

# Prevalence and predictors of potential drug-drug interactions

## Research Article

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**Abstract:** Objectives. The objective of this study was to estimate the prevalence of potential drug-drug interactions (DDIs) among outpatients of city region Novi Sad, Serbia, and to investigate predictors of potential DDIs. Methods. Cross-sectional prescription database study was conducted. In the analysis were randomly included 10% outpatients with polypharmacy (n=4467), who visited Health Center over 1-month period (November 1-30, 2011). All drug combinations with potential for clinical significant DDIs were identified, according to Drug Interaction Facts by David S Tatro. A logistic regression analysis was conducted to examine patient and drug therapy characteristics as predictors of potential DDIs. Results. The prevalence of clinical significant potential DDIs was 33.31%. Odds of exposure were the highest among those aged 65 years or older (odds ratio (OR)=5.204; 95% confidence interval (CI) 2.694-10.052, p<0.001), those with ≥ 4 diagnosed diseases (OR=4.451; 95% CI 3.349-5.914, p<0.001), and those who used ≥ 5 drugs (OR= 5.735; 95% CI 4.876-6.747, p<0.001). Chronic diseases as well as their therapy also presented predictors of DDIs. Conclusion. Approximately one-third of outpatients living in Novi Sad were exposed to potential DDIs. Based on the present results could be defined recommendations for the management potential clinical significant DDIs.

**Keywords:** *Drug-drug interactions • Prevalence • Predictors*

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## 1. Introduction

Adverse drug events (ADEs) are significant cause of mortality, hospital admissions, and visits to the emergency department [1-5]. One important contributing factor to ADEs are drug-drug interactions (DDIs), representing between 4.4% and 25% of all ADEs [6]. The withdrawal half of drugs from the market of the United States (US), because of safety reasons, during the period 1999-2003 were associated with important DDIs [7]. Furthermore, studies suggest that DDIs are substantial economic

burden [8-12]. Thus, accepting the statistics by Grymonpre and colleagues that DDIs cause roughly 2.8% of all hospitalizations, Hamilton and colleagues identified, using a "cost of illness" model, this could represent 245280 hospitalizations annually in the US, costing health care system \$ 1.3 billion [13].

DDIs are also important because they are often predictable ADEs and therefore avoidable or manageable. "Thus, for example, Obreli-Neto et al. identified that the incidence of DDI-related ADEs was 6% where approximately 37% requested hospital admission, and

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researchers assessed that all DDI-related ADEs could be avoided, 87% were ameliorable and 13% were preventable [14].” While van Roon *et al.*, based on the results of previous studies, estimated that more than 75% “major interactions” could be prevented [15]. Strategies which were identified for prevention DDIs are monitoring signs and symptoms of toxicity or effectiveness, avoid drug combination, adjust dose, and adjust administration time and contraindication for using drug combination. For example, coadministration of amiodarone and statins should be avoided, but if coadministration of these agents cannot be avoided, recommendation is to use the lowest possible statins dose. Thus, the dosage lovastatin or simvastatin should not exceed 40 or 20 mg/day, respectively, in patients taking amiodarone [16]. Also, patients should be advised to immediately report any unexplained muscle pain, tenderness, or weakness, and finally, pravastatin is not metabolized by CYP2C9 or CYP3A4 and because of that may be safer alternative [16].

Knowledge about exposure of population to clinical significant DDIs as well as the knowledge about risk factors for DDIs are the basis for taking measures to their management. For that purpose, the prevalence of potential DDIs was examined. Results presented that risk for DDIs varied widely, ranged between 0.63% and 47.4% [17-22]. Additionally, the frequency study of potential DDIs at geriatric outpatient in 6 European countries showed that there were differences in frequency, as well as in the type of potential DDIs [23]. By study of predictors to DDIs was also observed variability, those which are patient characteristics as well as those which are therapy characteristics [20-22,24-32]. Differences in healthcare settings, registered and reimbursed pharmaceutical specialities can contribute to different utilization patterns of prescription drugs. Also, physician prescribing attitudes and habit can vary [33-35]. Consequently, results can vary widely among countries and study findings from one country can not be extrapolated to other countries.

According to the authors’ knowledge, prevalence study of DDIs has not been performed in Serbia. Therefore, the primary objective of this study was to estimate the prevalence of potential DDIs among outpatient of city region Novi Sad, Serbia, and to investigate predictors of potential DDIs.

