ORIGINAL SCIENTIFIC ARTICLE

ANALYSIS OF POTENTIALLY INAPPROPRIATE DRUG PRESCRIBING IN HOSPITALIZED ELDERLY PATIENTS

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ABSTRACT

The study was conducted at the Clinical Centre Kragujevac, during the period March-May 2016. The study population consisted of patients older than 65 that were treated at different departments of the Clinic for Internal Medicine. Data were collected from hospital medical records of patients and anonymous semi-structured questionnaires. STOPP (screening tool of older people's prescriptions)/START (screening tool to alert to right treatment) criteria from 2014 were used to monitor the outcome of interest. Based on the outcome PIM (potentially inappropriate drugs)/PPO (potential prescribing omissions), respondents were divided into groups of cases - patients to whom at least one potentially inappropriate drug determined by STOPP criteria was prescribed and those with at least one potential prescribing omission determined by START criteria. Control groups were patients without these outcomes. Most commonly, PIM was detected in the treatment of cardiovascular system diseases (27.12%), followed by the use of drugs that predispose falls in elderly (20.34%). The most important risk factors for the occurrence of PIM were female gender (OR=3.27; 95% CI 1.01-10.64), polypharmacy (5-8 drugs used simultaneously) (OR=3.10; 95% CI 1.11-12.04) and with whom the patient lives (OR=11.26; 95% CI 1.46-86.68). The use of STOPP/START criteria is proved to be efficient in the detection of PIM/PPO at the secondary level of health care. Full attention should always be paid to patients who are at the highest risk for inappropriate drug prescription. Doctors should make their decisions conscientiously and in line with clinical evidence, not blindly believing the pharmaceutical representatives.

Keywords: *STOP/START, potential inappropriate prescribing, secondary health care, elderly.*

INTRODUCTION

The inappropriate prescribing of drugs to patients older than 65 is one of the major problems across the world due to its association with increased morbidity, mortality and health care costs. The elderly, as a growing population, are the largest drug consumers (1). Appropriate therapy is the use of drugs in clear clinical indication, for which there is a sufficient number of clinical evidence and for which an appropriate cost-benefit ratio is estimated. Potentially inappropriate prescribing (PIP) is considered when the choice of the drug or the length of the prescribed therapy could harm the patient more than help him/her, as well as an omission in prescribing of a drug that may significantly contribute to prevention of onset, alleviation or cure the disease (2). Potential inappropriate medication is defined by STOPP criteria, while potential prescription omission is defined by START criteria (3). The occurrence of potentially inappropriate drugs (PIM) or potential prescribing omissions (PPO) does not mean that medical problems will occur for certain, but there is always a possibility. The most commonly prescribed potentially inappropriate drugs in the literature are: concurrent use of long-acting benzodiazepine and tricyclic antidepressants, first-generation antihistamines, psychotropic drugs which have hypotension as a side effect (benzodiazepines, antipsychotics, etc.) in patients with hypotension which are prone to falls, inadequate and duplicate use of NSAIDs and opioids, unjustified concurrent use of two drugs that have the same mechanism of action and the absence of calcium and vitamin D in patients with osteoporosis. Also, the most common prescribing omission is the use of NSAID in patients with severe hypertension and theophylline in patients with HOBP (4-9). It is considered that the application of these criteria can significantly reduce the use of inappropriate drugs and the consequences, as well as the economic burden of the health system (10).

The aim of this study is to evaluate the prevalence of prescribing potentially inadequate drugs according to STOPP and START criteria from 2014, in hospitalized elderly patients (≥65 years) and to detect associated factors.

MATERIALS AND METHODS

Study design

The research was designed as an observational, non-therapeutic, prospective cross-sectional study, with a nested case-control study. The study was conducted at the Clinical Centre of Kragujevac, the Clinic for Internal Medicine, during the period March-May 2016. The study population consisted of patients older than 65 that were treated at different departments of the Clinic for Internal Medicine. Data were derived from the hospital medical records of patients, follow-ups and relevant medical documentation and anonymous semi-structured questionnaires. The questionnaire used for interviewing patients detected the necessary socio-demographic and clinical data: age, sex, place of residence, with whom the patient lives, level of education, workplace before retirement, the number of drugs in chronic therapy, life habits (use of alcohol and smoking, physical activity), comorbidity and allergies. The questionnaire used for interviewing doctors detected the data related to the working years, specialization, working hours per day, as well as the number of visits by pharmaceutical company representatives per month and the use of pharmacotherapy guides. Before the interview, each patient was informed about the goal and the significance of the research, that participation is voluntary and can be dropped at any time. The data were collected after obtaining a written consent for participation in the study. The test was carried out using the face-to-face technique. Identity of patients was protected by assigning an identification number that was used in the further work. Protection of rights and the safety of the respondents included in the study were provided, as confirmed by the positive decision of the Ethics Committee of the Clinical Centre of Kragujevac.

