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Original article

Comparative Analysis of Potential Drug-Drug Interactions at the Level of Public Pharmacy

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SUMMARY

Introduction/Aim. Understanding the mechanisms and classification of drug interactions can significantly reduce the occurrence of adverse effects and improve compliance. The drug selection process is complex and involves the patient's individual condition, physiological status, use of other drugs, and co-existing illnesses. It is particularly challenging to choose adequate therapy for elderly individuals due to physiological changes and polypharmacy.
The aim of this paper is to highlight the importance of an individualized approach to each patient when interpreting information provided by the existing drug databases. This approach involves considering the patient's age, comorbidities, and a proper assessment of the risk-benefit ratio.
Methods. A comparative analysis of potential drug-drug interactions was conducted on a sample of 215 outpatients. The analysis was performed using Lexicomp®, Medscape® and Epocrates® databases. The frequency of certain types of interactions by drug databases, the number of patients, and the distribution of interaction types by databases were determined. The frequency of drug combinations that could potentially cause serious and contraindicated interactions by databases were also determined.
Results. Based on the study, it can be concluded that there is a correlation between the number of prescribed drugs and potential interactions. According to frequency, the most common type of interaction requires therapy monitoring (type C interaction, Monitor). However, based on the severity categorization, the same drug combinations have different classifications of interactions in available databases.
Conclusion. The obtained data can provide guidance in making decisions about drug therapy choices. Patient-specific characteristics, including comorbidities, require a personalized therapeutic approach from specialists, where pharmacists play a significant role.

Keywords: **types of interactions, comparison, databases, drug-drug**

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INTRODUCTION

The use of multiple medications and/or the administration of more medications that are clinically indicated, increases the risk of drug-drug interactions (DDIs) and adverse drug effects (ADEs). Drug-drug interactions can cause preventable ADEs and medication-related hospitalizations. A review study pointed out that the incidence of hospital admissions due to the consequences of DDIs was 2.8% (1). The burden of taking multiple medications has also been associated with greater health-care costs, medication non-adherence, reduced functional capacity, and multiple geriatric syndromes. Adequate optimization of polypharmacy is very important in order to achieve the maximum therapeutic effect and avoid DDIs and adverse drug effects.

Interactions between drugs represent a change in the effect of one drug under the influence of another drug in situations where they are administered simultaneously. There are pharmacokinetic, pharmacodynamic interactions, interactions with biochemical parameters (*in vitro* and *in vivo*), chemical and pharmaceutical interactions (*in vitro*). Pharmacokinetic interactions can occur during all pharmacokinetic processes (absorption, distribution, metabolism and excretion). The most common pharmacokinetic interactions occur during the metabolism of drugs. Induction or inhibition of enzymes that metabolize a certain drug leads to a decrease or increase in the effect of a drug. The potency of enzyme induction or inhibition varies among drugs, and thus the clinical significance of a particular interaction varies. Pharmacodynamic interactions can be synergistic (when the combination of two or more drugs produces a greater effect than each of those drugs individually), additive (when the simultaneous administration of two or more drugs produces an effect that represents the sum of the individual effects of those drugs) and antagonistic (when one drug reduces the effect of another drug). Interactions with biochemical parameters can occur *in vitro*, when the drug is found in the taken biological material and interferes with laboratory analyses, and *in vivo*, when the effect of the applied drug affects the function of the liver or kidneys, which leads to a change in the results of laboratory analyses. Chemical and physical interactions occur between drugs in a bottle or syringe.

There is a number of potential interactions, but not all interactions are clinically relevant. Interactions according to the possible adverse outcome are divided into: serious (may cause permanent damage), moderate (may cause worsening of the patient's health condition) and minor (the consequence of the interaction may be unpleasant for the patient but does not impair health, nor the outcome of therapy). According to the number and reliability of the data on the existence of the interaction, they are divided into: very probable (controlled studies have proven that they occur), probable (it is very likely that they occur, but there are no controlled clinical studies that prove it), doubtful (they can happen and there are data about it, but controlled clinical studies need to be carried out), possible (they can happen, but there is not enough data about them), and unlikely (an interaction is suspected because there is not enough evidence to support it) (2).

AIM

The aims of the present study were to discover the most common, potentially serious drug interactions prescribed in daily practice; to examine which drugs most often occur in potentially serious interactions, so as to determine the distribution of types of interactions according to drug bases.

MATERIAL AND METHODS

In this study, the occurrence of potential drug interactions prescribed in daily practice was examined. The research was designed as an observational retrospective study. The study included 215 patients whose prescribed therapy was analyzed at single Public Pharmacy over a period of one month, with an approval from the Ethics Committee of the Pharmacy Cvejic, Serbia. Prescribed therapy from the prescription drug database for a period of one month was entered into three different drug databases to check for potential interactions. Lexicomp®, Medscape® and Epocrates® drug databases were used to identify potential interactions and their classification. These softwares are based on scientific literature and official notices from the manufacturers and are continuously updated. For each patient, the total number of potential interactions between drugs that were issued to patients based on a doctor's prescription was determined. Potential interactions were checked in all three drug bases and classified according to severity. The frequency of certain types of interactions by drug base, the number of patients

and their distribution by type of interaction by base, the frequency of combinations of drugs that give potential serious and contraindicated interactions by base, the frequency of occurrence of certain groups of drugs in serious and contraindicated interactions by base were determined. The relationship between the number of prescribed drugs and the number of potential interactions by bases was also determined.

The dependent variable was the number of potential interactions between drugs determined according to the databases Lexicomp®, Medscape® and Epocrates®. For each patient, the total number was determined, as well as the classification of potential interactions in individual categories in these databases.

