Strathprints Institutional Repository

Marković-Peković, Vanda and Škrbić, Ranko and Petrović, Aleksandar and Vlahović-Palčevski, Vera and Mrak, Jana and Bennie, Marion and Fadare, Joseph and Kwon, Hye-Young and Schiffers, Krijn and Truter, Ilse and Godman, Brian (2015) Polypharmacy among the elderly in the Republic of Srpska : extent and implications for the future. Expert Review of Pharmacoeconomics and Outcomes Research. ISSN 1473-7167 , http://dx.doi.org/10.1586/14737167.2016.1115347

This version is available at http://strathprints.strath.ac.uk/54726/

Polypharmacy among the elderly in the Republic of Srpska; extent and implications for the future

Vanda Marković-Peković[1,2]; Ranko Škrbić[3]; Aleksandar Petrović[4]; Vera Vlahović-Palčevski[5]; Jana Mrak[6]; Marion Bennie[7,8]; Joseph Fadare[9]; Hye-Young Kwon[10,11]; Krijn Schiffers[12]; Ilse Truter[13]; *Brian Godman[8,14]

[1]Ministry of Health and Social Welfare, Banja Luka, Republic of Srpska, Bosnia and Herzegovina. Email: v.mpekovic@mzsz.vladars.net

[2]Medical Faculty, Department of Social Pharmacy, University Banja Luka, Banja Luka, Mrkalja 18, Republic of Srpska, Bosnia and Herzegovina

[3]Medical Faculty, Department of Clinical Pharmacology, University Banja Luka, Banja Luka, Mrkalja 18, Republic of Srpska, Bosnia and Herzegovina. Email: ranko.skrbic575@gmail.com

[4]Računari, Banja Luka, Bore Stankovića 18, Republic of Srpska, Bosnia and Herzegovina. Email: petrovic@blic.net

[5]Department of Clinical Pharmacology, University Hospital, Rijeka, Rijeka, Croatia Email: vvlahovic@inet.hr

[6]Health Insurance Institute of Slovenia, Miklošičeva 24, SI-1507 Ljubljana, Slovenia. Email: jana.mrak@zzzs.si

[7]NHS National Services Scotland, Public Health and Intelligence Strategic Business Unit, Edinburgh, Scotland. Email: m.bennie@nhs.net

[8]Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom. Emails: marion.bennie@strath.ac.uk and Brian.godman@strath.ac.uk

[9]Departments of Pharmacology/Medicine, Ekiti State University/Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria. Email: jofadare@gmail.com

[10]Department of Global Health and Population, Harvard School of Public Health, Boston MA 02115, USA

[11]Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Seoul South Korea. Email: haeyoungkwon0111@gmail.com

[12]Erasmus University, Rotterdam, The Netherlands. Email: krijnschiffers@hotmail.com

[13]Drug Utilization Research Unit (DURU), Department of Pharmacy, Nelson Mandela Metropolitan University, Port Elizabeth 6031, South Africa. Email: E-mail: ilse.truter@nmmu.ac.za

[14]Department of Laboratory Medicine, Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden. Email: Brian.Godman@ki.se

*Author for correspondence: Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow G4 0RE, United Kingdom. Email: Brian.godman@strath.ac.uk. Telephone: 0141 548 3825. Fax: 0141 552 2562 and Division of Clinical Pharmacology, Karolinska Institute, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden. Email: Brian.Godman@ki.se. Telephone + 46 8 58581068. Fax + 46 8 59581070

Abstract

Introduction: Prescribing of medicines is a fundamental component of care for the elderly. However, increasing concern with polypharmacy and its impact on morbidity, mortality and costs. Aims: Analyze long-term prescription use and the prevalence of polypharmacy in the elderly in the Republic of Srpska. Subsequently use the findings to suggest potential future measures. Methods: Retrospective study of all elderly patients 2005 to 2010 stratified by age group (3 groups), sex and long term medicine use. Results: Polypharmacy (5 or more medicines) increased from 1.4% of the elderly taking medicines long term to 3.6% by 2010, with 53.6% of elderly taking 2 or more medicines long term. Most prevalent diseases were cardiovascular diseases and diabetes. Most prescriptions were in accordance with recent guidelines. However, concern with appreciable prescribing of digoxin and aminophylline. Conclusion: Whilst polypharmacy rates low in the Republic, increasing rates are a concern. Further studies are planned.

Introduction

The prescribing of medicines is a fundamental component of the care of the elderly, and optimizing drug prescribing for this group has become an important public health issue in recent years. This is due to the increasing prevalence of multiple medical conditions in the elderly leading to increasing rates of polypharmacy with its associated morbidity, mortality and costs (1-6). However, the issue of multiple medications is complex. In some patients, polypharmacy is appropriate to slow disease progression or alleviate symptoms, especially in patients with multiple comorbidities (1, 2, 4). However in others, polypharmacy can cause serious problems for patients and healthcare systems (1, 3, 4, 7, 8). These include adverse drug reactions and potentially harmful drug - drug interactions, increased exposure to potentially inappropriate medicines, poor adherence, reducing the health benefits of prescribed medications as well as an increase in geriatric syndromes including urinary incontinence, cognitive impairment and impaired balance leading to increased falls (1, 7, 9-17). As a result, polypharmacy can increase morbidity and mortality in the elderly, reducing their quality of life and increasing costs (1, 4, 7, 11, 12). For instance, the US Centre for Medicare and Medicaid services estimated that polypharmacy cost the US health plans more than US$50 billion annually at the end of the 1990s (4). Consequently, the leading challenge to the quality of medicine use in the elderly is to combine potential issues of polypharmacy, comorbidity and frailty with evidence and guidelines to avoid prescribing uncertainty of confusion, which may delay effective decision making regarding medicine use (18).

