ORIGINAL ARTICLE
UDC: 616.8-085:616.015.2
DOI: https://doi.org/10.2298/VSP190401105K

(CC BY-SA)

Risk factors for potential drug-drug interactions in a general neurology ward

Faktori rizika od potencijalnih interakcija između lekova kod bolesnika hospitalizovanih na neurološkom odeljenju

Marina J. Kostić, Radica S. Živković Zarić, Slobodan M. Janković

University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia

Abstract

Bacground/Aim. Treatment of neurological diseases usually requires polypharmacy, and it is crucial to detect potential drug-drug interactions (DDIs) and recognize risk factors on time, as consequences of DDIs could be serious. The aim of the study was to analyze risk factors for the occurrence and the number of potential DDIs among patients in a general neurological ward. **Methods.** This study was conducted with 144 inpatients in a general-care neurological department of a tertiary care hospital. The effects of risk factors for potential DDIs were evaluated by multiple linear regression. The study had retrospective cohort design. Frequencies of various types of potential DDIs (according to severity) were discovered by Medscape, Epocrates and Micromedex online interaction checkers. **Results.** The number of prescribed drugs, age of a patient, value of the Charlson comorbidity index and prescription of an antidepressant increase risk of potential DDIs in a general neurology ward. On the other hand, being paralyzed, number of prescribers for a single patient, being bedridden for at least one day of hospitalization decreased the number of potential DDIs *per* patient. Number of prescribed drugs *per* patient [odds ratio (OR) = 1.466 ± 0.250; $p = 0.000$) and age (OR = 1.027 ± 0.026; $p = 0.041$)] increased, and number of prescribers *per* patient (OR = 0.056 ± 0.028; $p = 0.016$), especially if the patients were paralyzed (OR = 0.214 ± 0.294; $p = 0.007$), decreased the risk of contraindicated, serious, "use alternative" or major potential DDIs. Antidepressants increased the risk of absolute number of all monitor/modify potential DDIs (OR = 1.257 ± 0.726; $p = 0.035$). **Conclusion.** Frequency of potential DDIs among neurological patients is considerable and influenced to the largest extent by advanced age, comorbidities, total number of prescribed drugs *per* patient and concomitant use of antidepressants.

Key words:
nervous system, diseases; combination drug therapy; drugs, interactions; risk factors.

Apstrakt

Uvod/Cilj. Lečenje neuroloških bolesti obično zahteva polifarmaciju, pa je važno otkriti potencijalne interakcije između lekova i prepoznati rizik na vreme jer posledice po bolesnika mogu biti ozbiljne. Cilj ove studije bio je da analizira faktore rizika od pojave, kao i broj potencijalnih interakcija između lekova. **Metode.** U studiju su bila uključena 144 bolesnika hospitalizovana na Odeljenju opšte neurologije Kliničkog centra Kragujevac. Faktori rizika od interakcija ispitivani su multiplom linearnom regresijom. Studija je imala retrospektivni kohortni dizajn. Frakvencija različitih tipova interakcija bila je prepoznata uz pomoć internet proveravača interakcija (Medscape, Epocrates i Micromedex). **Rezultati.** Broj propisanih lekova, starost bolesnika, vrednost Charlsonove skale komorbiditeta i propisivanje antidepresiva povećavali su rizik od interakcija na Odeljenju neurologije. Sa druge strane, paralizovanost, broj lekara koji su propisivali lekove po bolesniku, vezanost za postelju na jedan dan hospitalizacije snižavala je verovatnoću za pojavu interakcija između lekova. Broj propisanih lekova po bolesnku [*odds ratio* (OR) = 1,466 ± 0,250; $p = 0,000$)] i starost bolesnika (OR = 1,027 ± 0,026; $p = 0,041$) su povećavali, a broj propisivača po bolesniku (OR = 0,056 ± 0,028; $p = 0,016$), posebno kod paralizovanih bolesnika (OR = 0,214 ± 0,294; $p = 0,007$), su smanjili rizik od kontraindikovanih, ozbiljnih, 'koristi alternativu' ili velikih potencijalnih interakcija. Primena antidepresiva povećavala je rizik od nastanka "prati/promeni" interakcija (OR = 1,257 ± 0,726; $p = 0.035$). **Zaključak.** Učestalost potencijalnih interakcija između lekova kod neuroloških bolesnika je značajna i povezana je sa godinama života bolesnika, komorbiditetima, brojem propisanih lekova po bolesniku i istovremenom upotrebom antidepresiva.