## 2. Materials and methods

### 2.1. Study Design, Subjects, Data Collection

The study was conducted with the approval of the Ethics Committee of the Health center Novi Sad, Novi Sad,

Serbia and Ethics Committee of the Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia.

In the cross sectional study was analyzed the data about outpatient prescriptions in city region Novi Sad, which is the administrative seat of the northern Serbian province of Vojvodina, with population of approximately 340000 individuals. Data were obtained from the electronic prescription database of Health center Novi Sad, and data collection was done automatically by the computer server administrator. There was not access as well as direct manipulation of the data by researchers. Strict registration routines and internal controls support the accuracy of the electronic database. Prescription data refer to all reimbursed drugs by National Health Service, according to the List of drugs prescribed and dispensed under the mandatory health insurance scheme. The database does not include information on over-the counter drugs, herbal medicines and dietary supplements. In the study, it was included data on year of birth, sex and diagnoses of subjects, as well as date of the prescribing, strength, dose regimen, quantity (number of packs), and route of the drug administration. Diagnoses were coded according to the first level of International Statistical Classification of Diseases and Related Health Problems (ICD-10) [36] and drugs were coded according to first level of the Anatomical Therapeutic Chemical (ATC) classification system, as recommended by the World Health Organization [37]. In the analysis were randomly included 10% outpatients with polypharmacy (n=4467), who visited Health Center over 1-month period (November 1-30, 2011). Polypharmacy was defined as co-prescription of  $\geq 2$  drugs [29]. For each patient was assumed that consumption of drugs started at the same day when the drugs was prescribed, and the duration of treatment for each drug was calculated in days by multiplying of daily dose by the number of daily doses containing in prescribed packs. Potential for DDIs was studied when the exposure periods to two interacting drugs overlapped. Overlapping was defined as the presence of at least a day of co-prescription of two drugs, object and precipitant drugs [29].

### 2.2. Identification and analysis of potential DDIs

DDIs were identified according to Drug Interaction Facts by David S Tatro [16]. The authoritative compendium [38,39] classify existing documentation in the literature in five levels: established, probable, suspected, possible or unlikely, and severity of adverse effects in three levels: major, moderate or minor. Based on a combination of these two criteria, clinical significance of DDIs was ranked by number, from 1 to 5. Interactions ranked as

1 and 2 were considered as clinically significant [39]. For each subject exposed to overlapped prescriptions all pairs of drug combinations were analysed manually for potential DDIs by two clinical pharmacologists and a drug information pharmacist. In case of disagreement among three evaluators, the evaluation of potential DDI was discussed until consensus was achieved.

In the present study, Serbian registered drugs which were not listed in Drug Interaction Facts by David S Tatro were reclassified to substances included in the compendium if they have the same DDI profile or have documented group specific DDI effects. For example, bromazepam was reclassified to benzodiazepines that undergo oxidation.

### 2.3. Predictors of potential DDIs

In the present study, patient and drug therapy characteristics were studied as predictors of potential DDIs. It analyzed the following patient characteristics: age, sex, number of diagnoses, and ICD-10 code classification of diagnoses. For each patient, the number drugs prescribed and ATC code classification of drug therapy were analyzed as drug therapy characteristics. Selected predictor factors were chosen in accordance with the results of previous studies [22,25,28,31].

## 3. Statistical analysis

The selected sample for analysis was divided in two groups. Subjects with one or more potential DDIs were exposed group, and those without potential DDI were unexposed group. Descriptive statistics were used to calculate absolute and relative frequencies for categorical variables, mean and standard deviation for continuous variables. Independent sample T-test was used for continuous variables, and Chi-square test of independence for categorical variables to compare exposed and unexposed group of subjects. Logistic regression analysis was used to study predictors of potential DDIs. Exposure to clinical significant potential DDIs (Yes/No) was the dependent variable in the model, patient and drug therapy characteristics were independent variables in the model. Each exposed subject was included in the logistic regression analysis only once, regardless of the number of clinical significant potential DDIs which was exposed. The level of significance for all statistical tests was 5%. Analyses were conducted using IBM Statistics SPSS for Windows Version 20.0.