These factors, combined with aging populations worldwide, makes tackling inappropriate polypharmacy of the elderly of prime importance among all key stakeholder groups. These include health authorities looking to improve the care of the elderly within finite budgets (1, 2, 19-21). These concerns have resulted in a number of measures and interventions to reduce inappropriate prescribing, recently collated and updated in a Cochrane review (1, 22) as well as discussed by Jäger and colleagues (17). Polypharmacy has been variously defined. A number of studies use a numeric definition, which is typically 5 or more medicines (1, 3, 16, 17, 21, 23-27). However, others have used a definition of 6 or more medicines (28, 29), whilst Patterson and colleagues and others use a definition of 4 or more medicines (1, 30, 31). Some authors have also used a definition as low as 2 or more medicines (27, 32).

Polypharmacy is correlated with increasing age and the female gender (6, 33). It has also been described, and is being addressed in several European and other countries (6, 8, 17, 24, 25, 30, 34-39). However, it is difficult to estimate the true prevalence of polypharmacy. Recent surveys suggest prevalence rates among the elderly of between 28% (US) and 31% (Ireland) (1). However, a recent survey in the Lombardia Region in Italy suggest higher prevalence rates, with those exposed to chronic polypharmacy (5 or different chronic drugs) at 28.5 % and rising to 52.7 % when considering the elderly prescribed 5 or more different active substances (34). These rates are likely to grow, especially with growing elderly populations as seen in Europe (31, 40, 41). This will lead to increased morbidity, mortality and costs among the elderly unless addressed (42). These concerns have already resulted in a number of initiatives among healthcare professionals in the Balkan countries to improve the quality of prescribing in the elderly. These include the instigation of local pharmacotherapeutic groups with indicators for polypharmacy in Slovenia (20, 43, 44) and the development of new comprehensive screening tools to detect potentially inappropriate medications and clinically important drug-drug interactions in the elderly in Croatia (8).

Bosnia and Herzegovina is no different with a growing elderly population as life expectancy increases. To the best of our knowledge, no analysis has been undertaken on the use of medicines in the elderly population in Bosnia and Herzegovina. Any increase in inappropriate polypharmacy is a particular issue 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, especially with yearly pharmaceutical expenditure at only 75€ per capita in 2010 (45).

Primary health care in the Republic of Srpska is based on the family medicine concept represented by the family medicine team (46). Each team comprises one doctor, a family medicine specialist, and two nurses, and serves a defined and registered population. There are typically 2000 people per family medicine team. Service provision is driven by the contracts between the Health Insurance Fund (HIF) and primary health care providers, which define the scope of the services delivered and specify the use of evidence-based guidelines. The first set of guidelines were developed and introduced in 2004, followed by

the second revised and improved edition in 2009. This set of guidelines with recommended treatments serves as a basis for the essential drug list for primary health reimbursed by the HIF of the Republic of Srpska.

Consequently, the objective of this study was to analyze the long-term prescription drug use and the prevalence of polypharmacy in the elderly population in the Republic of Srpska. Subsequently use the findings to suggest, if pertinent, potential future measures that the Republic of Srpska could introduce to improve prescribing in the elderly. Potential measures will be based on published approaches including those in the recent Cochrane Review (1).

Methods

The Republic of Srpska has 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 entire population, meaning that all elderly are covered by a health insurance. The list of reimbursed drugs provided by HIF is based on Anatomical Therapeutic Chemical (ATC) classification (45, 46).

This was a retrospective study, analysing all prescriptions for people aged ≥ 65 years reimbursed by HIF and dispensed by retail pharmacies during 2005 and 2010. The HIF database provides the complete reimbursed prescription medication history of all patients, diagnoses, physician prescribers as well as the pharmacy where prescriptions are dispensed in the Republic of Srpska. The validity of the database is assured by regular monitoring and auditing of medicines dispensed from HIF contracted pharmacies, ensuring robustness of the findings. Data collection is unified and computerised, minimising the possibility of errors in data processing. Since all elderly, who are covered by HIF, were included in the study, problems concerning sampling, interviews and confidence were avoided.

The following data sets were extracted from the database: 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 groups: 65-74 years, 75-84 years and ≥ 85 years. The list of reimbursed medicines comprised 130 and 203 different medicines respectively in 2005 and 2010 by international non-proprietary name (INN - ATC level 5). This was a single list of medicines until 2008. After this, the list was divided into list A and list B. List A is the basic list of medicines including those for chronic diseases such as epilepsy, diabetes, cardiovascular diseases as well as chronic psychiatric conditions. Medicines are covered 100% up to the reference price level for patients exempt from the copayment. List B is a complementary list with a mandatory 50% copayment,

which typically includes second-line and/or more expensive treatments. Both lists A and B have prescribing indication limitations regarding reimbursement for certain medicines (45). For example, furosemide 500 mg tablets are included in list A with restricted prescribing, while furosemide 40 mg tablets are included within list B. In 2008 simvastatin and atorvastatin were switched to list B and restricted to specific diseases and conditions defined by ICD-10. These were secondary prevention of coronary disease (I20–I25), diabetes mellitus with hypercholesterolemia (E10–E11) and chronic kidney insufficiency (N18) and organ transplantation (Z24) with hypercholesterolemia

Long-term medicine use was defined as continuous drug dispensing for a whole year or at least two thirds of the year (32), which implies medicines were used for the treatment of chronic diseases. Medicine use was assumed to start on the day the medication was dispensed. The number of different medicines prescribed was stratified into three groups: namely 1, 2-4 and ≥ 5 medicines. Polypharmacy was defined as the use of five or more different reimbursed medicines - defined by the ATC-Code - during one year, which is in line with other publications (1, 3, 16, 17, 21, 23-27). The prevalence of medicine use was defined as the proportion of elderly patients who used 1, 2-4 and ≥ 5 different reimbursed medicines during one year. This is similar to the methodology used by Franchi et al and Kennerfalk et al (34, 47).