The Lexicomp® database checker for potential interaction divide interaction according to the severity into: A (no known interaction), B (no action needed), C (monitor therapy), D (consider therapy modification) and X (avoid combination) (Table 1).

Table 1. *Classification of interactions according to the Lexicomp® database*

A	Data does not indicate pharmacodynamic and pharmacokinetic interactions between certain agents	No known interaction
B	Data indicate that certain agents may interact with each other, but there is little or no evidence that their interaction has clinical significance	No action needed
C	Data indicate that the interaction of certain agents has clinical significance, and the benefit of the combined use of the given agents usually outweighs the risk	Monitor therapy
D	Interaction has clinical significance, an individualized approach is needed to determine whether the benefits of therapy outweigh the risk	Consider therapy modification
X	The risk of combined therapy usually outweighs the benefits - avoid the combination	Avoid combination

The Medscape® database for checking potential interactions divides interactions according to the severity of the outcome into: Minor - mild (mild interaction, unlikely or not significant); Monitor closely - monitor closely (potential for significant interaction, use with caution and monitor the effect of parallel drug use); Serious/Use alternative – serious (risk of life-threatening interaction, regular monitoring by a doctor or there is a need to use an alternative medicine); Contraindicated – contraindicated application (the combination is never used due to the high risk of dangerous interaction) (3).

According to the Epocrates® database, interactions are divided by the severity of side effects into: Caution advised (no drug replacement is required, only monitoring); Monitor/Modify therapy (monitor the effect of simultaneously applied drugs, if necessary, replace some of the drugs); Avoid/Use alternative (avoid combination, high possibility of side effects); Contraindicated (contraindicated combination). The independent variable is the number of prescribed medications.

Statistics

The Excel program was used for statistical data processing. The data were processed using the methods of descriptive statistics. Mean value, median, standard deviation, interquartile range were determined. The frequency of occurrence of certain types of interactions by bases, the frequency of patients who had certain types of interactions by bases, the frequency of occurrence of certain combinations of drugs in the types of interactions that are serious and contraindicated, as well as the frequency of certain drugs in those interactions were also calculated. The Kolmogorov-Smirnov test was used to determine the normality of the data distribution. Since

the distribution does not meet the normality test, we applied the Spearman's test to determine the correlation between the number of prescribed medications and the number of potential interactions.

RESULTS

A review of the database of drugs dispensed during a month in a health facility in 215 patients identified potential interactions. The average age of the patients was 71 years (71.79 ± 11.83). Of the total number of examined patients, 94 were men and 121 were women. The average number of prescribed drugs per patient was 6 (5.51 ± 1.88). A comparative review of potential interactions by databases yielded data indicating that the most common potential interactions are those requiring patient observation (C type interactions in the Lexicomp® database, Mo-

Table 2. *Distribution of interactions according to three different databases*

Type of interacton - Lexicomp® database	**A**	**B**	**C**	**D**	**X**
The number of patients who had the potential for a certain type of interaction	1	103	203	47	9
Distribution of interactions by type	1	153	844	54	9
Mean ± standard deviation	0.005 ± 0.068	0.71 ± 0.98	3.92 ± 3.28	0.25 ± 0.50	0.04 ± 0.20
Median	0	0	3	0	0
Interquartile range	0	1	3.5	0	0
Type of interacton -Medscape® database	**Minor**	**Monitor closely**	**Serious/Use alternative**		**Contraindicated**
The number of patients who had the potential for a certain type of interaction	75	190	58		1
Distribution of interactions by type	122	697	72		1
Mean ± standard deviation	0.57 ± 0.94	3.24 ± 2.80	0.33 ± 0.63		0.005 ± 0.068
Median	0	3	0		0
Interquartile range	1	3	1		0
Type of interacton - Epocrates® database	**Caution advised**		**Monitor/Modify therapy**		**Serious/Use alternative**
The number of patients who had the potential for a certain type of interaction	61		198		56
Distribution of interactions by type	95		778		73
Mean ± standard deviation	0.44 ± 0.83		3.62 ± 3.18		0.34 ± 0.71
Median	0		3		0
Interquartile range	1		4		1

nitor in the Medscape® and Epocrates® databases). Nine patients had a drug combination with contraindicated interactions according to the Lexicomp® database, one patient according to the Medscape® database, and none of patients according to the Epocrates® database. Across all databases, the most frequently registered interactions are those that should be monitored/modified (Table 2).

Figure 1 shows that in the examined sample of all type D interactions according to the Lexicomp® base, the largest number of patients would have as a result the combination of anticoagulants-antagonists of vitamin K and uric acid synthesis inhibitors (7 cases), followed by the combination of benzodiazepines and zolpidem (6 cases). There are poten-

