Long-term drug use and polypharmacy among the elderly population in the Republic of Srpska, Bosnia and Herzegovina

Stalna upotreba lekova i polifarmacija kod starije populacije u Republici Srpskoj, Bosna i Hercegovina

Vanda Marković-Peković*, Ranko Škrbić[†]

*Pharmaceutical Department, Ministry of Health and Social Welfare, Banja Luka, Republic of Srpska, Bosnia and Herzegovina; [†]Department of Clinical Pharmacology, Faculty of Medicine, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Abstract

Background/Aim. Prescription of drugs is a fundamental care component of the elderly. Elderly patients often take multiple drugs, and it is known that polypharmacy may lead to drug interactions and adverse events. The aim of this study was to analyze the long-term drug use and the prevalence of polypharmacy among the elderly population in the Republic of Srpska, Bosnia and Herzegovina. **Methods.** A retrospective study of outpatient drug use in 2005 and 2010 was conducted, analyzing prescriptions for patients aged ≥ 65 years reimbursed by the Health Insurance Fund. The study population was stratified by gender and age. Long-term drug use was defined as continuous drug dispensing for a whole year or at least two thirds of the year. Polypharmacy was defined as the use of 5 or more different reimbursed drugs. **Results.** Of all insured people aged ≥ 65 years, long-term drug use was identified in 10% (2005) and in 19% (2010), of whom 62% were women. Two to four different drugs were used by almost 49% (2005) and 54% (2010) of the elderly patients. The polypharmacy prevalence increased from 1.4% (2005) to 3.6% (2010); it increased in all the age groups of both genders. The largest increase was observed in the age group 65–74 years. Polypharmacy prevalence increase was higher in women. The most commonly used drugs were those for to treatment of cardiovascular diseases, in particular drugs for hypertension and cardiac treatment. **Conclusion.** The study findings point out to the increase of elderly population with a long-term drug use. Over a half of elderly patients use 2–4 different drugs on the long-term basis. The polypharmacy prevalence was low. It increased in the period of 5 years in both genders. The increase was more prominent in women of all the age groups. The use of multiple drugs and polypharmacy increased with ageing.

Key words:
drug, prescriptions; drug users; drug combinations; aged; bosnia-herzegovina.

Apstrakt

Uvod/Cilj. Propisivanje lekova je ključna komponenta zdravstvene zaštite starijih osoba. Stariji često koriste više lekova, a poznato je da polifarmacija može dovesti do interakcija lekova i neželjenih događaja. Cilj ove studije bio je da se analizira stalna upotreba lekova i prevalencija polifarmacije u starijoj populaciji u Republici Srpskoj, Bosna i Hercegovina. **Metode.** Izvršeno je retrospektivno istraživanje upotrebe lekova koji se izdaju na recept u 2005. i 2010. godini, kroz analizu lekova propisanih osobama starim ≥ 65 godina koji se izdaju na teret Fonda zdravstvenog osiguranja. Ispitivana populacija bila je podeljena prema polu i starosti. Stalna upotreba leka definisana je kao neprekidno izdavanje leka tokom cele godine ili najmanje dve trećine godine. Polifarmacija definisana je kao upotreba pet i više različitih lekova koji se izdaju na teret obaveznog zdravstvenog osiguranja. **Rezultati.** Od svih osiguranika starosti ≥ 65 godina, stalna upotreba lekova koji se izdaju na teret zdravstvenog osiguranja utvrđena je kod 10% (2005) i 19% (2010) starijih, od čega su 62% bile žene. Dva do četiri različita leka koristilo je gotovo 49% (2005) i 54% (2010) starijih osiguranika. Prevalencija polifarmacije porasla je sa 1,4% (2005) na 3,6% (2010), i to u svim starosnim grupama oba pola. Najveći porast primećen je u starosnoj grupi 65–74 godine. Porast prevalencije polifarmacije bio je veći kod žena. Najčešće su korišćeni lekovi za lečenje kardiovaskularnih bolesti, naročito lekovi za lečenje hipertenzije i bolesti srca. **Zaključak.** Rezultati istraživanja ukazuju na porast starije populacije koja stalno koristi lekove. Više od polovine starijih osiguranika stalno koristi 2–4 različita leka. Prevalencija polifarmacije je niska. U 5-godišnjem periodu porasla je kod oba pola. Porast je izraženiji kod žena svih starosnih grupa. Upotreba više lekova i polifarmacija rasli su sa godinama osiguranika.