Descriptive analyses were conducted on the data to demonstrate possible increases or decreases in the number of patients in the different age groups as well as any changes in the prevalence of different diseases and different medicines prescribed over time. No statistical analyses were undertaken to analyze any significant increase or decrease in the number of patients among the different age groups and sexes in 2010 compared to 2005. This was because there was no intervention and no opportunity for re-accessing individual patient level data . All analyses were undertaken using Microsoft Excel 2010 programme. The results were presented in tables.

Ethical approval was not needed since upon the review of the study protocol, which specified that all processing of individual patient data will be undertaken anonymously, with a unique temporary individual identifier, the study was approved by the Head of HIF. The data extraction was subsequently carried out within HIF with anonymous data, with patients fully de-identified. This is similar to other studies of this nature undertaken with health insurance company data, such as those conducted in the US (48).

Results

Table 1 describes the characteristics of the HIF patients aged ≥ 65 years with long-term medicine use in the Republic of Srpska. Among the elderly, long-term medicine use was identified in 10% and 19% patients in 2005 and 2010, respectively.

Table 1. Characteristics of the study population

Year	2005	2010
Total elderly (number)	200,093	227,804
Cohort (number of patients)	19,404	43,782
Gender - % Women	61.0	61.7
Age group (years), % of the total		
65-74	69.2	59.9
75-84	29.0	36.5
≥85	1.8	3.6

Of all the prescription medicines prescribed to the elderly, 29% (468,351) and 35% (954,135) were prescribed for long-term use in 2005 and 2010, respectively, and 60% of these were prescribed to women.

One medicine alone was taken by almost 50% and 43% of the elderly in 2005 and 2010, respectively. There was generally greater use of medicines among men than women in 2005 Table 2). However in 2010, there was generally greater use of medicines by women with the exception of those only prescribed one medicine (Table 2). The proportion of elderly who used one medicine only decreased in all age groups of both genders in 2010 versus 2005 (Table 2).

Table 2 – Prevalence of the use of different medicines by age and gender from the cohort of patients prescribed medicines long term

Year	2005			2010		
Medicines - number	1	2-4	≥5	1	2-4	≥5
Total (y) and %	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 (y) and %	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 (y) and %	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

Two to four different medicines were taken by almost 49% and 54% of the elderly in 2005 and 2010, respectively, and these were taken more by women than men. The proportion of patients who took 2-4 medicines increased in all age groups and for both genders in 2010

versus 2005, whilst those taking only one medicine decreased in both genders 2010 versus 2005 (Table 2).

In the total observed elderly population, polypharmacy prevalence using our definition also increased from 1.4% in 2005 to 3.6% in 2010. It increased in all age groups, with the largest increase seen in the age group 65-74 in men and ≥ 85 in women (Table 2). In men, polypharmacy prevalence increased from 1.6% to 3.4%, and in women from 1.3% in 2005 to 3.7% in 2010 (Table 2).

The most commonly used medicines were for the treatment of cardiovascular, metabolic, digestive and respiratory diseases (Table 3).

Table 3 – The most common diseases for which elderly patients were prescribed medicines (% of the total), ranked by 2010 figures

Disease (ICD-10)		2005			2010		
		Men (n=7561)	Women (n=11842)	Total (n=19403)	Men (n=16792)	Women (n=26989)	Total (n=43781)
I10	Hypertension	72.1	77.6	75.5	72.7	80.2	77.4
I20	Angina pectoris	34.7	31.5	32.7	24.0	22.7	23.2
I42	Cardiomiopathy	30.0	28.7	29.2	15.9	17.3	16.8
E11	Diabetes mellitus, type 2	10.9	13.3	12.4	14.3	17.0	16.0
E10	Diabetes mellitus, type 1	9.2	12.2	11.0	8.0	9.2	8.7
I50	Heart failure	2.3	2.3	2.3	8.5	9.0	8.8
K29	Gastritis and duodenitis	6.7	7.1	6.9	4.9	6.0	5.6
I25	Chronic ischaemic heart disease	6.9	5.7	6.2	6.0	5.1	5.5
I49	Cardiac arrhythmias	5.5	5.5	5.5	3.9	4.1	4.0
J42	Chronic bronchitis	11.2	6.1	8.1	5.8	3.7	4.5
J44	Other COPD	5.4	2.5	3.6	4.7	2.3	3.0
J45	Asthma	7.7	3.3	5.0	4.1	2.3	3.0
F32	Depressive episode	1.5	1.8	1.7	2.3	3.1	2.8
F20	Schizophrenia	2.5	2.8	2.7	1.1	1.3	1.2
F48	Other neurotic disorders	3.0	3.8	3.5	0.9	1.2	1.1
M54	Dorsalgia	2.2	2.9	2.6	0.6	0.9	0.8

NB: ICD = International Classification of Diseases; COPD - Chronic Obstructive Pulmonary Disease

Medicines for the treatment of hypertension, particularly angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCB), and medicines for cardiac therapy (digoxin, isosorbide mononitrate) were the most frequently prescribed cardiovascular medicines (Table 4). Medicines for diabetes and acid related disorders were the most

prescribed treatments for metabolic and digestive diseases, and aminophylline for obstructive airway diseases (Table 4).