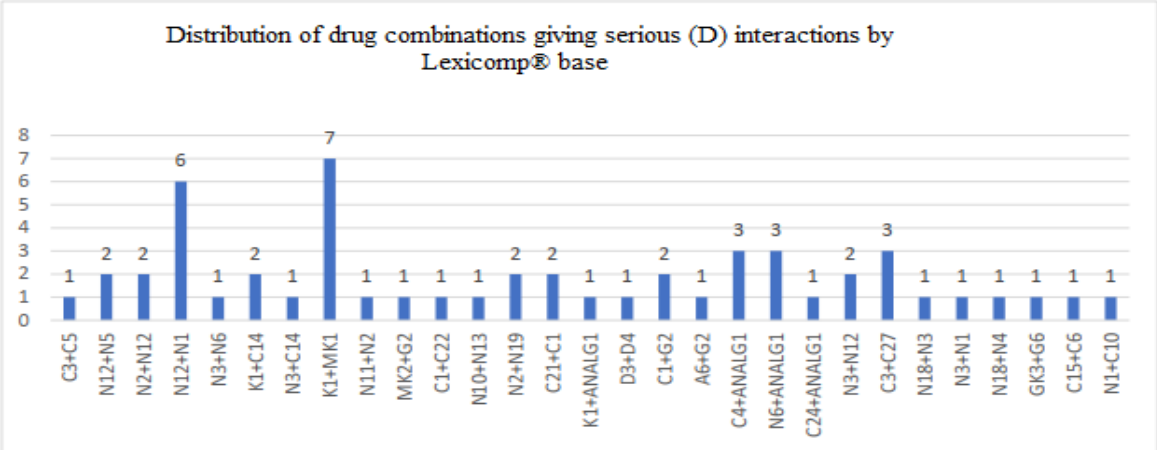

Figure 1. *Distribution of drug combinations giving serious (D) interactions by Lexicomp® database*

(C3-β-blockers; C5- centrally acting antihypertensive – methyldopa; N12- sedatives zolpidem, N5- atypical antidepressant - trazodone, N2- newer antiepileptics - pregabalin, lamotrigine, N1- benzodiazepines, N3- atypical antipsychotics - risperidone, C27- centrally acting antiadrenergics - moxonidine, N11- antiepileptics - carbamazepine, N19- antiepileptics - valproic acid, C10- calcium channel blockers - verapamil, N6- selective serotonin reuptake inhibitors (SSRIs), C14- class III antiarrhythmics - amiodarone, ANALG1-NSAID, K1- anticoagulants - vitamin K antagonists, C4- loop diuretics, MK1- uric acid synthesis inhibitors - allopurinol, MK2- bisphosphonates, G2- calcium carbonate, C1- Angiotensin-converting-enzyme inhibitors (ACE inhibitors), C22- sartans + hydrochlorothiazide, C21- sartans, N10- antipsychotics - butyrophenone derivatives - haloperidol, N13- antipsychotics - chlorpromazine, D3- insulins, D4- selective competitive SGLT2 inhibitors, N18- second generation antipsychotics (thiazepines, oxazepines, diazepines), N4- anticholinergic - biperiden, GK3- thyroid hormones - levothyroxine, G6- multivitamins and minerals, C15- statins, C6- calcium channel blockers dihydropyridine derivatives, C24- antiplatelet drugs - acetylsalicylic acid)

Table 3. *Contraindicated drug-drug interactions according to Lexicomp® database*

Database	Contraindicated interactions
Lexicomp®	1. Antiparkinsonian drugs (DOPA and derivatives) - antiemetics (metoclopramide) 2. β2 receptor agonists + anticholinergics – anticholinergics 3. β2 receptor agonists + anticholinergics – β2 receptor agonists + anticholinergics 4. Benzodiazepines - disulfiram 5. Second generation antipsychotics (thiazepines, oxazepines, diazepines) - β2 receptor agonists + anticholinergics 6. Atypical antipsychotics (risperidone) – β2 receptor agonists + anticholinergics

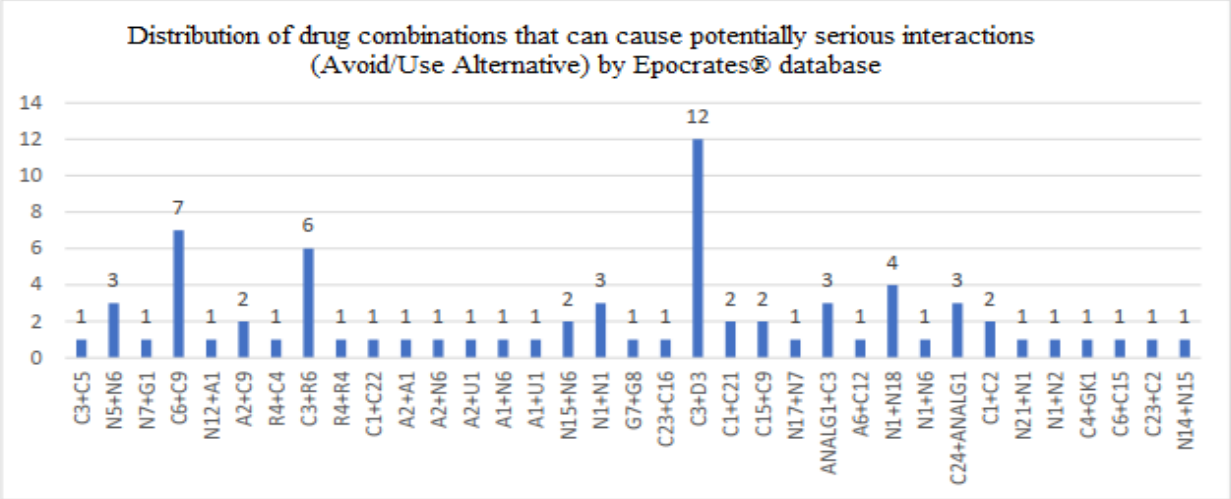

Figure 2. *Distribution of drug combinations that can cause potentially serious interactions (Avoid/Use alternative) by Epocrates® database*

(R6- β2 agonists + corticosteroids, A1- fluoroquinolones, N15- antidepressants - others - mirtazapine, A2- macrolides, U1- urinary spasmolytics, N21- tricyclic antidepressants, C - antiarrhythmics Ic, G1– antiemetics (metoclopramide), N7- antiparkinsonian drugs - DOPA and derivatives, N17- antiparkinsonian drugs -dopamine agonists, R4- β2 receptor agonists + anticholinergic, GK1– glucocorticoids, C2– ACE inhibitors + hydrochlorothiazide, C23– fibrates, C16– ACE inhibitors + indapamide, G7- mesalazine, G8- proton pump inhibitors, C12- potassium-sparing diuretics, N14- antidepressants - serotonin and noradrenaline reuptake inhibitors – SNRI)