Ključne reči:
lekovi, propisivanje; lekovi, korišćenje; lekovi, kombinacije; stare osobe; bosna i hercegovina.

Correspondence to: Vanda Marković-Peković, Pharmaceutical Department, Ministry of Health and Social Welfare, Trg Republike 1, 78 000 Banja Luka, Republic of Srpska, Bosnia and Herzegovina. E-mail: v.mpekovic@mzsz.vladars.net

Introduction

Prescription of medicines is a fundamental care component of the elderly, thus optimization of drug prescribing for this group has become an important public-health issue. The increasing prevalence of polypharmacy in frail elderly population has already been demonstrated [1,2]. The risk of morbidity and mortality associated with polypharmacy, combined with the trend of population aging worldwide, makes polypharmacy an area of prime concern [3].

Polypharmacy in the elderly has been described in several European countries [2–4], and it has been correlated with increased age and female gender [2,5]. Bosnia and Herzegovina is characterized by the demographic transition, with an increase in life expectancy and an expressed aging of population. To our knowledge, the analyses of the use of drugs in the elderly population have so far not been performed in Bosnia and Herzegovina. Given the already identified prevalent use of polypharmacy in the elderly by other researchers [6,7] and aging of our population, we assumed that polypharmacy could also be present in our elderly population.

Drugs commonly used only for short terms are discontinued soon and patients are not likely to have adverse drug reactions from them. Therefore, the objective of this study was to analyze the long-term prescription drug use and the prevalence of polypharmacy in the elderly population.

Methods

The study was performed in the Republic of Srpska, which is one of the two constitutive entities of Bosnia and Herzegovina with an estimated population of 1.4 million, and its own executive and legislative functional responsibilities including healthcare policies on its territory. The Health Insurance Fund (HIF) provides compulsory health insurance coverage for the population, including the list of reimbursed drugs which is based on Anatomical Therapeutic Chemical (ATC) classification [8].

This was a retrospective study, analyzing all prescriptions for people aged ≥ 65 years reimbursed by HIF and dispensed by retail pharmacies during 2005 and 2010. These two-time windows were chosen as the first (2005) and the last (2010) year for which it was possible to get the data from the HIF's database on the same way, as the study was conducted in 2011. The following data from the database were used in this study: dispensed drug, dispensing date, age, gender and disease diagnose [according to the WHO International Classification of Diseases (ICD) revision 10]. All processing of the individual data of dispensed drugs in the study were undertaken anonymously, with a unique temporary individual identifier specifying gender and year of birth applied. The study population was stratified by gender and age into 10-year classes: 65–74 years, 75–84 years and ≥ 85 years. A list of reimbursed drugs was comprised of 130 and 203 different drugs given under international non-proprietary name (ATC level 5) in 2005 and 2010, respectively.

Long-term drug use was defined as continuous drug dispensing for a whole year or at least two thirds of the year [9],

which implies drugs used for chronic diseases treatment. Drug use was assumed to start on the day the medication was dispensed. The number of different drugs used was stratified in three groups: 1, 2–4 and ≥ 5 drugs. Polypharmacy was defined as the use of five or more different reimbursed drugs – defined by the ATC-Code – during one year. This definition might enable comparisons with other studies as one of the most commonly used [10–12] because a consensus on the definition of polypharmacy is still lacking. The prevalence of drug use was defined as the proportion of elderly patients who used 1, 2–4 and ≥ 5 different reimbursed drugs during one year. Statistical analysis involved the overall statistical weight of the study population. Descriptive statistics were used to calculate prevalence proportions.