Based on the following outcome - PIM/PPO, respondents were divided into groups of cases - patients to whom at least one potentially inappropriate drug determined by STOPP criteria was prescribed or patients with at least one potential prescribing omission determined by START criteria. Control groups were patients without these outcomes. Cases and controls were matched by age (± 1 year). To monitor the outcome of the interest, STOPP/START criteria from 2014, made up of 80 STOPP and 34 START criteria, were used (3).

Study population

The study population consisted of patients with different socio-demographic and clinical characteristics, within the following inclusion criteria: aged 65 and above, hospitalization at one of the Internal Clinic Departments during the research period, prescription of at least two drugs at the same time and the presence of at least two concomitant chronic diseases. Average age was 73.44 years. Patients excluded from study were those with incomplete documentation, patients under 65, patients with malignant diseases or terminal stage of the disease and those who received health care through home care services or private health institutions.

A total of 18 prescribing physicians were interviewed: five from the Department of Endocrinology and Metabolic Units, seven from the Department of Gastroenterohepatology, two from the Department of Rheumatology and four from the Department of Allergology.

The following independent and confounding variables were measured:

Independent variables (causes): family history of illnesses, life habits of patients (alcohol use, smoking, physical activity), associated chronic diseases, drug/food allergies, number of drugs for chronic diseases, years of work experience of the physician and the number of patients examined

per day, physicians use of referent literature and participations in the programs of continuous medical education from the areas of rational therapy, number of visits by pharmaceutical company representatives. In order to monitor the influence of the previously mentioned factors on the observed outcome, they are formulated as continuous or categorical variables.

Confounding variables (sociodemographic characteristics): age, sex, socio-economic status, education level, independent living or in a community (with a partner or family).

Data analysis

Data were collected using Microsoft Excel 2007 and were processed descriptively at first. Kolmogorov-Smirnov test was used to determine data distribution. Mann Whitney was used to determine the significance of the difference in the values of the continuous variables between cases and controls. Chi-squared test was used to estimate the significance of the difference in frequency in the categorical variables. The influence of independent and confounding variables on the observed dichotomous outcomes (PIM/PPO) was tested using univariate and multivariate binary logistic regression. The strength of association is shown by a crude and adjusted odds ratio (OR) with a corresponding 95% confidence interval (95% CI). Probability value <0.05 was taken as statistically significant. Statistical program SPSS version 19.0 (SPSS Inc., Chicago, IL) was used for all analyses.

RESULTS

The study included a total of 109 elderly patients hospitalized at the Clinic for Internal Medicine at Clinical Centre Kragujevac, Serbia 60 (55.05%) of which were women and 49 (44.95%) men. Potentially inappropriate medication was observed in 59 cases, while the absence of a clinically indicated drug was detected in 17 cases (Table 1.). Regarding the distribution of outcomes depending on sex, both PIM and PPO occurred more often in women (n= 36 and 9) than in men (n=23 and 8).

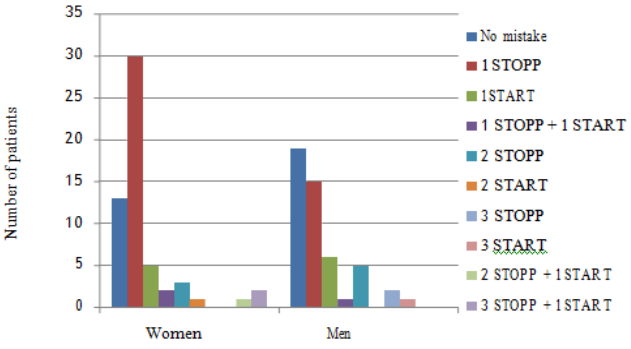
Table 1. Observed outcomes of interest depending on the hospital department

		Department at the Clinic for Internal Medicine				
		Endocrinology	**Metabolic unit**	**Gastroenterohepatology**	**Rheumathology**	**Allergology**
Outcome	No prescribing error	9	4	1 5	3	2
	PIM	14	6	1 8	6	15
	PPO	5	1	8	2	1

Characteristics of the observed population

Most patients lived in the city or a suburban area (55.5%), with their families (63.3%) and had completed only primary school (59.6%). Most of them were adhering to good living habits – 83.5% of patient were non-smokers and 92.7% of them never used alcohol. Most of the patients also had physical activity on daily basis (72.5%), especially after the deterioration of health status and hospitalization. However, a number of patients had 3 associated chronic diseases (36.7%) for which they were prescribed between 5 and 8 drugs as concomitant daily treatment (62.4%). Patients treated at the Clinic for Internal Medicine mostly had positive history of illnesses in their family (55%). Food or drug allergies were recorded in a small number of patients (24.8%).

Figure 1. Distribution of inappropriate prescription depending on gender



A total of 18 prescribing physicians were interviewed from all the departments of the clinic. All physicians stated that they visited some of continuous medical education on rational drug use during the last year and that they were using pharmacotherapy guides or other professional literature in their work, both for the treatment and the diagnostics. Most of them (89%) have been visited monthly by the representatives of pharmaceutical companies.