Ključne reči:
nervni sistem, bolesti; lečenje kombinovanjem lekova; lekovi, interakcije; faktori rizika.

Correspondence to: Radica S. Živković Zarić, University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, 34 000 Kragujevac, Serbia. E-mail: radica_zivkovic@yahoo.com

Introduction

Drug-drug interaction (DDI) could be defined as a change of a drug action when it is taken together with another drug/drugs, in terms of intensity of action, pharmacokinetic attributes or occurrence of adverse drug effects [1]. Early recognition of potential DDIs gives an opportunity to prevent them, which is significant not only from the healthcare provider′s but also from the patient′s point of view. Since polypharmacy is unavoidable in modern management of many diseases, creating an environment for the occurrence of DDIs, there is a growing concern that interactions will lead to the increased utilization of healthcare resources (e.g. outpatient visits, number and length of hospitalizations, etc.) within a healthcare system, accompanied with increased costs [2, 3]. It has already been shown that DDIs have a significant role in increased morbidity and mortality among hospitalized patients [4]. Discovery of potential DDIs is nowadays much easier with the use of online or offline interaction checkers which classify interactions according to severity, like Medscape [5], Epocrates [6] and Micromedex [7].

Drug-drug interactions on Medscape could be characterized as: contraindicated – which means that this combination of drugs should not be used due to high risk for dangerous interaction; serious – which indicates that this combination of drugs has potential for serious interaction and regular monitoring by doctor is required or alternate medication may be needed; then significant – which indicates that potential for significant interaction is high and monitoring by doctor is likely required, and minor – where interaction is unlikely, minor, or nonsignificant [8].

On Epocrates platform, DDIs are organized according to clinical management and involve different categories such as "Contraindicated," "Avoid/Use Alternative," "Monitor/Modify Therapy," and "Caution Advised". These categories are not intended to point the severity of proposed interactions, so all described interactions, even “Caution Advised” ones, may have serious clinical consequences and should not be dismissed categorically [9].

IBM Micromedex Complete Drug Interaction defines DDIs as: contraindicated – meaning drugs are contraindicated for concurrent use; major DDIs – indicating that interaction may be life-threatening and/or require medical intervention in order to minimize or prevent serious adverse reaction; moderate DDIs – implying that the exacerbation of the patient’s condition may be developed and the alteration of therapy is required; minor DDIs – where interactions would have limited clinical effects and generally not require a major alteration in therapy, and unknown DDIs. All described interactions are fully synopsized and referenced with excellent, good, fair or unknown level of documentation [10].

These online platforms encompass results regarding DDIs derived from different sources such as handbooks, textbooks, data from manufacturer and Internet sources. The main advantage of these checkers is their accessibility which enables doctor′s and pharmacist′s prompt reaction especially in the presence of harmful DDIs which decrease clinical outcomes or increase severity of patients′ status. In spite of these facts, interaction checkers differ in sensitivity or specificity, so, due to inconsistencies, health professionals should use more than one of them in practice. Also, some of these applications are free of charge, but some of them require payment which may limit their wide use [11].

The incidence of DDIs positively correlates with multiple, concurrent use of drugs and varies from 3–5%, if a patient takes a few drugs, to 20% in patients taking more than 10 drugs [12, 13]. Other risk factors which significantly contribute to the occurrence of DDIs are advanced age, comorbidities, weak coordination of healthcare for individual patients among health professionals of various specialties, non-adherence of patients, etc. [14]. Neurological patients are not an exception in terms of the occurrence of DDIs. The treatment of neurological diseases usually requires polypharmacy, and it is crucial to recognize risk factors, detect potential DDIs on time and prevent additional deterioration of health in these complex patients [15]. It has been shown recently that the advanced age of patients and the number of prescribed drugs are risk factors for the occurrence of DDIs in neurological patients [16]. Neurological diseases are among the most common reasons for hospitalization in modern society. A study in Italy showed that the prevalence of DDIs in a neurology ward was very similar to that in an internal medicine ward [16]. Dementia, for example, is a disease in expansion due to longer human life nowadays [17]. Also, there has been the result that nonvascular disease such as epilepsy increases the risk of DDIs in patients in a neurology ward [15]. It is known that antiepileptic drugs have a lot of behavioral side effects including depression, aberrant behaviors, and the development or worsening of irritability, impulsivity, anger, hostility, and aggression [18]. Neurological patients are frequently disabled, sometimes bedridden or out of control of their sphincters. When hospitalized, they frequently develop urinary or respiratory tract infections, requiring the prescription of antibiotics, which increases overall medication burden and predisposes to DDIs. All these give a certain specificity to DDIs problem in a neurology ward.