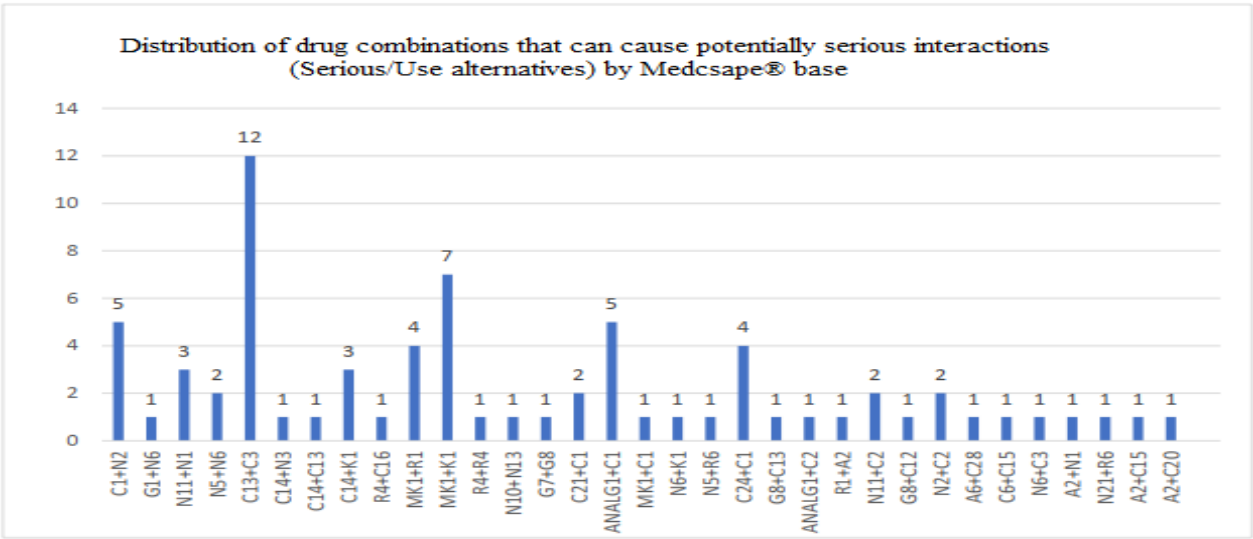

Figure 3. *Distribution of drug combinations that can cause potentially serious interactions (Avoid/Use alternative) by Medscape® database*

(C13- cardiotonic glycosides, R1– xanthine derivates (theophylline, aminophylline), C28 – ACE inhibitors + calcium channel blockers+ indapamide, C20– antiplatelet drug (clopidogrel))

tially three cases with the combination of loop diuretics and non-steroidal anti-inflammatory drugs (NSAIDs); selective serotonin reuptake inhibitors (SSRIs) and NSAIDs; and β-blockers and moxonidine. In these type D interactions, risperidone (5 times), zolpidem (4 times) and NSAIDs (4 times) were most frequently recorded (Figure 1, Table 3).

According to Epocrates®, the most common combination that should be avoided in our study is a simultaneous administration of β-blockers and insulin (Figure 2). Next is a simultaneous use of calcium channel antagonists - dihydropyridine derivatives and antiarrhythmics of the Ic group. Six cases had the potential for an Avoid/Use Alternative interaction due to a simultaneous administration of β-blockers and a fixed combination of β2 agonists + corticosteroids (Figure 2).

According to the Medscape® database, interactions of the Serious/Use Alternative type occurred most frequently with the combination of β- blockers and cardiotonic glycosides (12 cases) (Figure 3). The simultaneous use of uric acid synthesis inhibitors (allopurinol) and warfarin can also lead to a clinically significant interaction (7 cases). Allopurinol inhibits xanthine metabolism (aminophylline and theophylline), therefore, this combination should be avoided if possible or the patient should be monitored (4 cases). The simultaneous use of NSAIDs and ACE inhibitors may reduce the antihypertensive effect of ACE inhibitors (5 cases) (Figure 3).

The relationship between the number of interactions and the number of prescribed drugs in each of the three databases was examined. By data from the databases, we obtained a graphs that show a positive association between the number of prescribed drugs and the number of potential interactions (Figure 4, Figure 5, Figure 6).

The Spearman's correlation coefficient for Lexicomp® database was 0.747 ($p < 0.001$), for Epocrates® 0.718 ($p < 0.001$) and for Medscape® 0.745 ($p < 0.001$). These results indicated a positive correlation between the number of prescribed drugs and the number of potential interactions.