Prescribing Potentially Inappropriate Drugs to Older Patients (PIM)

Potentially inappropriate medication was recorded in 59 cases. In most cases, the prescription of only one PIM was recorded (78.69%), while prescribing 2 or 3 PIMs in the same patient was detected in a smaller percentage (16.39% and 4.92%), respectively.

The largest number of PIM was recorded in the therapy of cardiovascular disorders (27.12%). Prescription of drugs that predispose falls in elderly patients was recorded in 20.34% of cases. In all these cases, benzodiazepines were used. Drug prescribing without a clear indication and use of antihistamine of I generation as the first line of therapy were detected in 13.56%. Duplication of therapy, inappropriate antithrombotic/anticoagulant or endocrinology therapy was detected in 11.86%, 10.17% and 3.39%, respectively. Most often errors made are presented in Table 2.

Table 2. Distribution of PIM by pharmacological groups

PIM	Number of events
Cardiovascular system	
Application of beta blockers in combination with verapamil (risk of heart failure)	1
Application of thiazide diuretics in a patient with hypercalcemia	1
The use of antihypertensive agents with central effect (methyldopa) in the absence of intolerance or inefficiency of other antihypertensive agents	10
Administration of amiodarone as the first line of therapy in patients with supraventricular arrhythmias (higher risk of adverse effects than beta blockers, digoxin, verapamil or diltiazem)	4
Endocrine system	
Application of long-acting sulfonylurea derivatives (glimepiride) in patients with diabetes mellitus type 2	2
Antithrombotic and anticoagulant drugs	
NSAID in combination with antithrombotic drugs without present proton pump inhibitor (PPI) therapy as a peptic ulcer prophylaxis	6
Allergies	
Application of first-generation antihistamines (there are safer and less toxic antihistamines)	8
Duplication therapy	
Simultaneous application of two drugs with the same mechanism of action (NSAID)	7
Use of drugs that predispose falls in the elderly	
Benzodiazepines	12
Indication	
Application of the drug without a clear indication	8

Doctors prescribed two non-steroidal anti-inflammatory drugs in some cases, which was unnecessary duplication of therapy, with consequent increase in the risk of adverse effects. Use of NSAIDs in combination with antithrombotic drugs, without simultaneous prophylactic administration of PPI was recognized as a potential prescribing error. Proton pump inhibitor should reduce the risk of peptic ulcer and consequent bleeding in the digestive tract. A trend of frequent prescribing of benzodiazepines to elderly patients was also observed, which according to STOPP criteria were labeled as drugs to be avoided in this population.

Table 3. Socio-demographic characteristics of patients in whom PIM is detected

Characteristics		Cases n=59	Controls n=33	Statistics		Crude OR with 95% CI
Age (mean value ± standard deviation)		73.98 ± 6.72 (66-88)	72.69 ± 6.65 (66-92)	p=0.266	-	1.04 (0.98; 1.11)
Days spent in hospital (mean value ± standard deviation)		5.61 ±4.09	7.70 ±9.53	p=0.333	-	0.95 (0.88; 1.03)
Number of drugs for chronic therapy	1-4	3 (5.08%)	3 (9.09%)	p=0.026 U=1145.0 Z=-0.968	-	2.03 (1.03; 3.40)
	5-8	35 (59.32%)	24 (72.72%)			
	>9	24 (40.68%)	5 (8.47%)			
History of illness in family	yes	37 (62.71%)	11 (33.33%)	p=0.047 U=1043.0 Z= -1.908	χ^2=0.086 (2.952)	2.17 (0.98; 4.80)
	no	22 (37.29%)	22 (66.67%)			
With whom the patient lives	Alone	10 (16.95%)	1 (3.03%)	p=0.468 U=1195.0 Z= -0.725	χ^2=0.077 (5.132)	0.72 (0.40; 1.27)
	With a spouse	11 (18.64%)	11 (33.33%)			
	With family	38 (64.41%)	21 (63.63%)			
Place of living	Country-side	27 (45.76%)	13 (39.39%)	p=0.606 U=1222.0 Z= -0.516	χ^2=0.750 (0.101)	0.81 (0.37; 1.78)
	City	32 (54.24%)	20 (60.61%)			
Education	Primary school	37 (62.71%)	16 (48.48%)	p=0.538 U=1208.0 Z=-0.615	χ^2=0.608 (0.996)	0.80 (0.44; 1.43)
	High school	18 (30.51%)	13 (39.39%)			
	College	4 (6.78%)	4 (12.12%)			
The department at which the patient is hospitalized*	1	6 (10.17%)	9 (27.27%)	p=0.097 U=1051.0 Z=-1, 661	χ^2=0.112 (7,490)	1,31 (0,97; 1,78)
	2	6 (10.17%)	4 (12.12%)			
	3	18 (30,51%)	15 (45,45%)			
	4	6 (10,17%)	3 (9,09%)			
	5	15 (45,45%)	2 (6,06%)			
Allergy	yes	16 (27,12%)	8 (24,24%)	p=0,860 U=1269.0 Z=-0,177	χ^2=1,000 (0,000)	1,10 (0,43; 2,77)
	no	43 (72,88%)	25 (75,74%)			

*1-Endocrinology, Diabetes and Metabolic Disease, 2-Metabolic Unit, 3- Gastroenterohepatology, 4- Rheumatology, 5-Allergology

Most of the patients (88.13%) in whom PIM was detected reported that they had previously experienced hospitalization at one moment in their life. In the control group, 57.57% of patients have never been hospitalized before. Characteristics of patients in whom PIM was detected are given in Table 4.