The aim of our study was to analyze risk factors for the occurrence and number of potential DDIs among the patients admitted to a general-care neurological department of a tertiary care hospital.

Methods

The study was approved by the Ethics Committee of Clinical Center Kragujevac (number of approval: N - 0 l /14886). Our study was a retrospective analysis of a patient cohort treated at the General Ward of the Clinic

for Neurological Disorders (GW-CND), Clinical Center Kragujevac, a public tertiary care hospital situated in Kragujevac, capital of the Šumadija region, Serbia. The study included patients who were admitted to the Clinic during two months in 2017 (September and October) and two months in 2018 (March and April); the files of the patients admitted during the period in-between were not available to the investigators due to technical reasons. Inclusion criteria were: neurological diagnosis on admission, complete data in the patient′s file and age over 18 years. Exclusion criteria were: not being prescribed drug therapy, being prescribed less than two drugs and emergency admission. The study sample was consecutive, ie. all patients admitted to the Clinic during the above mentioned four-month period were included in the study.

The data were extracted from the patients′ histories. The outcome variables were potential DDIs discovered by the three interaction checkers (Medscape, Epocrates and Micromedex), classified according to the severity. Since the number of contraindicated and serious DDIs *per* patient was mostly zero or 1, we made composite outcomes for the purpose of this study consisting of potential contraindicated and/or "serious/use alternative" DDI occurrence according to the Medscape checker, contraindicated and/or "use alternative" potential DDI occurrence based on the Epocrates checker, and contraindicated and/or major potential DDI occurrence discovered by Micromedex interaction checker. Other outcomes were median number of the potential "monitor closely" DDIs according to the Medscape checker, median number of "monitor/modify" DDIs according to the Epocrates, and median number of moderate DDIs revealed by Micromedex interaction checker.

Predictor variables taken into account were derived from socio-demographic data, data about pharmacotherapy and clinical data believed to have certain influence on DDIs. Socio-demographic data were limited to the age and gender of patients, while the data about pharmacotherapy included: names of drugs which were prescribed, total number of prescribed drugs, number of prescribers for a single patient, Anatomical Therapeutic Chemical (ATC) classification code of the prescribed drugs, number of different pharmacological/therapeutic subgroups prescribed, prescribing events involving anticoagulants, anticonvulsants, antidepressants, anti-arrhythmic or antiplatelet drugs. The following data about clinical condition of patients were included: main diagnosis on admission, total length of hospitalization, transfer from intensive care unit or other department to the GW-CND, being paralyzed, being bedridden for at least one day during hospitalization and comorbidities like dementia, delirium, renal failure, liver cirrhosis, diabetes mellitus, bronchial asthma, chronic obstructive pulmonary disease, hypertension, heart failure, etc. (also summated by Charlson Comorbidity Index) [19].

The data collected in our study were analyzed using descriptive statistics. Continuous numeric variables were described by mean and standard deviation if the data were normally distributed or by median and range if the normality of data distribution was not reached. Values of categorical variables were presented as rates or percentages.

The influence of potential risk factors on the number of potential DDIs *per* patient was evaluated by multiple linear regression analysis. Statistical validity of the regression model was checked by analysis of variance (F value), percentage of outcome (number of DDIs *per* patient) variability explained (coefficient of determination, R^2) and by variance inflation factor (VIF) which should take values below 10. Extent of influence of potential risk factors on number of DDIs *per* patient was assessed by their B coefficients within the regression equation, including confidence intervals (CIs).

The influence of potential risk factors on the occurrence of potential contraindicated/serious/major DDIs was estimated by binary logistic regression analysis. Validity of the logistic regression model was checked by the Cox and Snell R^2, Nagelkerke's R^2 and Hoshmer Lemeshow test. The strength of influence of potential risk factors on the occurrence of potential contraindicated/serious/major DDIs was assessed by adjusted odds ratio (OR), including CIs. All calculations were performed by the Statistical Program for Social Sciences (SPSS version 18).