## 4. Results

### 4.1. General Characteristics

During the study, prescriptions for 4467 patients were analyzed, 2558 clinical significant potential DDIs were identified among 1488 exposed patients (Table 1). Nine hundred and twenty one (36%) DDIs were rated as 1 and 1637 (64%) as 2, corresponding to 136 drug combinations. The mean number of DDIs per exposed patient was 1.72 (ranged 1–10), and 852 patients (57.26%) were exposed to 1 potential DDIs, 393 (26.41%) to 2 potential DDIs, 133 (8.94%) to 3 potential DDIs and 110 (7.39%) to  $\geq 4$  potential DDIs. The mean age of exposed subjects were 62.81 years (SD = 14.75), ranged from 2 to 94 years and 857 (57.6%) were female (Table 1).

Ten the most frequently identified interacting drug combinations were responsible for 1437 (56.18%) of all potential DDIs. Sulfonylureas and ACE inhibitors (375 cases), potassium-sparing diuretics and ACE inhibitors (246 cases), sulfonylureas and thiazide diuretics (186 cases) were the most commonly observed drug pairs (Table 2). Interactions of two interacting drug pairs, opioid analgesics and benzodiazepines as well as benzodiazepines and clozapine included all potential interactions of bromazepam, in total 30 cases or 1.17% of all potential clinical significant DDIs (Table 2).

The logistic regression analysis presented that, odds of exposure to potential DDIs was increased with patient age. Thus, in the group aged of 20-64 years odds ratio (OR) was 4.642 (95% CI 2.424-8.892), while in the group aged of  $\geq 65$  years OR was 5.204 (95% CI 2.694-10.052), patients aged of  $< 20$  years were referent group. The subject gender was not related to exposure. Odds of exposure was positively associated with number of diagnosed diseases, OR subjects with 2 – 3 diseases was 2.377 (95% CI 1.915-2.949), those with  $\geq 4$  diseases was 4.451 (95% CI 3.349-5.914), using subjects with 1 disease as referent group. Endocrine, neurological, mental, respiratory and cardiovascular diseases were predictors, while musculoskeletal and connective tissue disorders were not predictors to potential DDIs (Table 3).

Odds of exposure of patients with major polypharmacy (coadministration  $\geq 5$  drugs) was 5.735 (95% CI 4.876-6.747) as compared with those with minor polypharmacy (coadministration 2-4 drugs) as referent group. Using of drugs for alimentary tract and metabolism, nervous, respiratory and cardiovascular system were associated with increased risk to potential DDIs,

**Table 1.** General characteristics according to exposure to clinical significant potential drug-drug interactions

Characteristic	Exposed (N=1488)	Unexposed (N=2979)	P value
Mean age ( $\pm$ SD) years	62.81 (14.75)	58.70 (18.49)	<0.001
Female sex, n(%)	857 (57.6)	1727 (58.0)	0.834
Mean number of drug consumed ( $\pm$ SD)	5.72 (2.18)	3.57 (1.54)	< 0.001
ATC code A (alimentary tract and metabolism), n(%)	637 (42.8)	660 (22.2)	< 0.001
ATC code B (blood and blood-forming organs), n(%)	185 (12.4)	217 (7.3)	< 0.001
ATC code C (cardiovascular system), n(%)	1274 (85.6)	2214 (74.3)	< 0.001
ATC code J (antiinfectives for systemic use), n(%)	299 (20.1)	524 (17.59)	0.046
ATC code M (musculoskeletal system), n(%)	153 (10.3)	209 (7.02)	< 0.001
ATC code N (nervous system), n(%)	647 (43.5)	968 (32.5)	< 0.001
ATC code R (respiratory system), n(%)	252 (16.9)	261 (8.8)	< 0.001
Mean number of diagnosed diseases ( $\pm$ SD)	3.02 (1.32)	2.11 (1.04)	< 0.001
ICD -10-CM code E00-E90 (Endocrine, alimentary and metabolic diseases), n(%)	573 (38.5)	487 (16.3)	< 0.001
ICD-10-CM code F01-F99 (Mental and behavioral disorders), n(%)	494 (33.2)	736 (24.7)	< 0.001
ICD -10-CM code G00-G99 (Diseases of the nervous system), n(%)	107 (7.2)	140 (4.7)	< 0.001
ICD-10-CM code I00-I99 (Diseases of the circulatory system), n(%)	1258 (84.5)	2203 (74.0)	< 0.001
ICD-10-CM code J00-J99 (Diseases of the respiratory system), n(%)	365 (24.5)	529 (17.8)	< 0.001
ICD-10-CM code M00-M99 (Diseases of the musculoskeletal system and connective tissue), n(%)	148 (9.9)	179 (6.0)	< 0.001

P value < 0.05 were considered statistically significant

while using of drugs for blood and blood-forming organs, musculoskeletal system as well as antiinfectives for systemic use were not associated with exposure to potential DDIs (Table 4).