Table 4 - The most frequently prescribed drugs (% of the total number of patients), ranked by 2010 figures

ATC-code	INN	2005			2010		
		Men (n=7561)	Women (n=11842)	Total (n=19403)	Men (n=16792)	Women (n=26989)	Total (n=43781)
C09BA02	Enalapril and diuretics	4.6	5.7	5.3	18.1	22.5	20.8
C09AA02	Enalapril	13.5	14.6	14.2	18.0	18.2	18.1
C08CA01	Amlodipine	17.4	18.4	18.0	14.9	16.7	16.0
C01DA14	Isosorbide mononitrate	19.8	16.2	17.6	13.7	12.8	13.2
C01AA05	Digoxin	10.0	10.9	10.5	9.6	10.6	10.3
A10BA01	Metformin	3.3	4.7	4.1	8.0	10.1	9.3
C09BA06	Quinapril and diuretics	1.9	2.8	2.4	5.4	7.3	6.6
C07AG02	Carvedilol	3.6	2.3	2.8	6.4	6.6	6.5
C07AB02	Metoprolol	na	na	na	4.9	6.7	6.0
A02BA02	Ranitidine	7.2	7.8	7.5	4.6	5.4	5.1
C08DA01	Verapamil	5.5	6.2	5.9	4.3	5.3	4.9
R03DA05	Aminophylline	9.1	4.4	6.2	6.1	3.4	4.4
C03CA01	Furosemide	na	na	na	4.1	4.0	4.1
A10AD05	Insulin aspart	na	na	na	3.5	4.2	3.9
S01ED01	Timolol	3.0	2.4	2.6	3.8	3.4	3.6
C10AA01	Simvastatin	1.8	1.4	1.6	3.6	2.8	3.1
C09AA06	Quinapril	3.0	3.5	3.3	3.0	3.2	3.1
A10BB09	Gliclazide	6.9	7.4	7.2	3.0	3.0	3.0
A10BB01	Glibenclamide	na	na	na	2.3	3.0	2.8
C08CA05	Nifedipine	4.2	3.9	4.0	2.5	2.5	2.5
N05BA01	Diazepam	4.6	5.4	5.1	2.1	2.4	2.3
C09AA01	Captopril	18.6	19.7	19.3	2.1	2.2	2.2
R03AC02	Salbutamol, aerosol	5.5	1.9	3.3	3.3	1.5	2.2
M01AE01	Ibuprofen	2.8	3.4	3.2	1.3	1.5	1.4

NB: ATC - Anatomical Therapeutic Chemical; INN - International Non-proprietary Name; na - not applicable

Discussion

The study findings demonstrate increasing long-term medicine use among the elderly in the Republic of Srpska. Over a 5-year period, the proportion of the elderly who have used one medicine alone on a long-term basis declined; however, the proportion of patients who used multiple medicines increased (Table 2). This increase in polypharmacy was observed in both men and women; however, the increase was more prominent in women of all age

groups. The use of multiple medicines and polypharmacy also increased with age. This is similar to the findings of Franchi et al who found that prescriptions for at least one chronic medicine increased from 73.8% of the elderly in 2000 to 82.5% in 2010 (34). However, these authors found that the prevalence of elderly taking only one medicine or two to four medicines decreased over time to 7.9% and 29.7% respectively; whilst those exposed to polypharmacy increased to 52.7% (34). This is an appreciably higher prevalence of polypharmacy than seen in our study (Table 2). The different results in the prevalence of polypharmacy between studies could potentially be explained by differing inclusion criteria between the studies, variations in the duration of medicine use and the research period, data collecting methodologies and the representativeness of the study population. Although low, the prevalence of polypharmacy appreciably increased during the five year study period in the Republic of Srpska, with over half of all elderly patients taking 2 to 4 different medicines on a long-term basis for the treatment of chronic diseases by 2010 (Table 2). This needs to be addressed if prescribing is subsequently seen as inappropriate.

Polypharmacy was slightly more prevalent in women than men and slightly more women were taking 2 to 4 medicines than men in 2010 (Table 2). This compares to similar rates for 2 to 4 medicines in 2005 and marginally higher polypharmacy rates in men than women in 2005 (Table 2). Many studies have reported a correlation between polypharmacy and female gender (26, 27, 31, 49), whilst a positive correlation between polypharmacy and men has been observed in only a limited number of studies (24, 50). Such discrepancies among study findings could be due to differences in physicians' prescribing attitude toward genders, as well as differences between genders in educational and socioeconomic characteristics (24). For instance, women consult health services more often and earlier than men, and are more accustomed to taking of medicines (51). It is also known that those who report poor self-perceived health status are most likely to take medication (52), and in the Republic of Srpska in 2010 more women (20%) then men (16%) rated their health as worse than 12 months ago (53).

Different reasons may have contributed to the observed increase in medicine use in the elderly in the Republic of Srpska in recent years (Table 2). Numerous new medicines and new dosage forms, mostly for the treatment of cardiovascular, metabolic, digestive, nervous and respiratory diseases, were included in the HIF list of reimbursable drugs during the observed period. Broader therapeutic options enabled better affordability and coverage of patients, particularly as a number of medicines were available in recent years that had previously not been reimbursed, i.e. 100% patient co-payment. Careful monitoring of medicines consumption combined with ongoing reforms enables the reimbursement of expensive targeted pharmaceuticals and other high-budget-impact medicines (54-56).

Furthermore, there has been an aging of the population in the Republic of Srpska during the past two decades. Whilst the overall population decreased by 12% in the Republic of Srpska during the study period, the proportion of people aged ≥ 80 tripled, with people aged ≥ 65 now constituting 19% of the population (53, 57). Population aging is known as a major risk factor for development of chronic diseases and multiple medication use (51, 58).

Diabetes, heart disease, hypertension and obstructive pulmonary disease are well known relevant morbidity-related predictors of polypharmacy (26, 32). All of these conditions are prevalent among the elderly in the Republic of Srpska (Table 3). In fact, cardiovascular diseases were a leading cause of morbidity and mortality in the Republic of Srpska's population in the last decade (59).