Results

In total, there were 144 inpatients who participated in the study. Mean age of hospitalized patients was 59.0 ± 1.4, and median number of prescribed drugs *per* patient was 7 (2–20). The most common comorbidity was hypertension (55.6%). The most common reason for admission was diagnostic evaluation of patients with neurological symptoms like headache or vertigo (34.7%). The outcome of hospitalization for the majority of patients (89.6%) was discharge for further treatment at home. According to the Medscape interaction checker, potential contraindicated and serious-use alternative DDIs were found in 49.5% of patients, while median number of potential "monitor closely" DDIs *per* patient was 3 (0–26). Epocrates interaction checker discovered potential contraindicated or "use alternative" DDIs in more than half of the patients (53.5%), and median number of potential monitor/modify DDIs *per* patient was 1 (0–22). Finally, according to the Micromedex interaction checker, 59% of patients had potential contraindicated or major DDIs, and median number of potential moderate DDIs *per* patient was 1 (0–16). Detailed characteristics of the study sample are shown in Table 1.

The results of multivariate analysis for the outcomes of the presence of potential contraindicated, serious, "use alternative" or major DDIs and absolute number of "monitor closely", "monitor/modify" or moderate DDIs are presented in Tables 2 and 3, respectively. Variables included in both logistic and multiple linear regression

Table 1

Characteristics of the study sample

Variable	Values
Age (years), mean ± SD	59.0 ± 1.4
Gender, n (%)	
male	74 (51.4)
female	70 (48.6)
Clinical data, n (%)	
degenerative diseases	33 (22.9)
neurological symptoms	50 (34.7)
epilepsy	4 (2.8)
brain tumor	5 (3.5)
cerebrovascular diseases	46 (31.5)
autoimmune diseases	6 (4.2)
Length of hospitalization (days), median (range)	10 (1–40)
Transfer from another ward, n (%)	5 (3.5)
Transfer from emergency department, n (%)	5 (3.5)
Patients bedridden for at least one day of hospitalization, n (%)	34 (23.6)
Paralyzed patients, n (%)	24 (16.7)
Delirium/dementia, n (%)	9 (6.3)
Renal failure, n (%)	24 (16)
Liver cirrhosis, n (%)	1 (0.7)
Diabetes mellitus, n (%)	27(18.8)
Asthma, n (%)	4 (2.8)
Chronic obstructive pulmonary disease, n (%)	6 (4.2)
Hypertension, n (%)	80 (55.6)
Heart failure, n (%)	13 (9)
Charlson Comorbidity Index, median (range)	2.5 (0–11)
Outcome of hospitalization, n (%)	
Discharged for treatment at home, n (%)	129 (89.6)
Transfer to another ward, n (%)	13 (22.9)
Death, n (%)	2 (1.4)
Information about drugs, median (range)	
number of prescribed drugs	7 (2–20)
number of pharmacological/therapeutic subgroups prescribed (2nd level of ATC classification)	6 (2–14)
number of prescribers for a single patient	1 (1–6)
Anticoagulant therapy, n (%)	30 (20.8)
Anticonvulsants, n (%)	25 (17.4)
Antidepressants, n (%)	19 (13.2)
Antiarrhythmic drugs, n (%)	50 (34.7)
Angiotensin-converting enzyme inhibitors, n (%)	52 (35)
Non steroidal anti-inflammatory drugs, n (%)	80 (55)
Dual anti-aggregation therapy, n (%)	4 (2.8)
Drug allergy, n (%)	10 (6.9)

n (%) – number (percentage) of patients; ATC – Anatomical, Therapeutic, Clinical; SD – standard deviation.

were: the age of patients, gender, length of hospitalization, main diagnosis on admission, number of prescribed drugs, number of pharmacological/therapeutic subgroups prescribed (2nd level of ATC classification), number of prescribers for a single patient, cognitive incompetence (delirium or dementia), Charlson comorbidity index, paralysis, being bedridden for at least one day of hospitalization, and receiving anticonvulsants, antidepressants or anticoagulants.

The analysis showed that the number of prescribed drugs *per* patient increased and being paralyzed decreased the likelihood of both contraindicated/serious/major and moderate/monitor closely potential DDIs. Only contraindicated/serious/major potential DDIs were influenced by age, which increased, and by the number of physicians who prescribed drugs to a single patient, which decreased their likelihood. On the other hand, Charlson Comorbidity Index and prescribing antidepressants increased the number of moderate/monitor closely potential DDIs, while being bedridden for at least one day of hospitalization decreased the number of this type of potential DDIs.

There were 80 patients having the diagnosis of hypertension in our sample, and among them we found 50 patients (ten with mild to moderate renal failure) with contraindicated or serious-use alternative/major potential DDIs. Frequency of contraindicated potential DDIs were 10% [between two different non-steroidal anti-inflammatory drugs (NSAID)] while frequency of the serious-use alternative/major potential DDIs were 96% [between NSAIDs and angiotensin-converting enzyme inhibitors (ACEI)], Table 4.