Results

Of all insured people aged ≥ 65 years, long-term drug use was identified in 10% (19,403) and 19% (43,781) patients in 2005 and 2010, respectively, of whom 62% were women. Out of the total elderly with long-term drug use, patients aged 65–74 accounted 69% and 60%, 75–84 29% and 36% and ≥ 85 2% and 4% in 2005 and 2010, respectively. Of all prescriptions to the elderly, 29% (468,351) and 35% (954,135) were prescribed for long-term drug use in 2005 and 2010, respectively, and 60% of these were prescribed to women.

One drug alone was used by almost 50% and 43% of the elderly in 2005 and 2010, respectively, and it was used more by men of all the age groups, except the group 65–74 in 2005. The proportion of elderly who used one drug only decreased in all the age groups of both genders in 2010 (Table 1).

Table 1

Prevalence of the use of different drugs by gender and age (%)

Age of patients (years)	Number of drugs used					
	2005			2010		
	1	2–4	≥ 5	1	2–4	≥ 5
All patients	49.8	48.8	1.4	42.9	53.6	3.6
65–74	50.9	47.4	1.2	44.1	52.6	3.3
75–84	47.4	50.8	1.9	41.3	54.8	3.9
≥ 85	44.2	53.3	2.6	38.9	56.7	4.5
Men	49.6	48.8	1.6	43.8	52.9	3.4
65–74	50.5	48.1	1.4	44.2	52.6	3.2
75–84	47.7	50.3	2.0	43.2	53.1	3.6
≥ 85	45.5	50.9	3.6	40.7	55.2	4.1
Women	49.9	48.8	1.3	42.3	54.0	3.7
65–74	51.2	47.7	1.1	43.9	52.7	3.4
75–84	47.2	51.1	1.8	40.1	55.8	4.1
≥ 85	43.6	53.4	2.1	37.9	57.4	4.7

Results are given as % of patients.

Two to four different drugs were used by almost 49% and 54% of the elderly in 2005 and 2010, respectively, and they were more used by women of all age groups, except the age group 65–74 in 2005. The proportion of patients who used 2–4 drugs increased in all age groups of both genders in 2010. With increasing age, the prevalence of use of 2–4 dif-

ferent drugs increased and only the prevalence of use of one drug decreased (Table 1).

The most commonly used drugs related to treatment of cardiovascular, metabolic, digestive and respiratory diseases (Table 2). Drugs for hypertension treatment, particularly angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCB), and the drugs for cardiac therapy (digoxin, isosorbide mononitrate) were the most frequently used cardiovascular drugs. Drugs for diabetes and acid related disorders were the most used for treatment of metabolic and digestive diseases, and aminophylline for obstructive airway diseases (Table 3).

In the total observed elderly population polypharmacy prevalence increased from 1.4% in 2005 to 3.6% in 2010. It increased in all the age group, and the largest increase was observed in the age group 65–74. In men, polypharmacy prevalence increased from 1.6% to 3.4%, and in women, it increased from 1.3% to 3.7% in 2005 and 2010, respectively. It increased in all the age groups, with the largest increase in the age group 65–74 in men and ≥ 85 in women (Table 1).

Discussion

The study findings point out to the increase of elderly population with long-term drug use. Over a 5-year period, the proportion of the elderly who have used one drug alone on a long-term basis declined, while the proportion of those who used multiple drugs increased. Polypharmacy prevalence increased in both men and women, and the increase was more prominent in women of all age groups. The use of multiple drugs and polypharmacy increased with ageing.