Table 4. Characteristics: Life habits of patients

Characteristics		Cases n=59	Controls n=33	Statistics		Crude OR with 95%CI
Smoker	yes	10 (16.95%)	6 (10.17%)	-	χ^2=0.876 (0.024)	0.79 (0.27; 2.30)
	no	49 (83.05%)	27 (45.76%)			
Use of alcohol	Daily	0	0	p=0.282 U= 1213.5 Z= -1.075	χ^2=0.355 (3.249)	1.64 (0.79; 3.42)
	Several times per week	0	1 (3.03%)			
	Once per week	0	0			
	Once per month	2 (3.39%)	2 (6.06%)			
	Once per year	1 (1.69%)	0			
	Never	56 (94.91%)	30 (90.91%)			
Physical activity	Daily	42 (71.19%)	21 (63.64%)	p=0.446 U= 1198.0 Z= -0.763	χ^2=0.496 (1.403)	1.21 (0.77; 1.90)
	>1 in a week	1 (1.69%)	2 (6.06%)			
	Rarely	16 (27.12%)	10 (30.30%)			

The largest number of participants from the "case" group had 3 (35.7%) or 5 (19.6%) concurrent chronic diseases. In the control group, most patients had 3 (41.3%) or 4 (21.7%) diseases present at the same time, for which they used chronic therapy. The statistical significance of the relationship between observed outcome and co-morbidity had not been established (p = 0.124).

Using adequate statistical tests as significant factors (p <0.05) for the observed outcome, showed to be factors listed in Table 5. However, when adjusted for other independent and confounding variables, some of factors were lost. By implementing the multivariate model the most important factors were the ones shown in Table 5.

Table 5. Results of multivariate binary logistic regression

Variable	Adjusted OR
Sex (women)	3.27 (1.01; 10.64)
Age	1.09 (1.00; 1.19)
Previous hospitalization (yes)	0.21 (0.05; 0.85)
Number of drugs for chronic diseases (5-8)	3.10 (1.11; 12.04)
History of illness in family (yes)	0.32 (0.11; 0.92)
With whom patient lives (with a spouse)	11.26 (1.46; 86.68)
Visits by representatives of pharmaceutical companies	0.08 (0.003; 2.18)

OBSERVED OUTCOME: THE ABSENCE OF PRESCRIBING A CLINICALLY INDICATED DRUG (PPO)

The absence of prescribing a clinically indicated drug was reported in 17 cases, determined by START criteria. One indicated drug that was omitted per patient was detected in most cases (86%), while two or three were left out in a smaller percentage (9% and 5%, respectively).

Potential prescription omission was detected in the treatment of cardiovascular system diseases in 52.94%, followed by musculoskeletal (29.41%) and urogenital tract disease therapy (17.65%). Errors occurred in drug application for central nervous system and eye therapy were detected in 5.88%. Out of 32 START criteria, 8 were detected in this study (Table 6).

Table 6. Distribution of PPO depending on the pharmacological group

Organ system	Number of events
Cardiovascular system	
Antithrombotic therapy in patients with a history of coronary, cerebral or peripheral vascular events	3
Application of statins in patients with a history of coronary, cerebral or peripheral vascular events	4
Beta blocker in patients with heart ischemia	2
Central nervous system and psychotropic drugs	
L-dopa in the treatment of idiopathic Parkinson's diseases	1
Musculoskeletal system	
Application of bisphosphonate, vitamin D and calcium in patients on long-term therapy with systemic corticosteroids	1
Vitamin D and calcium in patients with osteoporosis and/or previous fractures	4
Urogenital system	
Blocker of alpha-1 receptor in patients with prostatism to whom prostatectomy is not indicated	3
Eyes	
Topical prostaglandin, prostamide or beta blocker in patients with glaucoma open angle	1

Table 7. Characteristics of patients in whom PPO was detected - Socio-demographic characteristics