## 5. Discussion

In the present study the prevalence of clinical significance potential DDIs was 33.31%. In the previous studies were conducted in primary health care, incidence and prevalence of clinical important potential DDIs varied widely [17,19-22]. However, comparison of the results should be done cautiously. For example, Aparasu et al. used 24-month observed period and studied potential for 25 clinical significant DDIs [17] in the population at large, while Obreli Neto et al. studied potential DDIs for 12 drug pairs in the elderly using 6-month observed period [22], in the present study was used 1-month observed period and all clinical significant potential DDIs

were identified according to Drug Interaction Facts™ [16] in the population at large.

In the present study, drugs for cardiovascular disease were included in 7 of 10 the most commonly drug pairs. These results were expected, because the highest number of patients—3488 (78.1%) used cardiovascular drugs (B. Nikolic, unpublished data). Also, the results were consistent with the results of previous studies [29,40,41]. In the research report by Björkman et al. which was conducted to detect the frequency of potential DDIs in elderly outpatient in 6 European countries was presented that 9 of 10 most commonly drug-combinations that might need dose adjustment, and 4 of 9 drug-combinations recommended to be avoided, included drugs with ATC code C [23]. The three most frequent drug pairs in the present study included ACE inhibitors. Results from a clinical perspective could have important implication. For example, recommendation for the management of the most commonly interacting drug combination, sulfonylureas and ACE inhibitors (375

**Table 2.** Most common potential drug-drug interactions

Drug combination <sup>a</sup>	N (%)	Possible clinical consequences <sup>a</sup>	Clinical significance <sup>b</sup>
Sulfonylureas, ACE inhibitors	375 (14.66)	Risk of hypoglycemia may be increased.	2
Potassium-Sparing Diuretics, ACE inhibitors	246 (9.62)	Combining ACE inhibitors and potassium-sparing diuretics may result in elevated serum potassium concentration in certain high-risk (eg. renally impaired) patients.	1
Sulfonylureas, Thiazide diuretics	186 (7.27)	Thiazide diuretics increase fasting blood glucose and may decrease sulfonylurea hypoglycemia. This effect may occur after several days to many months of thiazide therapy. Hyponatremia also may occur.	2
Opioid analgesics, Benzodiazepines	129 <sup>c</sup> (5.04)	Increased risk of sedation and life-threatening respiratory depression, especially with overdosage.	1
Sympathomimetics (Beta-Agonists), Beta blockers	112 (4.38)	Pharmacologic effects of sympathomimetic beta-agonists may be antagonized by beta-blockers. Bronchospasm may occur.	1
Benzodiazepines, Clozapine	82 <sup>d</sup> (3.21)	The pharmacologic or toxic effects of certain benzodiazepines may be increased.	1
Beta-blockers, Serotonin Reuptake Inhibitors	81 (3.17)	Excessive beta-blockade (bradycardia) may occur	2
Beta blockers, NSAIDs	80 (3.13)	Impaired antihypertensive effect of beta-blockers	2
Beta-blockers, Penicillins	74 (2.89)	Antihypertensive and antianginal effects of atenolol may be impaired	2
Benzodiazepines, Carbamazepine	72 (2.81)	The pharmacologic effects of certain benzodiazepines may be decreased	2

<sup>a</sup> Drug interaction Facts by David S Tatro was used to identify potential DDIs and their possible clinical consequences

<sup>b</sup> Clinical significance of DDIs was ranked according to Drug interaction Facts by David S Tatro

<sup>c</sup> Number included 22 cases bromazepam and opioid analgesics interactions (it presented 0.86% of all potential clinical significant DDIs)

<sup>d</sup> Number included 22 cases bromazepam and clozapine interactions (it presented 0.86% of all potential clinical significant DDIs)

cases) is carefully observe for symptoms of hypoglycemia when initiating ACE inhibitor therapy in patients receiving sulfonylurea therapy [16], however if these two drugs were part of the normal treatment regimen of hypertension associated with diabetes, in that case the prevalence of this interaction for the subjects of the study would be reduced. Also, according to numerous reports, coadministration of opioids and benzodiazepines (BZs) is ubiquitous around the world, concomitant use ranged between 51% and 70% [42-44]. However, if BZs used therapeutically among methadone maintained patients to anxiety, mania or insomnia, the prevalence this DDI could be overestimated. Conclusions of other studies were somewhat different and because of that the clinical implications could be different. In the study conducted in Brazilian primary public health system the most commonly drug pairs were digoxin and furosemide/hydrochlorothiazide, captopril/losartan and spironolactone, and acidum acetylsalicylicum and ticlopidine [22]. In ambulatory medical care practices in the US, Aparasu et al. identified that warfarin included in the three most commonly DDIs pairs [17], similar to the results of study was conducted in Italian outpatients [31].