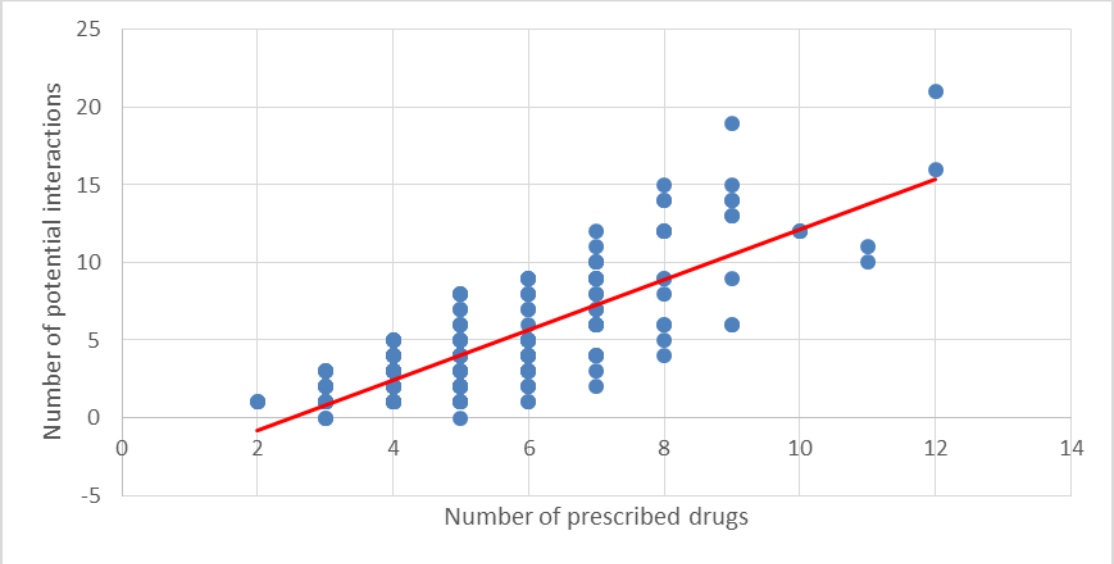

Figure 4. *Correlation of the number of prescribed drugs as an independent variable and the number of potential interactions as a dependent variable in the Lexicomp® database*

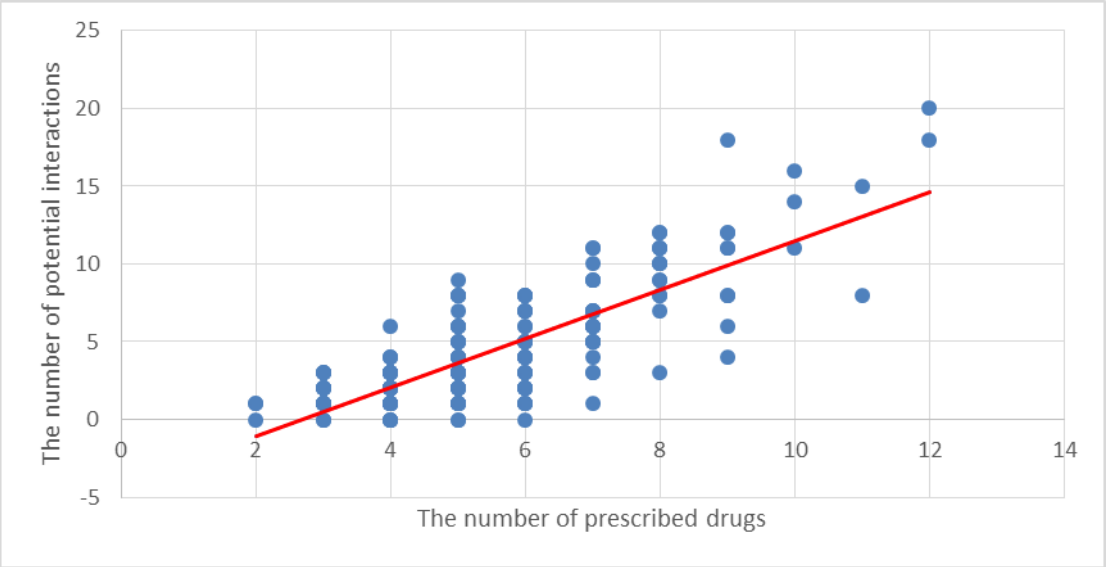

Figure 5. *Correlation of prescribed drugs as an independent variable and the number of potential interactions as a dependent variable in the Epocrates® database*

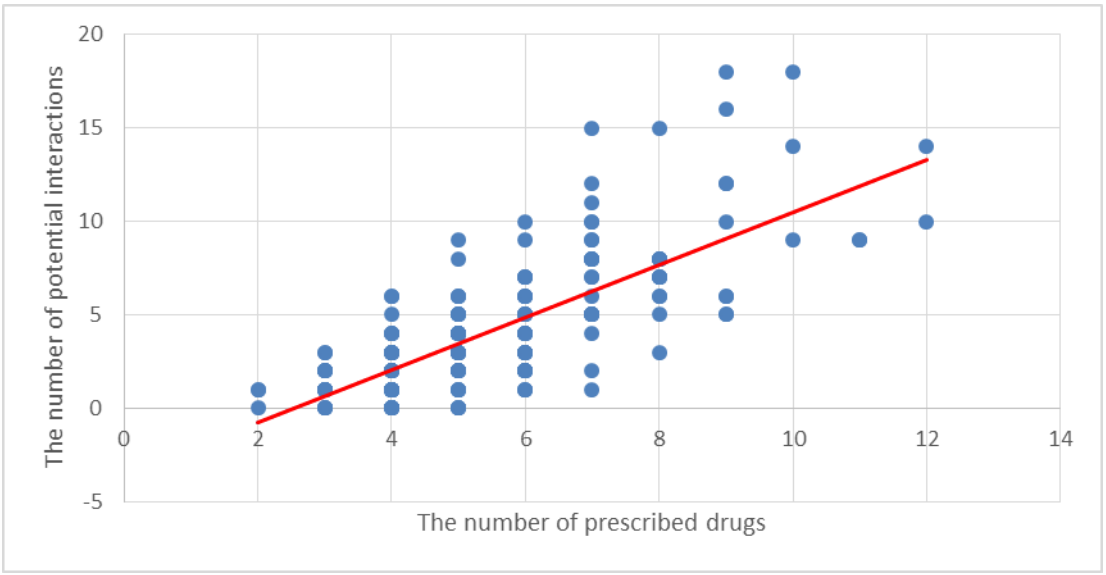

Figure 6. *Correlation of the ratio of the number of prescribed drugs as an independent variable and the number of potential interactions as a dependent variable in the Medscape® database*