Characteristics		Cases n=17	Control n=33	Statistics		Crude OR with 95% of CI
Age (mean value ± standard deviation)		69.35 (66-87)	75.21 (66-92)	p=0.967 U=821.5 Z= 0.041	-	0.979 (0.90; 1.06)
Days spent in hospital (mean value ± standard deviation)		7	16,8	p=0.447 U=811.5 Z= 0.124	-	0.96 (0.84; 1.08)
Number of drugs for chronic therapy	1-4	4 (23.53%)	3 (9.09%)	p=0.871 U=809.5 Z=0.162	χ^2=0.137 (5.144)	0.85 (0.37; 1.92)
	5-8	9 (52.94%)	24 (72.73%)			
	>9	4 (23.53%)	6 (18.18%)			
History of illness in family	yes	12 (70.59%)	11 (33.33%)	p=0.159 U=679.0 Z=-1.407	χ^2=0.246 (1.345)	2.12 (0.74; 6.08)
	no	5 (29.41%)	22 (66.67%)			
With whom the patient lives	Alone	1 (5.88%)	1 (3.03%)	p=0.916 U=815.5 Z= -0.105	χ^2=0.992 (0.016)	1.04 (0.51; 2.16)
	With a spouse	6 (35.29%)	11 (33.33%)			
	With family	10 (58.82%)	21 (63.63%)			
Place of living	Countryside	9 (52.94%)	13 (39.39%)	p=0.701	χ^2=0.896 (0.017)	0.82 (0.30; 2.23)

Characteristics		Cases n=17	Control n=33	Statistics		Crude OR with 95% of CI
	City	8 (47.06%)	20 (60.61%)	U=796.5 Z= -0.384		
Education	Primary school	12 (70.59%)	16 (94.12%)	p=0.547 U=762.5 Z= -0.602	χ^2=0.192 (3.296)	0.90 (0.42; 1.94)
	High school	3 (17.65%)	13 (76.47%)			
	College	2 (11.76%)	4 (12.12%)			
The department at which the patient is hospitalized*	1	5 (29.41%)	9 (27.27%)	p=0.132 U=651.0 Z= -1.058	χ^2=0.399 (4.054)	0.73 (0.49; 1.08)
	2	1 (5.88%)	4 (12.12%)			
	3	8 (47.06%)	15 (45.45%)			
	4	2 (11.76%)	3 (9.09%)			
	5	1 (5.88%)	2 (6.06%)			
Allergies	yes	3 (17.64%)	8 (24.24%)	p=0,433 U=757.5 Z= -0.784	χ^2=0.628 (0.235)	0.60 (0.16; 2.22)
	no	14 (82.35%)	25 (75.76%)			

*1-Endocrinology, Diabetes and Metabolic Disease, 2-Metabolic Unit, 3- Gastroenterohepatology, 4- Rheumatology, 5-Allergology

Most of the patients (88.23%) in whom PPO was detected, reported that they had previously been hospitalized in a certain period of their lives. In the control group, 57.57% of patients have never been hospitalized before. Characteristics of patients in whom PPO is detected are given in Table 8.

Table 8. Characteristics of patients in whom PPO was detected: Life habits of patients

Characteristics		Cases	Controls	Statistics		Crude OR 95%CI
Smoker	yes	2 (11.76%)	6 (18,.18%)	-	χ^2=0.624 (0.240)	0.52 (0.11; 2.49)
	no	15 (88.23%)	27 (81.82%)			
Use of alcohol	Daily	0	0	p=0.589 U=796.5 Z= -0.540	χ^2=0.699 (1.427)	0.86 (0.41; 1.81)
	Several times per week	0	1 (3,03%)			
	Once per week	0	0			
	Once per month	2 (11.76%)	2 (6.06%)			
Use of alcohol	Once per year	0	0			
	Never	15 (88.23%)	30 (90.91%)			
Physial activity	Daily	16 (94.12%)	21 (63.64%)	p=0.015 U=596.0 Z= -2.241	χ^2=0.043 (6.080)	0.33 (0.11; 0.96)
	>1 in a week	0	2 (6.06%)			
	Rarely	1 (5.88%)	10 (3.03%)			

Characteristics of patients which were recognized as important factors ($p < 0.05$) for the outcomes of interest - PPOs are listed in Table 9. Based on the value of the implemented binary logistic regression, some of the patients' characteristics were declared statistically insignificant for the observed outcome. However, a new factor was distinguished - the presence of multiple diseases in one patient increases the likelihood of PPO occurrence. The significance and magnitude of impact can be seen in the following table.

Table 9. Results of multivariate binary logistic regression

Risk factor	Adjusted OR (95% CI)
Length of hospitalization	0,071 (0,48; 1,03)
Previous hospitalization (yes)	**19,208 (1,13; 326,20)**
Number of drugs for chronic therapy (5-8)	0,404 (0,03; 5,99)
Comorbidities	**4,073 (1,71; 9,70)**
Allergy	0,099 (0,01; 0,96)
Visits by representatives of pharmaceutical houses (once per month)	**25,05 (1,65; 381,26)**
Education (primary school)	0,061 (0,01; 0,68)

Table 10. Characteristics of prescribing physicians / PIM connection

Characteristics	Statistics	Crude OR with 95% CI
Does the doctor attend some forms of continuous medical education regarding rational use of drugs?	U=1288.0 Z=0.000 p=1.00	1.22
Does the doctor have visits from pharmaceutical companies?	U=1099.5 Z= 1.517 p=0.129	1,35 (0.85; 2.15)
Does the doctor use guides and other professional literature when determining therapy?	U=1288.0 Z=0.0 p=1.00	2,21
Number of patients examined by a doctor during one working day	U=795.0 Z= - 3.501 p<0.01	0,83 (0.74; 0.93)