As part of the national cardiovascular program to reduce morbidity and mortality, a particular focus was placed on the development of clinical guidelines (60) as well as the selection of cardiovascular medicines reimbursed by the HIF. This resulted in new diuretics (furosemide, torasemide, spironolactone, and combinations with amiloride), beta-blockers (metoprolol, bisoprolol), antiarrhythmics (amiodarone) and ACEIs (ramipril, trandolapril) being included in the list of reimbursed drugs in 2010. These new clinical guidelines appeared to influence physicians' prescribing patterns, with these guidelines often recommending prescribing of several medicines to treat or prevent diseases (60-62).

Alongside this, older patients often have multiple co-morbidities leading to an increasing number of different medicines prescribed (Tables 3 and 4), which is seen in other studies (63). This could itself lead to relatively high prescribing of ranitidine amongst the elderly to potentially prevent GI side-effects or as prophylactic therapy in multiple drug use ("prescribing cascade") to reduce GERD (gastroesophageal reflux disorders) (Table 4). However, we cannot confirm this statement with certainty without specific research in this area. For example when choosing medicines to treat hypertension alone or in combination, among the five main classes of antihypertensive medicines (thiazide diuretics, beta-blockers, ACEIs, CCBs, and angiotensin receptor blockers - ARBs), the official national guidelines recommend taking into account any comorbidities patients may have, treatments that can be taken only once a day, and their price. Besides hypertension, three more CV diseases were among the top diseases of the elderly for which medicines were prescribed along with diabetes type 2 (Table 3).

Overall, ACEIs alone or in combination with other drugs were the most prescribed medicines in the Republic of Srpska for this population (Table 4). This is perhaps not surprising since, as mentioned, cardiovascular diseases were a leading cause of morbidity and mortality in the Republic of Srpska's population in the last decade (59) and hypertension was seen among 77% of the elderly population on long-term medicines in 2010 (Table 3). ACEIs have outcome advantages for patients with concomitant cardiovascular diseases, heart failure and diabetes including benefits to prevent nephropathy (64-66). In addition, where monotherapy is inadequate for controlling BP and preventing cardiovascular disease outcomes and stroke in the elderly, ACEIs are effective in combination with a diuretic. The guideline recommendations and the prevalence of CV disease in the Republic of Srpska, coupled with knowledge of therapeutics, probably led to the increased prescribing of ACEIs, alone and combination with hydrochlorothiazide, in

recent years, adding to earlier and more consistent treatment of patients with CV disease (Table 4). A high proportion of patients prescribed fixed-dosage combinations of ACEI with hydrochlorothiazide may be due to the guidelines indicating a strong preference for thiazide diuretics when combination therapies are needed, often for high risk patients (60, 67). In addition, lower doses may be used resulting in fewer side-effects and better compliance and adherence to prescribed antihypertensive medicines. Alongside this prescribing of captopril decreased (Table 4), helped no doubt by the broader availability of medicines dosed once-daily, e.g. enalapril, and a higher patient copayment (50%).

CCBs are also among the preferred medicines to treat hypertension in the elderly, and amlodipine was widely prescribed (Table 4). Amlodipine is seen as safe for use in patients with heart failure, hypertension, chronic stable angina and diabetes (68), which were all prevalent in the elderly in this study (Table 3). Among available beta-blockers, carvedilol is probably more widely prescribed to treat patients with cardiovascular disease with metabolic syndrome or diabetes as it affects insulin sensitivity less than metoprolol (61), and cardioselective metoprolol has a preferable side effect profile in older persons and a lower price than bisoprolol. These considerations probably resulted in the appreciable use of carvedilol and metoprolol in this study (Tables 3 and 4).

Guidelines for the management of dyslipidaemia in the Republic of Srpska recommend the prescribing of statins as safe and effective in patients who either already have cardiovascular disease, e.g. patients following a heart attack or stroke (61, 62), or patients who are at risk of developing cardiovascular disease as well, e.g. diabetic patients with distinct metabolic disorders alongside other pathophysiologies (60). This probably contributed to increasing use of statins in recent years (Table 4), augmented by the increasing prevalence of patients with diabetes (Table 3).

Current guidelines for patients with diabetes in the Republic of Srpska recommend early initiation of metformin as a first-line drug treatment for monotherapy, and combination therapy for patients with type 2 diabetes (61). Sulfonylureas are a second choice in patients with contraindications and/or intolerance to metformin. This recommendation was based primarily on metformin's glucose-lowering effects, relatively low cost, and generally low level of side effects (61). As a result, more than doubling the prescribing of metformin in recent years (Table 4) enhanced by, as stated, the increasing prevalence of patients with Type 2 diabetes (Table 3).

Alongside this, there has been reduced prescribing of some older medicines, e.g. ranitidine, gliclazide, nifedipine, ibuprofen, diazepam and captopril (Table 4) during the past five years. We believe this is as a direct consequence of the introduction of the new clinical guidelines into clinical practice in the Republic of Srpska.

A concern though is the continued high use of digoxin (Table 4), as it has a narrow therapeutic margin as well as frequent and potentially severe adverse effects (69). As a result, guidelines in the Republic of Srpska recommend that digoxin should not be prescribed as a first-line treatment for heart failure (70). Generally, digoxin should be

reserved for worsening or severe heart failure not responding to first-and second-line treatments (71). However, it remains a useful treatment option for heart failure associated with atrial fibrillation. The findings also showed that aminophylline is still frequently prescribed for treatment of chronic obstructive pulmonary disease (COPD) although rates are decreasing (Tables 3 and 4). This again was quite unexpected since in the guidelines for treating COPD, theophylline and its derivate aminophylline are traditionally relegated to a third line bronchodilator after inhaled anticholinergics and β_2-agonists (72). Its use as a first-line bronchodilator being replaced by safer and more potent preparations, particularly in elderly who have different pharmacokinetic profiles and greater risk of developing side effects to theophylline (73). Consequently, it is intended that there will be educational initiatives in the Republic of Srpska to address both anomalies.