DISCUSSION

The results show that the most common is the type of interaction which needs monitoring and it appears in all three bases. Situations in which it is necessary to change therapy if the benefit does not exceed the risk are less frequent (21.86% of patients according to Lexicomp®, 26.98% according to Medscape® and 25.05% according to Epocrates®). Contraindicated interactions appear the least often (Lexicomp® 4.19% of patients, Medscape® 0.46%, and in the Epocrates® database they are absent). In the largest number of serious interactions (they are not contraindicated, but if the benefit does not exceed the harm, they should be avoided), drugs from the group that act on the nervous system appear. According to the Lexicomp® base, in type D interactions, risperidone (five times) was most often recorded, followed by zolpidem (four times). The Epocrates® database reports five interactions each in-

volving benzodiazepines and SSRIs, and Medscape® shows SSRIs with four cases. Among the groups of drugs that appear among the most common in this type of interaction are antibiotics from the group of fluoroquinolones and macrolides (Epocrates® - fluoroquinolones involved in four interactions and macrolides in four, and Medscape® - macrolides in four interactions). According to Lexicomp®, NSAIDs also appear in four interactions. The most common adverse effect that may occur as a result of the combination of antipsychotics with the mentioned antibiotics is the prolongation of the QT interval; in this case, the first generation of antipsychotics has a higher potential for interaction. Additionally, anticholinergic effects often occur (4).

A correlation has been conducted between the number of prescribed medications and interactions for each database separately. A positive correlation has been determined for all databases, indicating that the higher the number of prescribed medications, the greater the potential for interactions to occur.

In the following text, serious and contraindicated interactions will be explained, arranged by groups of drugs appearing in the examined sample, especially based on databases. The first analyzed database is Lexicomp®, focusing on type D interactions. Risperidone appears in type D interactions according to Lexicomp® with SSRIs, amiodarone, zolpidem, oxazepam-type antipsychotics and benzodiazepines. This medication is metabolized via CYP2D6 and partially CYP3A4, serving as a substrate for P-glycoprotein. Risperidone is metabolized into an active metabolite. It inhibits CYP3A4, affecting the metabolism of drugs metabolized through this enzyme, such as zolpidem (5). SSRIs and amiodarone are potent inhibitors of CYP2D6, thereby increasing the concentration of risperidone in the plasma but not of the active metabolite. The combination with amiodarone is also pharmacodynamic and can lead to QT interval prolongation. With benzodiazepines and zolpidem, there is an increased risk of excessive sedation, and with antipsychotics from the oxazepam group, an additive effect of therapy is possible (central nervous system (CNS) depression, extrapyramidal syndrome (EPS), hypotension). Based on the data, risperidone and olanzapine have a higher potential to induce EPS compared to clozapine and quetiapine, where the EPS induction level is at the placebo level. The gradation would be: risperidone>olanzapine>quetiapine>clozapine (6). SSRIs, through the inhibition of CYP2D6, can affect the level of many drugs, including metoclopramide, as observed in the examined sample (Medscape®-Serious/Use Alternative). This inhibition can lead to adverse effects of metoclopramide such as extrapyramidal syndrome, sedation, hyperprolactinemia, hypotension, arrhythmias, and tardive dyskinesia (with prolonged use) (7).

The results show that in addition to the combination with risperidone and benzodiazepines, zolpidem also appears with trazodone and lamotrigine in type D interactions. All these drugs are CNS depressants and can lead to the potentiation of effects. Studies show that 61% of zolpidem is metabolized via CYP3A4, 22% via CYP2C9, 14% via CYP1A2 and < 3% via CYP2D6 and 2C19 (8). All drugs that are strong inductors (rifampicin, St. John`s wort, phenytoin, phenobarbital and the others), as well as inhibitors (azole antifungals, erythromycin, ritonavir etc.), affect the level of zolpidem in the blood and its pharmacological effect.

NSAIDs appear four times in potential type D interactions. Combinations with warfarin, loop diuretics, SSRIs and acetylsalicylic acid in antiplatelet doses (75 – 100 mg) have been registered. It should be considered that these conditions are most common in the older population, where polytherapy is prevalent. The continuous use of these medications, aside from damaging the stomach lining, can also reduce the effectiveness of antihypertensives (5). The simultaneous use of NSAIDs and ACE inhibitors may reduce the antihypertensive effect of ACE inhibitors. According to the Medscape® database, a combination of allopurinol and theophylline could occur in four cases and it is Serious/Use Alternative type because allopurinol inhibits xanthine metabolism (7). Due to the small therapeutic range of xanthine, side effects can occur more easily. Anticoagulants and NSAIDs are an undesirable combination due to an increased risk of bleeding. Warfarin, as a commonly used anticoagulant, has a narrow therapeutic range and a high potential for interactions at multiple levels. It is metabolized via CYP1A2, 2C9 and 3A4, making all strong inducers and inhibitors of these enzymes capable of causing clinically significant disruptions in warfarin levels and potentially dangerous pharmacological effects. The simultaneous use of uric acid synthesis inhibitors (allopurinol) and warfarin can also lead to a clinically significant interaction, where an increase in

the anticoagulant effect can occur (7). Additionally, drugs affecting vitamin K synthesis in the intestines (antibiotics) can disturb warfarin levels in the blood. Warfarin binds extensively to plasma albumins, so drugs like NSAIDs, sulfonamides and others can displace it, increasing the free fraction of warfarin. NSAIDs with loop diuretics can worsen renal function with a significant concern in older and renal-compromised patients. The effect of loop diuretics is diminished with concomitant use of NSAIDs due to opposing actions on prostaglandin synthesis (NSAIDs reduce PGE2 synthesis, while furosemide increases it) (9). Lexicomp® categorizes this interaction as serious, warranting a potential change in therapy, while the other two databases suggest monitoring without necessarily altering the combination.