Table 11. Characteristics of prescribing physicians / PPO connection

Characteristics	Statistics	Crude OR
Does the doctor attend some forms of continuous medical education in the field of drug use?	p=1,00	0,218
Does the doctor have visits by representatives of pharmaceutical houses?	U=822.5 Z= - 0,039 p=0,049	2,14 (0,62; 4,08)
Does the doctor use guides and other professional literature when determining therapy?	p=1,00	0,218
Number of patients examined by a doctor during one working day	U=766.5 Z= - 0,520 p=0,603	1,04 (0,93; 1,18)

DISCUSSION

Medication therapy for elderly patients is confronted by major challenges due to the frequent occurrence of comorbidity, polypharmacy, decreased liver and kidney function, greater susceptibility to drug adverse events, and more frequent occurrence of complications (4,5). Compliance with the recommendations given in the pharmacotherapy guides can help to counter the effects of inadequate drug prescribing, reducing the risk of adverse reactions or potential drug interactions, shortening the time of treatment and improving therapeutic outcomes. In order to provide the best therapy and achieve the best possible outcome for a patient, STOPP/START criteria have been formulated (3,4,6,7). The knowledge about factors associated with the wrong choice of therapy in the elderly population allows planning and introducing appropriate corrective measures to improve the quality of drug prescription, which may lead to the significant improvement in the health and economic outcome of the treatment (5,8). Based on the above mentioned, we conclude that there are a number of factors that are directly or indirectly related to inadequate use of drugs. In order to prevent the occurrence of potential prescribing errors, which would significantly contribute to the improvement of the quality of life of elderly patients, there is a need for their control. Researchers from Serbia have been observing the problem of prescribing potentially inappropriate drugs to elderly patients in primary and secondary health care (9-12). Our study showed that mistakes are significantly lower at the secondary health care level than at the primary health care level. In addition to the occurrence in a small percentage, mistakes have also been characterized by low variability - smaller distribution by organ systems in hospital-treated patients, which was expected. Although patients with multiple associated diseases were in worse health condition and using larger number of drugs in their chronic therapy, doctors took more care of the drugs they administered. Prescription of inappropriate drug (PIM) was recorded three times more often than the absence of a clinically indicated drug (PPO).

Evaluating PIM as an outcome of interest, it has been found that its occurrence is more common in women than in men. It was estimated that the chance for its occurrence in the female population is 3 times higher than in males. Simultaneous use of more drugs, polypharmacy, was recognized as the most important risk factor associated with PIM (9-13). Many studies indicate the importance and need for reducing polypharmacy in order to avoid unwanted effects and interactions of drugs (9-13). Considering the overall health of elderly patients and the number of comorbidities requiring treatment, the simultaneous use of a large number of drugs becomes inevitable. As it has been proven in this study, the use of a large number of drugs in chronic therapy is strongly associated with the occurrence of PIM in the observed population. By using the aforementioned adequacy indicators, the risk of such outcome could be reduced in many ways. In addition to using different mechanism of action drugs in the therapy, patients often resort to self-drug administration without informing their physician, which results in drug interactions and/or adverse effect occurrence. By increasing the prescription control and using good clinical practice guides, these unwanted consequences could be minimized. The likelihood of missing the necessary drug in therapy, due to doctor's attempts to avoid polypharmacy in such patients, is even 4 times higher than in patients with smaller comorbidity. Elderly very often come out of doctors' clinics without fully understood therapeutic guidelines, forgetting to take drugs or duplicate them. They are self-initiated by taking new or discontinuing the use of drugs according to the current subjective feeling. Persons with this kind of tendency should be supervised by family or professional persons (14). Polypharmacy was detected as a predisposing factor for PIM in this study, which was defined as the use of 5-8 drugs in a daily therapy. These patients have a triple chance of getting a drug that is not appropriate for their health - PIM. The same findings were obtained by researchers from Kragujevac and Dublin during the examination of the problem of prescribing potentially inappropriate drugs in the elderly population, at the level of primary health care level (12,15). In the study conducted in Kragujevac, it was found that the simultaneous application of more than 9 drugs is one of the predisposing factors. Contrary to the results of this study, they found that PIM in elderly patients is associated with poor life habits of patients and frequent visits by representatives of pharmaceutical companies (12). Our data are in accordance with the results of the study conducted in England, which claims that physicians who more often encounter pharmaceutical representatives often unnecessarily prescribe drugs without clear clinical indication. The reason for this is that the doctors have been influenced by pharmaceutical representatives, blindly accepting their claims (16). Contrary to that, our study showed that visits of pharmaceutical representatives have been the risk factor for the drug absence in prescribing a clinically indicated drug (PPO). There was a slight difference in risk factors between the levels of health care. B. Hill Taylor et al. analyzed the results of 13 relevant clinical studies that examined the application of the STOPP/START criteria and their outcomes, and found that the results of this study largely agree with the findings obtained in other studies (17). They also found that female gender is one of the predictors of prescribing potentially inappropriate drugs in the older population. Most important factors that increase the risk of PIM and PPO as outcomes, in most studies, as in this study are: age (> 75 and 85 years), sex (females), polymedication and comorbidities (17). In a study conducted in nursing homes in New Zealand, it has been demonstrated that the likelihood of PIM occurring is higher in patients with higher and middle risk of falls than those with low risk (18). What has not been done in this study and which is important for discovering the source of the observed problem is the detection of protective factors, which researchers in Kragujevac pointed out in their study (12). At the level of secondary health care, it was noted that errors were distributed in the area of a few organ systems and the same drugs were generally wrongly prescribed. The results of this study generally agree with the results of other studies. In most cases, benzodiazepines should be avoided as