Table 2

Multivariate regression analysis (binary logistic regression) for the outcome presence of "contraindicated", "serious", "use alternative" or "major" potential drug-drug-interactions (DDIs)

Interaction checker	Combination of two types of DDIs	Cox and Snell R^2	Nagelkerke's R^2	Hoshmer Lemeshow test	Significant variables	Adjusted OR (95% CI)	*p*
Medscape	Contraindicated and serious/ Use alternative	0.230	0.307	0.416	Number of prescribed drugs	1.466 (1.237–1.738)	0.000
					Age	1.027 (1.001–1.053)	0.041
					Number of prescribers *per* patient	0.556 (0.345–0.895)	0.016
Epocrates	Contraindicated and Use alternative	0.295	0.395	0.221	Number of prescribed drugs *per* patient	1.499 (1.253–1.793)	0.000
Micromedex	Contraindicated and Major	0.126	0.291	0.917	Number of prescribed drugs *per* patient/	1.573 (1.313–1.886)	0.000
					paralyzed patient	0.214 (0.069–0.656)	0.007

***Note*: Variables included in the last step of the model – "Contraindicated and Serious/Use Alternative" detected by Medscape (number of prescribed drugs *per* patient, age, number of prescribers for a single patient); "Contraindicated and Use Alternative" detected by Epocrates (number of prescribed drugs *per* patient); "Contraindicated and major" detected by Micromedex (number of prescribed drugs *per* patient, paralyzed patient).**
R – coefficient of determination; OR – odds ratio; CI – confidence interval.

Table 3

Multivariate regression analysis for the outcome of absolute number of "significant", "monitor/modify" or "moderate" potential drug-drug interactions

Interaction checker	Outcomes	R^2	F (*p*)	Number of excluded variables	Significant variables	B	95% CI	VIF
Medscape	Significant	0.545	2.195 (0.141)	13	Number of prescribed drugs *per* patient/	1.120	(0.902–1.109)	1.109
					paralyzed patient	-1.900	(0.884–1.131)	1.131
Epocrates	Monitor/ modify	0.509	1.370 (0.244)	12	Number of prescribed drugs *per* patient/	0.657	(0.737–1.356)	1.356
					paralyzed patient	-1.160	(0.734–1.363)	1.363
					Antidepressants	1.257	(0.885–1.130)	1.130
Micromedex	Moderate	0.386	1.135 (0.289)	12	Number of prescribed drugs *per* patient	0.385	(0.737–1.365)	1.256
					Charlson Comorbidity Index	0.185	(0.687–1.445)	1.455
					Patients bedridden for at least one day of hospitalization	1.140	(0.885–1.130)	1.363

***Note*: Variables included in the last step of the model – "Significant or Monitor closely" interactions detected by Medscape (number of prescribed drugs, immobile patients); "Monitor/modify" interactions detected by Epocrates (number of prescribed drugs, immobile patients, antidepressants); "Moderate" interactions' detected by Micromedex (number of prescribed drugs, Charlson Comorbidity Index, immobile patients at least for one day of hospitalization).**
R^2 – coefficient of determination; F (*p*) – value of F-test (probability of null hypothesis); B – unstandardized coefficient; CI – confidence interval; VIF – Variance Inflation Factor.

Table 4

The most common drug-drug interactions (DDIs) in a general neurology ward

Drugs	Type of DDIs by interaction checker		
	Medscape	Epocrates	Micromedex
Acetylsaclycilic acid and ketorolac	Contraindicated	Contraindicated	Contraindicated
Diclofenac and ketorolac	Contraindicated	Avoid-UA	Contraindicated
Acetylsaclycilic acid and fosinopril	Serious UA	Monitor/Modify	Moderate
Acetylsaclycilic acid and enalapril	Serious UA	Monitor/Modify	Moderate
Acetylsaclycilic acid and ramipril	Serious UA	Monitor/Modify	Moderate
Acetylsaclycilic acid and ibuprofen	Serious UA	Avoid-UA	Major
Ketorolac and ramipril	Serious UA	Monitor/Modify	Moderate
Ketorolac and perindopril	Serious UA	Monitor/Modify	Moderate
Diclofenac and enalapril	Serious UA	Monitor/Modify	Moderate
Diclofenac and quinapril	Serious UA	Monitor/Modify	Moderate
Ibuprofen and ramipril	Serious UA	Monitor/Modify	Moderate

UA – use alternative.