## 5.1. Patient characteristic predictors

Consistent with the findings of some previous studies, in the present study exposure to potential DDIs increased with patient age. Also, a positive association was confirmed between years and exposure to potential DDIs in primary health care in the study conducted in Denmark, the risk of the interaction increased from 0.6% in patients aged < 20 years to 36.2% in those aged ≥ 80 years [29]. The potential for DDIs was studied and in the US outpatients, in the group aged of 25-44 years adjusted OR was 0.81(95% CI 0.40-1.65), rose with aged and in the oldest (aged > 74 years) was 5.57 (95% CI 2.60-11.92), patients aged < 25 years were referent group [17]. These findings could be attributed to the increased complexity of drug therapy regimens found in older, which resulted in a higher prevalence of potential DDIs. However, in the study conducted by Gagne et al. in Italy, using subjects aged 50-64 years as a referent group, the odds of exposure to a potential DDIs was higher in older patients, however odds of exposure for the oldest (aged ≥ 85 years, OR=2.02 (95% CI of 1.66-2.46)) was lower than for those aged of 65-74 years

**Table 3.** Patient characteristics associated with clinical significant potential drug-drug interactions

Predictor factor	Odds ratio (95% CI)	P value
Age (years)		
0-19	1.000	
20-64	4.642 (2.424-8.892)	< 0.001
≥65	5.204 (2.694-10.052)	< 0.001
Sex		
Female	1.000	
Male	1.047 (0.913-1.201)	0.512
Number of diagnosed diseases		
1	1.000	
2 – 3	2.377 (1.915-2.949)	< 0.001
≥ 4	4.451 (3.349-5.914)	< 0.001
ICD -10-CM code		
ICD -10-CM code E00-E90 (Endocrine, alimentary and metabolic diseases)	2.511 (2.132-2.956)	< 0.001
ICD-10-CM code F01-F99 (Mental and behavioral disorders)	1.501 (1.273-1.770)	< 0.001
ICD-10-CM code G00-G99 (Diseases of the nervous system)	1.796 (1.345-2.397)	< 0.001
ICD-10-CM code I00-I99 (Diseases of the circulatory system)	1.357 (1.110-1.659)	0.003
ICD-10-CM code J00-J99 (Diseases of the respiratory system)	1.667 (1.388-2.001)	< 0.001
ICD-10-CM code M00-M99 (Diseases of the musculoskeletal system and connective tissue)	1.242 (0.966-1.595)	0.090

P values < 0.05 were considered statistically significant

(OR=2.11 (95% CI of 1.85-2.41) as well as those aged of 75-84 years (OR=3.12 (95% CI of 2.74-3.56) [31]. Some studies failed to document a positive association between years and exposure to potential DDIs [45,46].

The present results indicated that the sex was not associated with the occurrence of potential DDIs. These results were expected, given that there was no statistical significant difference between the sex and the number of clinical significant potential DDIs (female: M = 0.56, SD = 1.018; male: M = 0.59, SD = 1.053,  $p = 0.469$ ), or the number of morbidity (female: M = 2.39, SD = 1.183; male: M = 2.44, SD = 1.267,  $p = 0.145$ ), as well as the number of prescribed drugs (female: M = 4.30, SD = 2.015; male: M = 4.28, SD = 2.087,  $p = 0.746$ ) (B. Nikolic, unpublished data). In general, published results concerning the influence of sex on exposure to potential DDIs are variable. Thus, the study by Nobili *et al.*, also study by Secoli *et al.* did not verify statistical significant difference with respect to sex [27,46]. While, Cruciol-Souza *et al.* identified female sex as a predictor of potential DDIs in hospitalized Brazilian patients [25]. Costa *et al.* also reported higher risks for potential DDIs