One conclusion from our findings (Tables 3 and 4) is that an appreciable proportion of patients in the Republic of Srpska are being prescribed recommended medicines in line with the new guidelines. However, we acknowledge further research is needed to clarify this before more definitive conclusions can be drawn. One reason for this hypothesis is that similar to other studies (47, 51), the elderly population in the Republic of Srpska mostly took medicines for cardiovascular, alimentary tract and metabolism and respiratory system diseases (Tables 3 and 4). These similarities in consumption patterns may reflect common therapeutic needs among elderly patients, and applying a standard prescription scheme regarding patients' ages (74).

We believe the major advantage of this study is the large and reliable data set analyzed, covering all reimbursed prescriptions to every individual aged $\geq$ 65 in the Republic of Srpska. This is the only comprehensive and consistent database of outpatient prescriptions in the Republic of Srpska, ensuring robustness with the findings. However, we acknowledge that the use of medicines in our population may have been underestimated as the HIF database does not include prescription medicines not reimbursed by the HIF as well as non-prescription medicines, e.g. OTC medicines. In addition, we do not know whether all analyzed medicines were actually taken by patients. However, we believe our findings are still valid and provide a base case for assessing future initiatives in the Republic of Srpska.

In conclusion, the study findings point to an increase in the elderly population with long-term medicine use. Whilst the prevalence of polypharmacy in the Republic of Srpska appears low compared with other studies, it has increased. This may well be due to the increasing prevalence of chronic diseases among the elderly alongside the ageing of the population, instigation of clinical guidelines for chronic diseases in the Republic as well as more medicines being available on the reimbursement lists to treat chronic conditions, especially CV diseases. However, there were concerns with high use of digoxin and theophylline (Table 4). Future research activities are planned to enhance knowledge about prescribing in this population to confirm or not the generally positive findings and the tentative explanations. This includes possible drug interactions among the elderly, greater monitoring of medicine use among the elderly, as well as monitoring adherence to current guidelines.

Alongside this, educational activities among physicians regarding the prescribing of digoxin in patients with heart failure and theophylline for COPD. The possibility for including other measures to address potentially inappropriate prescribing using for instance measures introduced in Croatia, Slovenia and Serbia will also be explored in future studies, building on recent research (75-77).

Five year view

It is anticipated that the rates of polypharmacy will grow in the Republic of Srpska over the coming five years with an ageing population and greater prevalence of patients with chronic diseases. Alongside this, educational interventions along with other measures to improve the appropriateness of prescribing and reduce inappropriate prescribing including digoxin and aminophylline. This could include measures used in other Balkan countries as well as across Europe and other continents. As a result, help to improve the care of the elderly in the Republic of Srpska within limited resources.

Acknowledgements and financial disclosure

Key points

- The prevalence of polypharmacy in the Republic of Srpska is currently low but increasing
- This increase is similar across countries where there is also an increase in the number of patients prescribed medicines long-term, as well as increased prevalence of patients prescribed two to four different medicines. Alongside this, there is a fall in the number of elderly taking one medicine alone long term
- Polypharmacy is most prominent in the age group 85 and older
- Women take more different medicines across all age groups than men; however, this was not universal. One medicine alone was taken by more men of all age groups
- Cardiovascular diseases including hypertension, angina, and ischaemic heart disease as well as heart failure are among the most prevalent conditions in the elderly along with diabetes (Types 1 and 2) and chronic bronchitis/ other forms of chronic obstructive pulmonary disease
- Medicines prescribing in the Republic of Srpska appears typically based on national guideline criteria. This is illustrated by reduced prescribing of a number of older medicines as a consequence of the new guidelines, e.g. gliclazide, nifedipine, captopril, ibuprofen, diazepam

References

1.   Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. The Cochrane database of systematic reviews. 2014;10:Cd008165.
2.   NHS Scotland. Polypharmacy Guidance March 2015. Available at URL: http://www.sehd.scot.nhs.uk/publications/DC20150415polypharmacy.pdf.
3.   Hovstadius TS, Petterson G, Astrand B. Prevalence and therapeutic intensity of dispensed drug groups for individuals with multiple medications: a register-based study of 2.2 million individuals. JPHSR. 2010;1:145–55.
4.   Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: misleading, but manageable. Clinical interventions in aging. 2008;3(2):383-9.
5.   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. Pharmacoepidemiology and drug safety. 2011;20(5):488-96.
6.   Jyrkka 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. European journal of clinical pharmacology. 2006;62(2):151-8.
7.   Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. The American journal of geriatric pharmacotherapy. 2007;5(4):345-51.
8.   Matanovic SM, Vlahovic-Palcevski V. Potentially inappropriate prescribing to the elderly: comparison of new protocol to Beers criteria with relation to hospitalizations for ADRs. European journal of clinical pharmacology. 2014;70(4):483-90.
9.   Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. The American journal of geriatric pharmacotherapy. 2011;9(1):11-23.
10.   Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. The American journal of geriatric pharmacotherapy. 2011;9(6):364-77.
11.   Hamilton HJ, Gallagher PF, O'Mahony D. Inappropriate prescribing and adverse drug events in older people. BMC geriatrics. 2009;9:5.
12.   Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C, et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck((R))). Drugs & aging. 2013;30(10):821-8.
13.   Nobili A, Garratini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. Journal of Comorbidity 2011;1:28-44.
14.   Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults. Age and ageing. 2015;44(1):90-6.
15.   Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs & aging. 2014;31(4):283-9.