Discussion

The results of our study showed that the number of prescribed drugs, the age of a patient, the value of the Charlson comorbidity index and the prescription of an antidepressant increase the risk of potential DDIs in a general neurology ward. On the other hand, being paralyzed, a number of prescribers for a single patient, being bedridden for at least one day of hospitalization decrease the number of potential DDIs *per* patient. There are differences in sensitivity and specificity of available interaction checkers. Micromedex is rated as the most specific in general and the most sensitive for serious potential DDIs, while Epocrates and Medscape share the second place [11]. Accordingly, we revealed in our study the largest number contraindicated, serious, "use alternative" or major potential DDIs using Micromedex while the Medscape pointed to the largest number of "monitor closely", "monitor/modify" or moderate potential DDIs. The routine use of these interaction checkers could provide better care of these patients especially due to prompt access to these Internet platforms. On the other hand, complete set of information about consequences of potential DDIs and final desicion about final outcome of therapy could be summarized in the presence of other information derived as from medical and practical knowledge as well as from medical records of patients [20, 21].

Neurological disorders are one of the most common reasons for treatment in hospital facilities in modern society [16]. It is known that neurological diseases have chronic and progressive clinical course and due to these reasons patients in the neurological ward needed to be treated mostly with more than one drug. Polypharmacy increases the risk of development of potential DDIs which can contribute to the deterioration of primary medical condition of neurological patients [15]. Our results showed that the most frequently prescribed drugs were anticonvulsants, anticoagulant drugs, antidepressants, antiarrhythmic medicines, NSAIDs and ACEIs. These different groups of drugs have ability to increase the possibility of the development of clinically relevant DDIs and due to this reason neurological patients are more vulnerable population regarding DDIs, and require special concern in detecting potential DDIs on time and preventing additional deterioration of health [15–18].

Antidepressants have many indications and are frequently prescribed to neurological patients [22]. It is not surprising that patients who have been prescribed antidepressants have a higher risk of potential DDIs since the majority of antidepressant drugs are substrates for one or more of the cytochrome P-450 isozymes. Co-medication with inducers (eg. carbamazepine or phenytoin) or inhibitors (eg. valproate or imidazoles) may decrease or increase (50–60%), respectively, serum concentrations of antidepressants such as amitriptyline and nortriptyline, affecting their efficacy and safety [23]. On the other hand, selective inhibitors of serotonin reuptake may interact pharmacodynamically with anticoagulant and antiplatelet drugs increasing the risk of bleeding [24].

The number of prescribers *per* patient was a mitigating factor for a number of interactions not only in our study but also in the study conducted in the Netherlands by Vingerhoets et al. [25]. Nevertheless, in one more study within the settings of general practice, Andersson et al. [26] have established that potential DDIs in primary health care arise more often when multiple prescribers are involved in the treatment of a single patient. This difference could be explained by the settings themselves, as in a hospital, physicians communicate with each other directly while caring for patients, while in the primary care, they work mostly in shifts and rarely meet next to the patient to discuss the therapy.

It is not surprising that advanced age bears the higher risk for the development of potential DDIs, as there are numerous reasons. Aging is associated with important changes in the metabolism of drugs: biochemical composition of tissues is different, renal clearance is frequently reduced, the hepatic function is decreased, the physiological capacity of many organs is progressively diminished, and susceptibility to disease enhanced with increased vulnerability. Polypharmacy is of great concern in elderly patients as it increases the frequency of adverse drug reactions, new hospital admissions and prolongs actual hospitalization [27]. From Table 2 we can see that advanced

age increased the risk of occurrence of contraindicated and serious-use alternative potential DDIs. These findings confirmed once again that elderly patients require more attention of prescribing physicians, especially during hospital treatment, in order to limit prescribing to only absolutely essential drugs and recognize earlier potential DDIs.

Large number of prescribed drugs *per* neurological patient and numerous comorbidities in our study increased the risk of moderate and serious potential DDIs. Concurrent prescription of many drugs is frequently found in patients with multimorbidity and suffering from complex neurological diseases. Majority of other studies also found a relationship between the number of prescribed drugs per patient and the number of potential DDIs [15], as chances of DDIs statistically increase with the multiplication of prescribed drugs. It is important that physicians systematically search for potential DDIs when faced with polypharmacy (if necessary with the help of a clinical pharmacist), as majority of DDIs are preventable.