they predispose falls in older patients and the patients should avoid their use for more than a month (8-15,17-20). The use of aspirin often occurs in literature without a clear indication, without the presence of cerebrovascular, cardiovascular or peripheral vascular complications (8,9,13). NSAIDs are found as the most common drugs that were prescribed without a clear indication to the patients of this study, which are very common detected as unduly duplicated therapy. Researchers from Ireland came to the same results (13,15,19). The use of non-steroidal anti-inflammatory drugs in patients with severe essential hypertension is one of the STOPP criteria; however, a trend of their frequent prescription among primary care physicians was observed, followed by theophylline treatment as monotherapy in the treatment of HOBP and proton pump inhibitors in maximal doses longer than 8 weeks, while at the level of secondary health care - in this study, no case was reported (9,12,13,15).

Observing PPOs as outcomes of interest, it has been found that their occurrence is slightly more common in women than in men. In patients who have been hospitalized at least once, the probability of missing clinically indicated drug (PPO) is surprisingly high. Factors that increase the risk of the aforementioned outcome are found to be frequent visits by representatives of pharmaceutical companies (minimum once a month) and comorbidities. Researchers in a study conducted in Serbia in 2014, found that the likelihood of PPO occurring in older patients was increased by their age and comorbidities (9). However, the difference is that they have defined and isolated diseases that are directly related to the observed outcome (DM, osteoporosis, myocardial infarction, HOBP, stroke or angina pectoris), while in this study this has not been performed. Trend of falling under the influence of promotional material and blind belief in the propaganda of pharmaceutical houses was noticed among doctors. They are prone to prescribe drug for personal benefit or pure curiosity about the functioning of new drugs on the market (14).

Most often omitted drugs in literature were antimicrobial drugs and statins in patients with a positive history of cerebral, coronary and peripheral vascular events, as well as vitamin D and calcium supplements in osteoporosis and/or previous fracture and/or T bone density index > -2.5; measured in several places. Most of the studies highlight the same criteria for PPO (12,13,15). In addition, in 15.5% of the study participants in Kragujevac, the use of an ant aggregation drug (aspirin, clopidogrel) in the presence of cerebral, coronary and peripheral vascular events in patients with normal heart rhythm has been omitted (12). Another START criteria that was not detected in this study and is identified in primary health care is the absence of warfarin therapy in patients with chronic atrial fibrillation (13). Researchers found that the probability of missing the necessary drug in therapy is lower in patients who are treated in smaller health institutions and who visit specialist physicians more often. They also concluded that this risk is lower in those patients who have heavier illnesses (18). At the level of secondary health care, it was found that in most cases the errors were 1 PIM and 1 PPO, while at the same time the presence of 2 or more omitted drugs was considerably lower. Results of PPOs found in a study conducted in 2012 do not differ from those found in our study (benzodiazepines, aspirin, NSAIDs, etc.) However, researchers have determined diseases that might be risk factors for the occurrence of PIP: diabetes mellitus type 2, atrial fibrillation, osteoporosis, COPD and ischemic heart disease (20).

This study has several limitations. Primarily, it was conducted in one hospital, mirroring the characteristics of the functioning of the health system of the only one environment, so its results cannot be absolutely generalized. Also, in order to get a more realistic picture of the correctness and rationality of prescribing drugs in hospital conditions, it is necessary to conduct the research on a larger sample of respondents. For the same purpose, a quantitative assessment should also be carried out by a qualitative (e.g. method-based theory) in order to discover the reasons for such prescribing and the factors contributing to it. In this way, we could work on the plan of solving and minimizing inadequate prescription. Although measures have been taken to reduce bias to a minimum, there is still the possibility of information bias. Given that the questionnaires were compiled on the basis of relevant medical literature sources, that the questions for all participants were the same, that they were anonymous, with each respondent having their own identification code, their attendance is expected to be minimal. All data were obtained from the hospital medical records and other relevant sources, so any mistake in them could have influenced the conclusions made in this study.