Different reasons may have contributed to the observed increase of drug use in the elderly. Numerous new drugs and new pharmaceutical and dosage forms, mostly for treatment of cardiovascular, metabolic, digestive, nervous and respiratory diseases, were included in the list of reimbursable drugs during the observed period. Broader therapeutic options enabled better affordability and coverage of patients, and better insight in the extent of drugs used by the elderly, as these drugs were available on the market although previously not reimbursed. Furthermore, aging of our population was evident: in the last two decades the overall population decreased by 12% while the proportion of people aged ≥ 80 tripled; people aged ≥ 65 constituted 19% of the population [13, 14]. Population aging is known as a main risk factor for the development of chronic diseases and multiple drug use [6]. Diabetes, heart disease, hypertension and obstructive pulmonary disease are well-known relevant morbidity-related predictors of polypharmacy [9, 15], and all of them were shown as prevalent among our elderly. Also, a number of new clinical guidelines have been applied since 2004 that have certainly influenced physicians' prescribing patterns, as guidelines often recommend the use of several drugs to treat or prevent a disease. Prescription of multiple drugs may itself lead to the need for additional medication, e.g. ranitidine prescription due to the adverse gastrointestinal effects from drug intake.

The prevalence of polypharmacy in our study population was low. When defined as the use of five or more drugs, some previous studies reported that polypharmacy occurred in 4% and 29% of elderly patients with long-term drug use [9, 16]. In order to compare the data with neighboring countries and according the available literature, polypharmacy was documented in about 10% elderly in Belgrade, Serbia [12], while the other researchers focused more on the analysis of potentially inappropriate drug prescribing in the elderly [17–20]. Different results and limited comparability can be explained by differing inclusion criteria between studies, variations in duration of drug use and the research period, data collecting method and the representativeness of the study population. Considering the study methodology, our study results are similar to some previous findings [9]. Although low, polypharmacy prevalence increased during the period of five years. The development of chronic polypharmacy in long-term drug use is a slow process and the elderly who use more than four long-term drugs simultaneously are more likely to add another drug in a short time than those who use fewer than four long-term drugs [9]. According to the study findings, over a half of our elderly patients are already using 2–4 different drugs on the long-term basis for treatment of chronic diseases. Therefore, a special prescribing attention should be in particular focused to these patients, as the number of long-term drugs which a patient already uses is the best predictor of polypharmacy [9].

More men of almost all age groups used one drug only both years, while more women used multiple drugs, except in 2005 when polypharmacy was more prominent in men. Many studies have reported a correlation between polypharmacy and female gender [7, 15, 21, 22], and a positive correlation between polypharmacy and male gender were found only in two [3, 23]. Such discrepancies among study findings could be due to differences in physicians' prescribing attitude toward genders, as well as to differences between genders in educational and socioeconomic characteristics [3]. It is known that women consult health services more often and earlier than men, and are more accustomed to the use of drugs [6]. As in the total population, women had a higher share in the elderly insured population and they were prescribed by more prescriptions. Also, those who report poor self-perceived health status are most likely to take medications [24], and in 2010 more women (20%) then men (16%) rated their health as worse than 12 months ago [14]. Further research exploring the relationship between gender and polypharmacy is needed.

The prevalence of polypharmacy, as well as the use of 2–4 different drugs increased in all age groups, and it displayed a clear age trend. Along with aging and increased availability of drugs, new national guidelines might also contribute to explaining the age trend in the development of polypharmacy. Older patients are more often exposed to several diseases, and they may receive, as a result of the guidelines, more often than others, an increasing number of different drugs [11]. The results of this study may also be interpreted to imply that a larger proportion of patients are receiving recommended drug treatment in line with the new guidelines, but further research is needed to clarify this issue as well.