Interestingly, in our study, the occurrence of serious or moderate potential DDIs was less frequent in paralyzed patients and in patients bedridden for at least one day of hospitalization. The protective role of these medical conditions was not described previously, but it could be explained by clinicians paying more attention to patients unable to get out of the bed, which includes search for potential DDIs [25].

Despite the results of other studies, where the length of hospitalizations was a favorable factor for the occurrence of potential DDIs as in a neurology as in other wards [28, 29], that was not shown in our study. These differences could be observed in light of modest sample size in our study, but choosing a General Ward of Neurology Department we tried to provide representative population which could compare to other cohorts.

A lot of patients from our study sample were taking combination of NSAIDs and ACEIs. NSAIDs inhibit cyclooxygenase, thus decreasing prostaglandin production; as a consequence, blood flow through renal afferent arteriole decreases and glomerular filtration rate falls. On the other hand, inhibition of angiotensin II synthesis decreases vasoconstriction and blood pressure, which impairs renal blood flow and glomerular filtration rate. The ultimate result of combining ACEIs and NSAIDs is the decrease of glomerular filtration rate [30]. Although this potential DDI was less frequent in our study than in the Romanian one [31], a significant proportion of patients may experience a decrease in renal function due to the impaired perfusion of the kidneys. Simultaneous administration of two NSAIDs is also a matter of concern, since every year, about 1% to 1.5% of patients taking NSAIDs experience severe gastrointestinal side effects like perforation, ulcer or bleeding [31].

Our study has several limitations related to the modest sample size, the use of just three instead of full battery of interaction checkers and technical availability of medical records of patients in only certain periods of year (two months in the spring, and two months in the fall). This could induce omitting some significant factors which also contribute to the occurrence of potential DDIs. Also, using these checkers we found a lot of potential DDIs which were only theoretically defined and their clinical importance was not verified. The strength of our study was a detailed, in-depth analysis of the patients′ files, with the validation of extracted data, which increases the reliability of the results.

Conclusion

The frequency of potential DDIs among neurological patients is considerable and influenced to the largest extent by advanced age, comorbidities, total number of prescribed drugs *per* patient and concomitant use of antidepressants. More prescribers *per* patient and medical conditions that make patients bedridden protect from the occurrence of potential DDIs. However, both physicians and pharmacists in hospitals should pay more attention to potential DDIs in order to early detect them, which could contribute not only to the prevention of the serious and/or irreversible consequences, but also preclude the prolongation of hospital admission and additional increase in the treatment costs of these patients.

Acknowledgement

This study was partially supported by bilateral scientific project between Serbia and Montenegro entitled "Risk factors for DDIs in tertiary care hospitals", and by the Grant No 175007 given by the Serbian Ministry of Education, Science, and Technological Development.

Conflicts of interest

None.

R E F E R E N C E S

1. *Lu Y, Shen D, Pietsch M, Nagar C, Fadli Z, Huang H,* et al. A novel algorithm for analyzing drug-drug interactions from MEDLINE literature. Sci Rep 2015; 5: 17357.
2. *Marengoni A, Onder G.* Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ 2015; 350: h1059.
3. *Dumbreck S, Flynn A, Nairn M, Wilson M, Treweek S, Mercer S*, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. BMJ 2015; 350: h949
4. *Smithburger PL, Kane-Gill SL, Seybert AL.* Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. Int J Pharm Pract 2012; 20(6): 402–8.
5. Medscape. Multi-drug interaction checker. Available from: Ahttp://reference.medscape.com/druginteractionchecker [accessed date: 2018 May 10].
6. Epocrates, Inc. Interaction checker. Available from: https://online.epocrates.com/interaction-check [accessed date: 2018 May 10].