CONCLUSION

Detection of mistakes in drug prescribing and determination of their prevalence and/or sources in a particular environment represents an important step in the drug use rationalization. This would reduce the occurrence of drug adverse effects and their interactions, thus preserving the fragile health of geriatric patients. In order to achieve the desired goal, it is necessary to improve recognition of the drugs to be avoided in the elderly population, based on their adverse effects and drug interactions. The use of STOPP/START criteria appeared to be effective in the detection of PIM/PPO at the secondary health care level. Attention should be directed to patients at the highest risk of PIM or PPO. They are persons prone to falls, vascular diseases and osteoporosis, have a number of associated chronic diseases and consequently they take more drugs daily. Physicians should pay more attention to each patient individually. They should be encouraged to make the conscientious decisions that are in line with clinical evidence, avoiding to believe blindly to the pharmaceutical representatives. It is important to reduce unnecessary polypharmacy. Overall, functioning of the health care system should be improved, so that doctors can make decisions in the optimal working conditions. In order to achieve abovementioned, it is necessary to work on education of both patients and doctors.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethicalstandards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written and informed consent was obtained from each participant prior toenrollment in the study

CONFLICT OF INTEREST

There are no conflicts of interest.

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REFERENCES

1. Hamilton H, Gallagher P, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. BMC Geriatric. 2009; 9:5.
2. O'Connor M, Gallagher P, O' Mahony. Inappropriate prescribing. Criteria, Detection and Prevention. Drugs Aging 2012; 29(6): 437-52.
3. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age and aging. 2014; 0: 1-6.
4. Reich O, Roseman T, Rapold R, Blozik E, Senn O. Potentially Inappropriate Drug Use in Older Patient In Swiss Managed Care Plan: Prevalence, Determinants and Association with Hospitalization. PLoS ONE 2014; 9(8): e105425
5. Pretorius R, Gataric G, Swedlung S, Miller J. Reducing the Risk of Adverse Drug Events in Older Adults. American Family Physician. 2013; 87(5) 331-36.
6. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. 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. 2008; 46(2):72-83.
7. Gallagher P, O'Mahony. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age and Ageing. 2008; 37: 673–79
8. San-Jose A, Agusti A, Vidal X, Formiga F, Gomez-Hernandez M, Garcia J et all. Inappropriate prescribing to the oldest old patients admitted to hospital: prevalence, most frequently used drugs, and associated factors. BMC Geriatrics. 2015; 15:42.
9. Vezmar Kovacevic S, Simisic M, Stojkov Rudinski S, Culafic M, Vucicevic K, Prostran M, Miljkovic B. Potentially Inappropriate Prescribing in Older Primary Care Patients. PLoS ONE. 2014; 9(4).
10. Stojanovic M, Vukovic M, Jovanovic M, Dimitrijevic S, Radenkovic M. GheOP3 S tool and START/STOPP criteria version 2 for screening of potentially inappropriate medications and omissions in nursing home residents. J Eval Clin Pract. 2019; 1–7.
11. Nedin-Rankovic G, Jankovic S, Velickovic-Radovanovic R et all. Analysis of drug prescribing in patients on hemodialysis treatment. Acta Medica Medianae. 2018; 57(1):12-8.
12. Projovic I, Vukadinovic D, Milovanovic O, Jurisevic M, Pavlovic R, Jacovic S, Jankovic S, Stefanovic S. Risk factors for potentially inappropriate prescribing to older patients in primary care. Eur J Clin Pharmacol. 2016; 72(1): 93-107.
13. Galvin R, Moriarty F, Cousins G, Cahir C, Motterlini N, Bradley M. et all. Prevalence of potentially inappropriate prescribing and prescribing omissions in older Irish adults: findings from The Irish Longitudinal Study on Ageing study (TILDA). Eur J Clin Pharmacol. 2014; 70: 599–606.
14. Kojicic K. Analiza faktora povezanih sa propisivanjem potencijalno neodgovarajućih lekova kod pacijenata starije životne dobi. Racionalna terapija. 2017; 9(2): 1-11.
15. Cahir C, Fahey T, Teeling M, Teljeur C, Feely J, Bennett K. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. BJCP. 2010; 69(5): 543-52.
16. Watkins C, Moore L, Harvey I, Carthy P, Robinson E, Brawn R. Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study. BMJ. 2003; 326 (7400): 1178–79.
17. Hill-Taylor B, Sketris I, Hayden J, Byrnes S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence if potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. J Clin Pharm Ther. 2013; 38: 360-72.
18. Ailabouni N.J, Nishtala PS, Tordoff J.M. Examining potentially inappropriate prescribing in residential care using the STOPP/START criteria. European Geriatric Drug. 2016; 7: 40-6.
19. Yayla M, Bilge У, Binen E, Keskin A. The Use of START/STOPP Criteria for Elderly Patients in Primary Care. Scientific World Journal. 2013; (10):165873.
20. Dalleur O, Spinewine A, Henrard S, Losseau C, Speybroeck N, Boland B. Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs Aging. 2012; 29: 829-37.