16.   Wallace J, Paauw DS. Appropriate prescribing and important drug interactions in older adults. The Medical clinics of North America. 2015;99(2):295-310.

17.   Jäger C, Szecsenyi J, Steinhäuser J. Design and Delivery of a Tailored Intervention to Implement Recommendations for Multimorbid Patients Receiving Polypharmacy into Primary Care Practices. BioMed Research International. 2015;Article ID 938069:1-9.

18.   Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Archives of internal medicine. 2006;166(6):605-9.

19.   NHS Scotland. PolypharmacyGuidance October 2012. Available at URL:http://www.central.knowledge.scot.nhs.uk/upload/Polypharmacy%20full%20guidance%20v2.pdf

20.   Wladysiuk M, Tabor A, Godman B. 'HTA for Crisis': sharing experiences during the 7th EBHC Symposium. Expert review of pharmacoeconomics & outcomes research. 2013;13(1):47-9.

21.   Godman B, Paterson K, Malmstrom RE, Selke G, Fagot JP, Mrak J. Improving the managed entry of new medicines: sharing experiences across Europe. Expert review of pharmacoeconomics & outcomes research. 2012;12(4):439-41.

22.   Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. The Cochrane database of systematic reviews. 2012;5:Cd008165.

23.   Ruggiero C, Dell'Aquila G, Gasperini B, Onder G, Lattanzio F, Volpato S, et al. Potentially inappropriate drug prescriptions and risk of hospitalization among older, Italian, nursing home residents: the ULISSE project. Drugs & aging. 2010;27(9):747-58.

24.   Slabaugh SL, 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.

25.   Junius-Walker U, Theile G, Hummers-Pradier E. Prevalence and predictors of polypharmacy among older primary care patients in Germany. Family practice. 2007;24(1):14-9.

26.   Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Patterns of drug use and factors associated with polypharmacy and excessive polypharmacy in elderly persons: results of the Kuopio 75+ study: a cross-sectional analysis. Drugs & aging. 2009;26(6):493-503.

27.   Bjerrum L, Sogaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study. European journal of clinical pharmacology. 1998;54(3):197-202.

28.   Jyrkka J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs & aging. 2009;26(12):1039-48.

29.   Kim HA, Shin JY, Kim MH, Park BJ. Prevalence and predictors of polypharmacy among Korean elderly. PloS one. 2014;9(6):e98043.

30.   Lewis T. Using the NO TEARS tool for medication review. BMJ (Clinical research ed). 2004;329(7463):434.

31.   Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivela SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. Journal of clinical epidemiology. 2002;55(8):809-17.

32.   Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM. The development of polypharmacy. A longitudinal study. Family practice. 2000;17(3):261-7.

33.   Holbeach E, Yates P. Prescribing in the elderly. Australian family physician. 2010;39(10):728-33.

34.   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. European journal of clinical pharmacology. 2014;70(4):437-43.

35.   Fadare JO, Agboola SM, Opeke OA, Alabi RA. Prescription pattern and prevalence of potentially inappropriate medications among elderly patients in a Nigerian rural tertiary hospital. Therapeutics and clinical risk management. 2013;6:115-20.

36.   Guthrie B, Treweek S, Petrie D, Barnett K, Ritchie LD, Robertson C, et al. Protocol for the Effective Feedback to Improve Primary Care Prescribing Safety (EFIPPS) study: a cluster randomised controlled trial using ePrescribing data. BMJ open. 2012;2(6).

37.   Šter MP, Gorup C, Klančič D. Polypharmacy and inappropriate drug prescribing in elderly nursing home residents. Zdrav Vestn 2009;78:231 – 40.

38.   Gallagher P, O'Mahony D. 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(6):673-9.

39.   Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, Beers MH. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Archives of internal medicine. 2003;163(22):2716-24.

40.   Kaplan W, Wirtz V, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World 2013 Update Report. 2013. Available at URL: http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf?ua=1.

41.   Garattini S, Bertele V, Godman B, Haycox A, Wettermark B, Gustafsson LL. Enhancing the rational use of new medicines across European health care systems. European journal of clinical pharmacology. 2008;64(12):1137-8.

42.   Ogura S, Jakovljevic M. Health financing constrained by population aging - an opportunity to learn from Japanese experience. Ser J Exp Clin Res 2014. 2014;15(4):175-81.

43.   Bagari Bizjak N, Fürst J, Kramberger B, Povše M, Mrak J. Kakovost predpisovanja v družinski medicini. Recept. 2011;9(1):93-5.

44.   Mrak J, Fürst J, Premuš M. Kakovostno predpisovanje zdravil - model pristopa k polifarmakoterapiji. SLOVENSKO s, 2014 s VARNA UPORABA ZDRAVIL Ljubljana: Slovensko zdravniško društvo; 2014 str 131-135.

45.   Markovic-Pekovic V, Skrbic R, Godman B, Gustafsson LL. Ongoing initiatives in the Republic of Srpska to enhance prescribing efficiency: influence and future directions. Expert review of pharmacoeconomics & outcomes research. 2012;12(5):661-71.

46.   Petrusic T, Jakovljevic M. Budget Impact of Publicly Reimbursed Prescription Medicines in the Republic of Srpska. Frontiers in public health. 2015;3:213.

47.   Kennerfalk A, Ruigomez A, Wallander MA, Wilhelmsen L, Johansson S. Geriatric drug therapy and healthcare utilization in the United kingdom. The Annals of pharmacotherapy. 2002;36(5):797-803.