7. Truven Health Analytics LLC. Micromedex® solutions. Available from: https://www.micromedexsolutions.com/home/dispatch/PFDefaultActionId/pf.LoginAction/ssl/true? [accessed date: 10 May2018].
8. Medscape. Drug Interaction Checker. Available from: https://reference.medscape.com/drug-interactionchecker.
9. Epocrates. Interaction Check. Available from: https://online.epocrates.com/interaction-check IBM Watson Health.
10. IBM Micromedex Complete Drug Interactions. Available from: 23 https://www.ibm.com/downloads/cas/GZEMAEL8
11. *Kheshti R, Aalipour M, Namazi S*. A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract 2016; 5(4): 257–63.
12. *Aparasu R, Baer R, Aparasu A*. Clinically important potential drug-drug interactions in outpatient settings. Res Social Adm Pharm 2007; 3(4): 426–37.
13. *Guerzoni S, Pellesi L, Pini LA, Caputo F*. Drug-drug interactions in the treatment for alcohol use disorders: a comprehensive review. Pharmacol Res 2018: 133: 65–76.
14. *Nightingale G, Pizzi LT, Barlow A, Barlow B, Jacisin T, McGuire M*, et al. The prevalence of major drug-drug interactions in older adults with cancer and the role of clinical decision support software. J Geriatr Oncol 2018; 9(5): 526–33.
15. *Namazi S, Pourhatami S, Borhani-Haghighi A, Roosta S*. Incidence of Potential Drug-Drug Interaction and Related Factors in Hospitalized Neurological Patients in two Iranian Teaching Hospitals. Iran J Med Sci 2014; 39(6): 515–21.
16. *Busa G, Burlina A, Damuzzo V, Chiumente M, Palozzo AC*. Comorbidity, Polytherapy, and Drug Interactions in a Neurological Context: An Example of a Multidisciplinary Approach to Promote the Rational Use of Drugs. J Pharm Pract 2018; 31(1): 58–62.
17. *Lichtner V, Dowding D, Esterhuizen P, Closs SJ, Long FA, Corbett A*, et al. Pain assessment for people with dementia: a systematic review of systematic reviews of pain assessment tools. BMC Geriatr 2014; 14: 138.
18. *Brodie MJ, Besag F, Ettinger AB, Mula M, Gobbi G, Comai S*, et al. Epilepsy, Antiepileptic Drugs, and Aggression: An Evidence-Based Review. Pharmacol Rev 2016; 68(3): 563–602.
19. *Charlson ME, Pompei P, Ales KL, MacKenzie CR*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5): 373–83.
20. *Kim BY, Sharafoddini A, Tran N, Wen EY, Lee J*. Consumer Mobile Apps for Potential Drug-Drug Interaction Check: Systematic Review and Content Analysis Using the Mobile App Rating Scale (MARS). JMIR Mhealth Uhealth 2018; 6(3): e74.
21. *Şimşek A, Taner N, Macit Ç, Berk B, Mercanoğlu G*. The Importance of Computerized Drug Interaction Checker Programs Used in Community Pharmacies to Avoid Potential Drug Interactions: A Preliminary Study with Clarithromycin. IMJ 2019; 20(1): 67–71.
22. *Bleakley S*. Antidepressant drug interactions: evidence and clinical significance. Progress in Neurology and Psychiatry 2016; 20(3): 21–7.
23. *Gidal BE, French JA, Grossman P, Le Teuff G*. Assessment of potential drug interactions in patients with epilepsy: impact of age and sex. Neurology 2009; 72(5): 419–25.
24. *Teles JS, Fukuda EY, Feder D*. Warfarin: pharmacological profile and drug interactions with antidepressants. Einstein (Sao Paulo) 2012; 10(1): 110–5.
25. *Vingerhoets RW, Wieringa MH, Egberts TC, Jansen MM, Jansen PA*. Multiple physicians are not independently associated with inappropriate prescribing: a cross-sectional study of geriatric patients. Br J Clin Pharmacol 2014; 77(1): 213–5.
26. *Andersson ML, Böttiger Y, Kockum H, Eiermann B*. High Prevalence of Drug-Drug Interactions in Primary Health Care is Caused by Prescriptions from other Healthcare Units. Basic Clin Pharmacol Toxicol 2018; 122(5): 512–6.
27. *Dagli RJ, Sharma A*. Polypharmacy: a global risk factor for elderly people. J Int Oral Health 2014; 6(6): i-ii.
28. Royal College of Physicians of Ireland. National Clinical Programme for Neurology model. Available from: https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/neurology-model-of-care.pdf [accesed 2018 May 24].
29. *Moura CS, Acurcio FA, Belo NO*. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci 2009; 12(3): 266–72.
30. *Adhiyaman V, Asghar M, Oke A, White AD, Shah IU*. Nephrotoxicity in the elderly due to co-prescription of angiotensin converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs. J R Soc Med 2001; 94(10): 512–4.
31. *Bucsa C, Moga DC, Farcas A, Mogosan C, Dumitrascu DL*. An investigation of the concomitant use of angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and diuretics. Eur Rev Med Pharmacol Sci 2015; 19(15): 2938–44.

Received on April 1, 2019
Revised on July 24, 2019
Accepted on September 30, 2019
Online First October, 2019