Similar to other studies, our elderly mostly used drugs for cardiovascular, alimentary tract and metabolism and respiratory system diseases [6, 25]. These similarities in consumption patterns may reflect common therapeutic needs among elderly patients, and applying a standard prescription scheme regarding patient's age [26]. High use of cardiovascular drugs is

Table 2

Most common diseases for which elderly were prescribed drugs (%)

Disease (ICD-10)		2005				2010			
		Men (n = 7,561)	Women (n = 11,842)	Total (n = 19,403)	Frequency ranking	Men (n = 16,792)	Women (n = 26,989)	Total (n = 43,781)	Frequency ranking
I10	Hypertension	72.1	77.6	75.5	1	72.7	80.2	77.4	1
I20	Angina pectoris	34.7	31.5	32.7	2	24.0	22.7	23.2	2
I42	Cardiomiopathy	30.0	28.7	29.2	3	15.9	17.3	16.8	3
E11	Diabetes mellitus, type 2	10.9	13.3	12.4	4	14.3	17.0	16.0	4
E10	Diabetes mellitus, type 1	9.2	12.2	11.0	5	8.0	9.2	8.7	5
I50	Heart failure	2.3	2.3	2.3	14	8.5	9.0	8.8	6
K29	Gastritis and duodenitis	6.7	7.1	6.9	7	4.9	6.0	5.6	7
I25	Chronic ischaemic heart disease	6.9	5.7	6.2	8	6.0	5.1	5.5	8
I49	Cardiac arrhythmias	5.5	5.5	5.5	9	3.9	4.1	4.0	9
J42	Chronic bronchitis	11.2	6.1	8.1	6	5.8	3.7	4.5	10
J44	Other COPD	5.4	2.5	3.6	11	4.7	2.3	3.0	11
J45	Asthma	7.7	3.3	5.0	10	4.1	2.3	3.0	12
F32	Depressive episode	1.5	1.8	1.7	16	2.3	3.1	2.8	13
F20	Schizophrenia	2.5	2.8	2.7	15	1.1	1.3	1.2	14
F48	Other neurotic disorders	3.0	3.8	3.5	12	0.9	1.2	1.1	15
M54	Dorsalgia	2.2	2.9	2.6	13	0.6	0.9	0.8	16

ICD – International Classification of Diseases, 10th revision; COPD – chronic obstructive pulmonary disease.

Table 3

Most frequently prescribed drugs (%)

ATC-Code	INN	2005				2010			
		Men (n = 7,561)	Women (n = 11,842)	Total (n = 19,403)	Frequency ranking	Men (n = 16,792)	Women (n = 26,989)	Total (n = 43,781)	Frequency ranking
C09BA02	Enalapril and diuretics	4.6	5.7	5.3	10	18.1	22.5	20.8	1
C09AA02	Enalapril	13.5	14.6	14.2	4	18.0	18.2	18.1	2
C08CA01	Amlodipine	17.4	18.4	18.0	2	14.9	16.7	16.0	3
C01DA14	Isosorbide mononitrate	19.8	16.2	17.6	3	13.7	12.8	13.2	4
C01AA05	Digoxin	10.0	10.9	10.5	5	9.6	10.6	10.3	5
A10BA01	Metformin	3.3	4.7	4.1	12	8.0	10.1	9.3	6
C09BA06	Quinapril and diuretics	1.9	2.8	2.4	19	5.4	7.3	6.6	7
C07AG02	Carvedilol	3.6	2.3	2.8	17	6.4	6.6	6.5	8
C07AB02	Metoprolol	na	na	na	na	4.9	6.7	6.0	9
A02BA02	Ranitidine	7.2	7.8	7.5	6	4.6	5.4	5.1	10
C08DA01	Verapamil	5.5	6.2	5.9	9	4.3	5.3	4.9	11
R03DA05	Aminophylline	9.1	4.4	6.2	8	6.1	3.4	4.4	12
C03CA01	Furosemide	na	na	na	na	4.1	4.0	4.1	13
A10AD05	Insulin aspart	na	na	na	na	3.5	4.2	3.9	14
S01ED01	Timolol	3.0	2.4	2.6	18	3.8	3.4	3.6	15
C10AA01	Simvastatin	1.8	1.4	1.6	20	3.6	2.8	3.1	16
C09AA06	Quinapril	3.0	3.5	3.3	14	3.0	3.2	3.1	17
A10BB09	Gliclazide	6.9	7.4	7.2	7	3.0	3.0	3.0	18
A10BB01	Glibenclamide	na	na	na	na	2.3	3.0	2.8	19
C08CA05	Nifedipine	4.2	3.9	4.0	13	2.5	2.5	2.5	20
N05BA01	Diazepam	4.6	5.4	5.1	11	2.1	2.4	2.3	21
C09AA01	Captopril	18.6	19.7	19.3	1	2.1	2.2	2.2	22
R03AC02	Salbutamol, aerosol	5.5	1.9	3.3	15	3.3	1.5	2.2	23
M01AE01	Ibuprofen	2.8	3.4	3.2	16	1.3	1.5	1.4	24