48.   Chitnis A, Wang R, Sun SX, Dixit S, Tawah A, Boulanger L. Impact of initiation of asenapine on patterns of utilization and cost of healthcare resources associated with the treatment of bipolar I disorder. Journal of medical economics. 2015:1-23.

49.   Rozenfeld S, Fonseca MJ, Acurcio FA. Drug utilization and polypharmacy among the elderly: a survey in Rio de Janeiro City, Brazil. Revista panamericana de salud publica = Pan American journal of public health. 2008;23(1):34-43.

50.   Chan DC, Hao YT, Wu SC. Polypharmacy among disabled Taiwanese elderly: a longitudinal observational study. Drugs & aging. 2009;26(4):345-54.

51.   Venturini CD, Engroff P, Ely LS, Zago LF, Schroeter G, Gomes I, et al. Gender differences, polypharmacy, and potential pharmacological interactions in the elderly. Clinics (Sao Paulo, Brazil). 2011;66(11):1867-72.

52.   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. Journal of gerontology. 1992;47(5):M137-44.

53.   Republika Srpska Institute of Statistics [Women and men in Republika Srpska. Bulletin No 6]. Žene i muškarci u Republici Srpskoj broj 6, 2012. Serbian.

54.   Jakovljevic MB. Targeted immunotherapies overtaking emerging oncology market value based growth. Journal of BUON : official journal of the Balkan Union of Oncology. 2015;20(1):350-1.

55.   Dragovic A, Zugic A, Jakovljevic MB. Macroeconomic policy impact on oncology-related public expenditure in an emerging european market – signs of early recovery Ser J Exp Clin Res 2015;16(1):43-50.

56.   Jakovljevic MB, Jovanovic M, Lesch OM. Accessibility and affordability of alcohol dependency medical care in serbia. Frontiers in psychiatry. 2014;5:192.

57.   Republika Srpska Institute of Statistics . [Demographic statistics. Bulletin No 5]. Demografski bilten broj 5, 2002. Serbian.

58.   Jakovljevic M, Laaser U. Population aging from 1950 to 2010 in seventeen transitional countries in the wider region of South Eastern Europe. SEEJPH. 2015;Posted 21 February. DOI 10.12908/SEEJPH-2014-42.

59.   Markovic-Pekovic V, Stoisavljevic-Satara S, Skrbic R. Utilisation of cardiovascular medicines in Republic of Srpska, Bosnia and Herzegovina, 5 years study. Pharmacoepidemiology and drug safety. 2009;18(4):320-6.

60.   Ministry of Health and Social Welfare of the Republic of Srpska. [Guidelines for Clinical Practice. Cardiovascular diseases: Hypertension/Atrial fibrilation/Myocardial infarction/Angina pectoris]. Bolesti sistema krvotoka: Akutni infarkt miokarda. Atrijalna fibrilacija. Angina pektoris i bol u grudima. Arterijska hipertenzija, 2004. Serbian.

61.   Ministry of Health and Social Welfare of the Republic of Srpska. [Guideline for Diabetes mellitus]. Nacionalni vodič za Diabetes Mellitus, 2004. Serbian.

62.   Ministry of Health and Social Welfare of the Republic of Srpska . [Guideline for Hyperlipoproteinemia]. Vodič lipoproteinemije, 2004. Serbian.

63.   Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. BMC clinical pharmacology. 2010;10:16.

64.   Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998;317(7160):703-13.

65.   Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. The New England journal of medicine. 2005;353(25):2643-53.

66.   SIGN. Management of Diabetes. Available at URL: http://www.sign.ac.uk/pdf/qrg116.pdf.

67.   Lionakis N, Mendrinos D, Sanidas E, Favatas G, Georgopoulou M. Hypertension in the elderly. World journal of cardiology. 2012;4(5):135-47.

68.   Dickerson LM, Gibson MV. Management of hypertension in older persons. American family physician. 2005;71(3):469-76.

69.   Digoxin: serious drug interactions. Prescrire Int. 2010;19(106):68-70.

70.   Ministry of Health and Social Welfare of the Republic of Srpska . [Guideline for Heart failure]. Vodič srčana insuficijencija, 2007. Serbian.

71.   NICE. Chronic heart failure. NICE clinical guideline 108. Available at URL: https://www.nice.org.uk/guidance/cg108/resources/guidance-chronic-heart-failure-pdf.

72.   Barnes PJ. Theophylline. American journal of respiratory and critical care medicine. 2013;188(8):901-6.

73.   Berbecaru-Iovan S PF, Berbecaru-Iovan A. Considerations on the Broncholdilator Therapy in Elderly Patients with Obstructive Bronchial Syndrome. Current Health Sciences Journal. 2013;39:197-203.

74.   Ribeiro AQ, Rozenfeld S, Klein CH, Cesar CC, Acurcio Fde A. [Survey on medicine use by elderly retirees in Belo Horizonte, Southeastern Brazil]. Revista de saude publica. 2008;42(4):724-32.

75.   Vukovic M, Gvozdenovic BS, Rankovic M, McCormick BP, Vukovic DD, Gvozdenovic BD, et al. Can didactic continuing education improve clinical decision making and reduce cost of quality? Evidence from a case study. The Journal of continuing education in the health professions. 2015;35(2):109-18.

76.   Vezmar Kovacevic S, Simisic M, Stojkov Rudinski S, Culafic M, Vucicevic K, Prostran M, et al. Potentially inappropriate prescribing in older primary care patients. PloS one. 2014;9(4):e95536.

77.   Stefanovic SM, Jankovic SM. Knowledge of the pharmacological profile of a patient improves the quality of prescribing, the outcomes of treatment, and the utilization of health services in primary health care. European journal of clinical pharmacology. 2011;67(11):1091-101.