**Table 4.** Drug therapy characteristics associated with clinical significant potential drug-drug interactions

Predictor factor	Odds ratio (95% CI)	P value
Number of drugs prescribed		
Minor polypharmacy (2-4 drugs)	1.000	
Major polypharmacy (≥ 5 drugs)	5.735 (4.876-6.747)	< 0.001
ATC code		
ATC code A (alimentary tract and metabolism)	1.790 (1.529-2.096)	< 0.001
ATC code B (blood and blood-forming organs)	1.020 (0.805-1.293)	0.868
ATC code C (cardiovascular system)	1.319 (1.079-1.611)	0.007
ATC code J (antiinfectives for systemic use)	1.135 (0.942-1.368)	0.184
ATC code M (musculoskeletal system)	1.235 (0.960-1.589)	0.100
ATC code N (nervous system)	1.546 (1.324-1.804)	< 0.001
ATC code R (respiratory system)	1.438 (1.154-1.793)	0.001

P values < 0.05 were considered statistically significant

in females in the US Centre for family practice [21]. In contrast, Johnell *et al.* showed a lower probability of potentially serious DDIs in female elderly Swedish outpatients [30].

The present results supported the findings of previous studies demonstrating that larger number of diagnosed diseases were associated with occurrence of potential DDIs [21,22,31]. In the present study, chronic disease except musculoskeletal disorders were predictors to potential DDIs. Study by Secoli *et al.* presented that diagnosis of hypertension, diabetes mellitus and heart problems were predictors, but lung, rheumatic diseases, mental health (nervous or psychiatric) problems and cancer were not [46]. In the study conducted in primary public health system in Brazil, hypertension was predictor to potential DDIs, while diabetes was not [22]. Variations could be consequence of the study setting and health status of subjects, as well as used study method (chosen sources for identification DDIs and criteria for assessment of DDIs).

## 5.2. Drug therapy predictors

In consistency with previous studies, the present study also demonstrated that the risk for potential DDIs increased with the number of prescribed drugs [47-52]. Major polypharmacy identified as a risk factor for DDIs, patients with ≥ 5 prescribed drugs had the 5.735 times higher risk to potential DDIs, as compared with those with minor polypharmacy as a referent group. Also, Sloan identified that the potential for an interaction

increased from 5.6 % in patients receiving 2 drugs to 100 % in patients receiving  $\geq 8$  drugs [53].

With respect to the influence of ATC codes on the exposure to potential DDIs, there are not consensus among results published studies. In the present study, ATC codes C, A, R i N were associated with the occurrence of potential DDIs. Obreli Neto et al. reported ATC codes A, B and C as predictors of potential DDIs [22]. While ATC codes B, C, S and J were associated with occurrence of potential DDIs in the study by Cruciol-Souza et al. [25]. Variation in published results might be due to differences in patient health status (population at large, elderly), study setting (outpatients and hospitalized patients). Additionally, prescribing habits, differences in registered and reimbursed drugs could contribute variations.

## 6. Limitations

The present study has some limitations. The compendium was used to identify clinical significant potential DDIs is one of the primary sources for drug information, and other studies used other sources. But, some studies presented disagreement among authoritative drug compendia in listing as well as ranking clinical significance of DDIs [38,39]. Because of these differences performing DDIs prevalence studies presents challenge making it difficult to compare results across studies.

The present prevalence study was conducted using outpatient prescriptions database, which included all drugs that were prescribed under the mandatory health insurance scheme in Serbia. Non-prescription drugs, including over-the-counter products, herbal medicines, and dietary supplements have not been registered in the

database and were not considered, thus possibly underestimating drug exposures and consequently of the risk to potential DDIs. For example, acetylsalicylic acid have not been registered in Health Center prescription database, but in other countries DDIs for this drug were reported frequently [23,43,46].

On the other hand, lack of information about compliance as well as inclusion in the analysis of all drugs prescribed chronically for the patients, regardless of when the treatment really started could contribute to overestimation the prevalence of potential DDIs. Additionally, information on physician prescribing decision were not captured. For example, in certain clinical situations, the benefits of co-prescribing drugs with the potential to interact could be outweighed the risks of their coadministration.

## 7. Conclusion

The present study showed that approximately one-third of outpatients living in Novi Sad were exposed to clinical significant potential DDIs. A large proportion of these combinations were likely part of normal drug regimen. However, some of the combinations could have negative effects. Therefore, more attention must be focused on detecting and monitoring patients using such combinations, in particular, elderly, sicker patients on multiple drug therapy for chronic diseases.

Based on the present results of large study population could be defined recommendations for the management potential clinical significant DDIs. Guidelines could be integrated in existing computerized physician order entry system in Health Center as a form of clinical decision support.

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