ATC – Anatomical Therapeutic Chemical; INN – International non-proprietary name; na – not applicable.

not a surprising finding, as cardiovascular diseases are a leading cause of morbidity and mortality in the population of the Republic of Srpska in the last decade [27]. As part of the national cardiovascular program a particular focus was put on the development of clinical guidelines [28] and a selection of cardiovascular drugs reimbursed by the HIF. New diuretics (furosemide, torasemide, spironolactone, combinations with amiloride), beta-blockers (metoprolol, bisoprolol), antiarrhythmics (amiodarone) and angioteusin-converting enzyme inhibitors (ACEIs) (ramipril, trandolapril) were included to the list of reimbursed drugs in 2010, with a tougher prescribing restrictions related to the dose, indications and copayment.

ACEI were the most prescribed antihypertensive drugs as they can be considered the first-line or combination therapy, especially if diabetes or heart failure is present. A high proportion of patients who used fixed-dosage combinations of ACEI with hydrochlorothiazide may be due to the guidelines indicating a strong preference for thiazide diuretic when combination therapies are needed, often for high risk patients [28, 29], and when lower doses may be used resulting in fewer side-effects and better compliance and adherence to prescribed antihypertensive drugs. The use of captopril decreased due to a broader availability of drugs dosed once-daily and a higher patient copayment (50%).

Calcium channel blockers (CCBs) are among the preferred for hypertension treatment in the elderly [28], and amlodipine was widely prescribed as a safe drug for use in patients with heart failure, hypertension, chronic stable angina and diabetes [30], which were all prevalent in our elderly. Among all available beta-blockers, carvedilol was probably more widely used in treatment of cardiovascular patients with metabolic syndrome or diabetes as it affect insulin sensitivity less than metoprolol [31], and cardioselective metoprolol has a preferable side effect profile in older persons and a lower price than bisoprolol. Digoxin is traditionally overprescribed though the indications for this drug are sparse. This drug has been used in one out of ten patients on the long-term basis. According to cardiovascular guidelines, digoxin is no more the first line treatment for heart failure, but remains a useful drug for heart failure associated with atrial fibrillation. It is an inexpensive, but potentially risky drug for elderly patients due to its problematic safety profile associated with numerous side effects and potentially serious drug interactions.

Current guidelines for diabetes recommend early initiation of metformin as the first-line drug for monotherapy and combination therapy for patients with type 2 diabetes. This was based primarily on metformin's glucose-lowering effects, relatively low cost, and generally low level of side effects [32]. The data of this study clearly showed that aminophylline is still a more frequently prescribed drug for treatment of chronic obstructive pulmonary disease (COPD) of our patients than any other bronchodilator. This was quite unexpected since in the major guidelines for treatment of COPD, theophylline and its derivate aminophylline are relegated to a third line bronchodilator after inhaled anticholinergics and β2-agonists. Theophylline has narrow therapeutic index with potentially serious side effects, and theophylline clearance is significantly reduced in elderly patients. It is promising that the use of some traditional drugs, like ranitidine, gliclazide, captopril, nifedipine, ibuprofen and diazepam significantly decreased over the period of five years as a direct consequence of the introduction of new clinical guidelines into clinical practice.