The combination of NSAIDs and SSRIs may increase the risk of bleeding. Serotonin produced by platelets induces platelet aggregation and coronary vasoconstriction. Selective serotonin reuptake inhibitors (SSRIs) reduce serotonin concentration in platelets and blood, inhibiting platelet aggregation. This effect is potentiated by NSAIDs, leading to bleeding, especially with prolonged use of both drugs (10). The simultaneous use of aspirin and ibuprofen leads to antagonistic effects on platelets. Ibuprofen used before aspirin competitively inhibits access to the acetylating site of cyclooxygenase in platelets which is an active site for inactivation and achieving the aspirin effect. This interaction could be clinically significant, as only 10% - 15% of functional platelets can lead to aggregation (11). The mentioned study overcame this issue by administering aspirin two hours before a single dose of ibuprofen. However, with repeated dosing of ibuprofen three times a day, the interaction was not avoided. On the other hand, twice-daily extended-release diclofenac tablet did not reduce the antiplatelet effect of aspirin. The binding site for diclofenac is separate from the binding site for aspirin, ibuprofen and flurbiprofen with a shorter duration and lower intensity of action (11). A simultaneous use of aspirin and other NSAIDs may increase the risk of bleeding and reduce the cardioprotective effect of aspirin. NSAIDs given together with ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics can lead to hyperkalemia. Medscape® registers this interaction as Serious/Use Alternative while Epocrates® suggests monitoring without necessarily avoiding the combination.

Among the drugs that had more than one combination in type D interactions are warfarin (K1), calcium carbonate (G2) and ACE inhibitors (C1). Warfarin could interact with class III antiarrhythmics (amiodarone- C14), uric acid synthesis inhibitors (MK1) and NSAIDs (ANALG1). Amiodarone inhibits the metabolism of warfarin in the liver. The initial dose of warfarin, when combined with amiodarone, must be reduced by 33% - 50% to avoid bleeding (12). This interaction is categorized as serious in the Medscape® database. Drugs whose plasma concentration may increase due to P-gp inhibition by amiodarone include warfarin, digoxin, simvastatin and many others. The most common serious interaction in the Medscape® database arises from the combination of β-blockers and cardiac glycosides, due to potential bradycardia and hyperkalemia. Digoxin acts positively inotropic opposite to β-blockers, so a simultaneous use can reduce the effectiveness of cardiac glycosides in heart failure. Cardiac glycosides can also cause hypomagnesemia, which is potentiated by prolonged use of proton pump inhibitors. Proton pump inhibitors, by increasing stomach pH, can increase the level of cardiac glycosides, which is considered a serious interaction in the Medscape® database. Amiodarone inhibits P-glycoprotein transport, which can increase the concentration of digoxin and the possibility of bradycardia and AV block (5). According to the Epocrates® database, it is recommended to avoid the combination of calcium channel antagonists-dihydropyridine derivates and antiarrhythmics of Ic group if it is used simultaneously with another drug that inhibits CYP3A4, considering that propafenone is a moderate inhibitor of CYP3A4, and can lead to an increase in the concentration of amlodipine, felodipine and nifedipine, to prolongation of the QT interval and arrhythmias (12).

In the examined sample, type X potential interactions appeared in nine patients. Inhalation anticholinergics are the most common group of drugs found in this type of interaction. They are found individually and in fixed combinations with β2 agonist+ anticholinergic with an anticholinergic, double β2 agonist+ anticholinergic where one is short-acting for occasional use and the other long-acting. The fixed combination of β2 agonist+ anticholinergic also appears in interactions with risperidone and oxazepines type of antipsychotics. All these antipsychotics have more or less anticholinergic effects, so side effects are the result of double

anticholinergic action (constipation, abdominal pain, dry mouth). Other X interactions include the combination of levodopa with the antiemetic metoclopramide and disulfiram with benzodiazepines. Metoclopramide is a dopamine antagonist and can reduce the effect of levodopa. This combination is classified as Avoid/Use Alternative in the Epocrates® database, meaning the intensity of the interaction is considered milder than in the Lexicomp® database. Disulfiram can reduce the oxidation of benzodiazepines in the liver increasing the possibility of CNS depression. According to the Epocrates® classification, the interaction type Avoid/Use Alternative corresponds to type D in Lexicomp® and the interaction type Contraindicated corresponds to type X. The most common drugs appearing in Serious interactions are SSRIs and benzodiazepines. SSRIs in the examined sample could interact with trazodone, macrolides, fluoroquinolones, mirtazapine and benzodiazepines. Benzodiazepines also interact with oxazepine type antipsychotics, tricyclic antidepressants and pregabalin. SSRIs inhibit microsomal enzymes, especially CYP2D6, so there may be an increase in the concentration of trazodone and mirtazapine and potential side effects such as hyponatremia, prolonged QT interval, CNS depression, antiplatelet effect and increased bleeding risk. Also, all these drugs increase the level of serotonin in the brain, leading to serotonin syndrome (increased heart rate, hypertension). The combination with benzodiazepines can lead to CNS depression because SSRIs prolong their half-life (13). Fluvoxamine and paroxetine have a sedative effect, so the combination with benzodiazepine can potentiate this effect. These interactions of SSRIs with trazodone and benzodiazepines are considered serious in the Medscape® database. The use of benzodiazepines and tricyclic antidepressants can lead to hypotension, including orthostatic hypotension, as well as CNS depression (14). One patient used a combination of selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, which should be avoided according to the Epocrates® and Medscape® databases. Since both drugs increase the levels of serotonin and norepinephrine in the synaptic cleft, serotonin syndrome may occur.

