French consensus panel list. Eur J Clin Pharmacol 63(8):725–731
21. Lindblad CI, Hanlon JT, Gross CR, Sloane RJ, Pieper CF, Hajjar ER et al (2006) Clinically important drug-disease interactions and their prevalence in older adults. Consensus statement. Clin Ther 28(8): 1133–1143
22. Malone DC, Abarca J, Hansten PD, Grizzle AJ, Armstrong EP, Van Bergen RC et al (2004) Identification of serious drug-drug interactions: results of partnership to prevent drug-drug interactions. J Am Pharm Assoc 44(2):142–151
23. Hanlon JT, Schmader ES (2005) Editorial. Drug-drug interactions in older adults—which ones matter? Am J Geriatr Pharmacother 3(2): 61–63
24. Naranjo et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239–245
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
26. Graf J (2010) Analgesic use in the elderly: the "pain" and simple truth: comment on "The comparative safety of analgesics in older adults with arthritis". Arch Intern Med 170(22):1976–1978
27. Pickering G (2012) Analgesic use in the older person. Curr Opin Support Palliat Care 6(2):207–212
28. Lanas A (2005) Gastrointestinal injury from NSAID therapy. How to reduce the risk of complications. Postgrad Med 117(6):23–28, 31
29. Scheiman JM (2008) Prevention of NSAID-Induced Ulcers. Curr Treat Options Gastroenterol 11(2):125–134
30. Smalley W, Stein CM, Arbogast PG, Eisen G, Ray WA, Griffin M (2002) Underutilization of gastroprotective measures in patients receiving nonsteroidal antiinflammatory drugs. Arthritis Rheum 46(8): 2195–2200
31. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P (2011) Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 342: c7086
32. European Medicines Agency. European Medicines Agency finalises review of recent published data on cardiovascular safety of NSAIDs. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/10/WC500134090.pdf. Accessed October 10th 2013
33. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons (2009) Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 57(8): 1331–1346
34. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. BMJ 329(7456):15–19
35. van der Hooft CS, Dieleman JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH (2008) Adverse drug reaction-related hospitalisations: a population-based cohort study.Pharmacoep idemiol. Drug Saf 17(4):365–371
36. Schneeweiss S, Hasford J, Göttler M, Hoffmann A, Riethling AK, Avorn J (2002) Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 58(4):285–291
37. Pouyanne P, Haramburu F, Imbs JL, Bégaud B (2000) Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. French Pharmacovigilance centres. BMJ 320(7241):1036
38. Sinha U, Raha S, Wilkins E (2000) Adverse drug reactions and hospital admission of older patients. Age Ageing 29(6):551–552
39. Helldén A, Bergman U, von Euler M, Hentschke M, Odar-Cederlöf I, Ohlén G (2002) Adverse drug reactions and impaired renal function in elderly patients admitted to the emergency department: a retrospective study. Drugs Aging 26(7):595–606
40. Huic M, Macolic V, Vrhovac B, Francetic I, Bakran I, Giljanovic S (1994) Adverse drug reactions resulting in hospital admission. Int J Clin Pharmacol Ther 32(12):675–682
41. Onder G, Pedone C, Landi F, Cesari M, Della Vedova C, Bernabei R (2002) Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 50(12):1962–1968
42. Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ (2006) Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 54(10):1516–1523
43. Hajjar ER, Cafiero AC, Hanlon JT (2007) Polypharmacy in elderly patients. Am J Geriatr Pharmacother 5(4):345–351
44. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN (2008) Polypharmacy: misleading, but manageable. Clin Interv Aging 3(2):383–389
45. Barry PJ, Gallagher P, Ryan C, O'Mahony D (2007) START (screening tool to alert doctors to the right treatment)—an evidence-based screening tool to detect prescribing omissions in elderly patients. Age Ageing 36(6):632–638
46. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D (2008) STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther 46(2):72–83
47. Holt S, Schmiedl S, Thürmann PA (2010) Potentially inappropriate medications in the elderly: the PRISCUS list. Dtsch Arzteblatt Int 107(31–32):543–551