The major advantage of this study is the large and reliable data set analyzed, covering all reimbursed prescriptions to every individual aged ≥ 65. As all insured elderly were included, certain known problems concerning sampling, interview and confidence were avoided. The use of drugs may be underestimated as this database does not include prescription drugs not reimbursed by the HIF and non-prescription drugs. We do not know whether or not all analyzed drugs were actually used. It was not possible to determine the appropriateness of any drugs used.

Conclusion

The study findings point out to an increase of elderly population with a long-term drug use. Over a half of our elderly patients use 2–4 different drugs on the long-term basis. The prevalence of polypharmacy was low, but it increased in the period of 5 years. This increase, observed in both genders, was more prominent in women of all the age groups. The use of multiple drugs and polypharmacy increased with ageing. Our elderly patients should be carefully monitored in terms of quality of care, patient safety, and costs of treatment.

Acknowledgements

R E F E R E N C E S

1. *Nobili A, Franchi C, Pasina L, Tettamanti M, Baviera M, Monesi L*, et al. Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM-elderly project. Pharmacoepidemiol Drug Saf 2011; 20(5): 488−96.
2. *Jyrkkä J, Vartiainen L, Hartikainen S, Sulkava R, Enlund H*. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+Study. Eur J Clin Pharmacol 2006; 62(2): 151−8.
3. *Slabaugh LS, Maio V, Templin M, Abouzaid S*. Prevalence and risk of polypharmacy among the elderly in an outpatient setting: a retrospective cohort study in the Emilia-Romagna region, Italy. Drugs Aging 2010; 27(12): 1019−28.
4. *Junius-Walker U, Theile G, Hummers-Pradier E*. Prevalence and predictors of polypharmacy among older primary care patients in Germany. Fam Pract 2007; 24(1): 14−9.
5. *Holbeach E, Yates P*. Prescribing in the elderly. Aust Fam Physician 2010; 39(10): 728−33.
6. *Venturini CD, Engroff P, Ely LS, Zago LF, Schroeter G, Gomes I*, et al. Gender differences, polypharmacy, and potential pharmacol-

ogical interactions in the elderly. Clinics (Sao Paulo) 2011; 66(11): 1867−72.

7. *Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä S, Isoaho R.* Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002; 55(8): 809−17.

8. *Markovic-Pekovic V, Skrbić R, Godman B, Gustafsson LL.* Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions. Expert Rev Pharmacoecon Outcomes Res 2012; 12(5): 661−71.

9. *Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM.* The development of polypharmacy. A longitudinal study. Fam Pract 2000; 17(3): 261−7.

10. *Haider SI, Johnell K, Weitoft GR, Thorslund M, Fastbom J.* The Influence of Educational Level on Polypharmacy and Inappropriate Drug Use: A Register-Based Study of More Than 600,000 Older People. J Am Geriatr Soc 2009; 57(1): 62−9.

11. *Hovstadius B, Hovstadius K, Astrand B, Petersson G.* Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. BMC Clin Pharmacol 2010; 10(1): 16.

12. *Gazibara T, Nurkovic S, Kisic-Tepavcevic D, Kurtagic I, Kovacevic N, Gazibara T,* et al. Pharmacotherapy and over-the-counter drug use among elderly in Belgrade, Serbia. Geriatr Nurs 2013; 34(6): 486−90.

13. Republika Srpska Institute of Statistics. Demographic statistics. Demographic statistics. Banja Luka: Republički zavod za statistiku; 2002. (Serbian)

14. Republika Srpska Institute of Statistics. Women and men in Republika Srpska. Banja Luka: Republički zavod za statistiku; 2012. (Serbian)

15. *Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S.* Patterns of Drug Use and Factors Associated with Polypharmacy and Excessive Polypharmacy in Elderly Persons. Drug Aging 2009; 26(6): 493−503.