Macrolide antibiotics are CYP3A4 inhibitors, with erythromycin having the highest inhibitory potential. It can inhibit the metabolism of solifenacin, statins and clopidogrel. These medications, along with propafenone and fluoroquinolones, may prolong the QT interval, potentially leading to arrhythmias. Individuals using propafenone as an antiarrhythmic should avoid prescribing macrolide antibiotics, as well as fluoroquinolones, as they can inhibit its metabolism in the liver and prolong the QT interval. If necessary, an antibiotic from another group is preferable. Ciprofloxacin is also a CYP3A4 inhibitor, with moderate to strong inhibition of CYP1A2. Drugs that can prolong the QT interval, including macrolides and fluoroquinolones, also include antiarrhythmics (amiodarone, sotalol, flecainide), antipsychotics (haloperidol, risperidone, olanzapine, quetiapine, thioridazine), antidepressants (tricyclic-TCA and SSRIs), methadone, sumatriptan, ondansetron (15). Propafenone is metabolized by CYP2D6, CYP3A4 and CYP1A2. Strong inhibitors and inducers of these enzymes can significantly change the concentration of the drug and lead to unwanted effects or subdose.

Beta-blocker given with insulin can lead to hypoglycemia, and if given with NSAIDs for an extended period, it may worsen hypertension and hyperkalemia. Disturbances in potassium levels in the body can cause arrhythmias that can be life-threatening. Drugs that can lead to hypokalemia as a result of potassium loss include loop diuretics, glucocorticoids and laxatives. Drugs that induce the entry of potassium into cells are sympathomimetics or insulin (16). Several patients from the examined sample used loop diuretics and β2 agonist in combination with anticholinergics, as well as glucocorticoids with loop diuretics. In both situations, there is a possibility of hypokalemia, muscle weakness and arrhythmias.

The only combination registered in the Medscape® database as contraindicated is amitriptyline (TCA) with ACE inhibitor + calcium channel blocker + indapamide. This combination can lead to a prolongation of the QT interval by TCA and indapamide. Additional risk factors include electrolyte imbalance (hypokalemia, hypocalcemia, hypomagnesemia), hyperthermia, treatment with cardiac glycosides, fasting, prolonged QT interval syndrome (17). The difference in the classification of interactions between databases is evident since this combination in the Epocrates® database only needs to be monitored (Monitor).

This study has limitations because it measured the occurrence of potential interactions without

knowing whether they actually occurred. Also, the data in the databases is of variable nature due to the collection of new data.

CONCLUSION

Based on the conducted research, we can conclude that there is a correlation between the number of prescribed drugs and potential interactions. According to frequency, the most common type of interaction requires monitoring of therapy (type C interaction). Our research has determined that the available drug databases have different classifications of drug interactions according to the categorization of severity. The obtained data can be guidelines when making decisions about the therapeutic choice of drugs. Individual characteristics of patients, including associated diseases, require a personalized therapeutic approach by specialists, in which pharmacists play an important role.

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Komparativna analiza potencijalnih interakcija lekova na nivou javne apoteke

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SAŽETAK

Uvod/Cilj. Razumevanje mehanizma i klasifikacije interakcije lekova može značajno redukovati pojavu neželjenih efekata i poboljšati komplijansu. Proces odabira leka je kompleksan i uključuje sagledavanje individualnog stanja bolesnika, fiziološkog stanja, upotrebu drugih lekova i postojanje drugih bolesti. Ş obzirom na fiziološke promene u organizmu i prisustvo polifarmacije, poseban je izazov odabrati adekvatnu terapiju kod starijih osoba.

Cilj ovog rada je ukazivanje na značaj individualnog pristupa svakom pacijentu prilikom tumačenja informacija koje pružaju postojeće baze lekova. Ovaj pristup uključuje i uzimanje u obzir starosti pacijenta, pridruženih bolesti i adekvatnu procenu odnosa rizika i koristi.

Metode. Komparativna analiza potencijalnih lek–lek interakcija izvedena je na uzorku od 215 vanbolničkih pacijenata. Analiza je urađena uz pomoć Lexicomp®, Medscape® i Epocrates® baza. Određivana je frekventnost određenih tipova interakcija po bazama, broj pacijenata i distribucija tipova interakcija po bazama. Određivana je, takođe, frekventnost kombinacija lekova koje bi potencijalno mogle prouzrokovati ozbiljne i kontraindikovane interakcije.

Rezultati. Na osnovu ispitivanja možemo zaključiti da postoji korelacija između broja propisanih lekova i potencijalnih interakcija. Na osnovu analizirane frekventnosti, najčešći tip interakcije zahteva praćenje terapije (C tip interakcije, Monitor). S druge strane, ista kombinacija lekova ima različitu klasifikaciju interakcije na osnovu ozbiljnosti, kao što se može videti u dostupnim bazama podataka.

Zaključak. Dobijeni podaci iz baza mogu biti vodič prilikom izbora terapije. Međutim, individualne karakteristike pacijenata, uključujući komorbiditete, zahtevaju individualan terapijski pristup specijaliste, u kojem farmaceuti igraju bitnu ulogu.

Ključne reči: **tipovi interakcija, poređenje, baze podataka, lek–lek**