16. *Franchi C, Tettamanti M, Pasina L, Djignefa CD, Fortino I, Bortolotti A,* et al. Changes in drug prescribing to Italian community-dwelling elderly people: the EPIFARM-Elderly Project 2000-2010. Eur J Clin Pharmacol 2014; 70(4): 437−43.

17. *Nerat T, Kos M.* Analysis of inappropriate medication prescribing in Slovenian elderly patients based on the Beers and Laroche criteria. Zdrav Var 2011; 50(1): 34−44.

18. *Juloski J, Despotović N, Vujisić A, Erceg P, Milosević DP, Marjanović S,* et al. Nonsteroidal anti-inflammatory drugs: as inappropriate pharmacotherapy in the elderly. Adv Gerontol 2011; 24(2): 308−11.

19. *Popović B, Quadranti-Radošević N, Matanović-Mimica S, Lisica-Diminić I, Ljubotina A, Duliba-Pezelj D,* et al. Potentially inappropriate prescribing in elderly outpatients in Croatia. Eur J Clin Pharmacol 2014; 70(6): 737−44.

20. *Rolevski M, Kučević B, Boljević G, Mugoša S, Mikov M.* Potentially inappropriate medication use in the elderly in Montenegro. BMC Pharmacol Toxicol 2012; 13(Suppl 1): A35.

21. *Bjerrum L, Søgaard J, Hallas J, Kragstrup J.* Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. Eur J Clin Pharmacol 1998; 54(3): 197−202.

22. *Rozenfeld S, Fonseca MJ, Acurcio FA.* Drug utilization and polypharmacy among the elderly: a survey in Rio de Janeiro City, Brazil. Rev Panam Salud Publica 2008; 23(1): 34−43.

23. *Chan DD, Hao Y, Wu S.* Polypharmacy among disabled Taiwanese elderly: a longitudinal observational study. Drugs Aging 2009; 26(4): 345−54.

24. *Chrischilles EA, Foley DJ, Wallace RB, Lemke JH, Semla TP, Hanlon JT,* et al. Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. J Gerontol 1992; 47(5): 137−44.

25. *Kennerfalk A, Ruigómez A, Wallander M, Wilhelmsen L, Johansson S.* Geriatric drug therapy and healthcare utilization in the United kingdom. Ann Pharmacother 2002; 36(5): 797−803.

26. *Ribeiro AQ, Rozenfeld S, Klein CH, César CC, de Acurcio FA.* Survey on medicine use by elderly retirees in Belo Horizonte, Southeastern Brazil. Rev Saude Publica 2008; 42(4): 724−32.

27. *Markovic-Pekovic V, Stoisavljevic-Satara S, Skrbic R.* Utilisation of cardiovascular medicines in Republic of Srpska, Bosnia and Herzegovina, 5 years study. Pharmacoepidemiol Drug Saf 2009; 18(4): 320−6.

28. Ministry of Health and Social Welfare of the Republic of Srpska. Guidelines for Clinical Practice. Guidelines for Clinical Practice. Cardiovascular diseases: Hypertension/Atrial fibrilation/Myocardial infarction/Angina pectoris. Banja Luka: Ministry of Health and Social Welfare of the Republic of Srpska; 2004. (Serbian)

29. *Lionakis N, Mendrinos D, Sanidas E, Favatas G, Georgopoulou M.* Hypertension in the elderly. World J Cardiol 2012; 4(5): 135−47.

30. *Dickerson LM, Gibson MV.* Management of hypertension in older persons. Am Fam Physician 2005; 71(3): 469−76.

31. *Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M,* et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31(7): 1281−57.

32. Ministry of Health and Social Welfare of the Republic of Srpska. Guideline for Diabetes mellitus. Banja Luka: Ministry of Health and Social Welfare of the Republic of Srpska; 2004. (Serbian)