Original Article

Potential drug-drug interactions among hospitalized patients in a developing country

Sarah Mousavi (Pharm D) [*1]
Golshan Ghanbari (Pharm D) [2]

1. Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.
2. Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

* Correspondence:
Sarah Mousavi, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Hezar Jerib Avenue, Isfahan, Iran.

E-mail:
s.mousavi@pharm.mui.ac.ir
Tel: 0098 313680011
Fax: 0098 313680011

Abstract

Background: Drug-drug interactions (DDIs) may often lead to preventable adverse drug events and health damage. Particularly in hospitals, this might be an important factor as multiple drug therapies are common. The objective of this study was to identify the frequency and levels of potential DDIs in internal medicine wards in an Iranian university hospital.

Methods: A cross-sectional study was conducted by reviewing charts of 448 hospitalized patients in internal medicine wards of a teaching hospital, from November 2014 to May 2015. "Lexicomp drug interaction software" and Micromedex Drug-Reax system were used for screening the potential DDIs. The identified DDIs were categorized by level of severity. Logistic regression was applied to determine the odds ratio for specific risk factors of potential DDIs e.g., age, gender, hospital stay and number of medications.

Results: The mean age of patients was 61 years, the length of hospital stay for patients was 9 days and the number of drugs per patient was 9. Potential interactions were detected in 386 patients. The most common types of interactions were type C (78.6%), moderate (60.9%) and delayed onset (56.5%). There was a significant association of the occurrence of potential DDIs with seven or more numbers of prescribed medications (OR: 0.048, 95% CI:0.02-0.12, p<0.0001).

Conclusion: The present study has recorded a high prevalence of potential DDIs in internal medicine wards. Patients with polypharmacy were at high risk for DDIs. Education, computerized prescribing systems, drug information, and pharmaceutical care are important measures that were recommended to minimize harm associated with DDIs.

Keywords: Drug interactions, Internal medicine, Hospital pharmaceutical service, Iran.

Drug-drug interaction (DDI) constitutes one of the potential mechanisms leading to often preventable adverse drug events and health damage (1). Multiple drug therapies are very common for the treatment of various medical illnesses. Such therapy may be the potential source of DDI. According to published studies, 1% of all hospital admissions are caused by DDIs, corresponding to 16% of all patients hospitalized due to adverse drug reactions (ADR) (2, 3). At least 15% of the patients admitted to hospitals have one DDI at admission (4). The clinical outcome of a potential DDI is often unknown, and epidemiological data dealing with this problem are rare. A study conducted in Switzerland reported that 56.2% of patients are exposed to one or more major or moderate potential DDIs (pDDIs) in internal medicine wards (5). Another study by Galley et al. showed that from a total of 160 patients in the internal medicine ward, 221 cases of interaction exists, in which 24 were of the major type, 15 of the moderate type and 82 minor interactions. Also the presence of certain diseases such as renal failure, or the use of more than 6 drug items, could increase the probability of drug interactions (6).

According to the World Health Organization (WHO), as of 2000, Iran ranks 58 in health care and 93 in health-system performance (7). Based on the last census taken at Statistical Center of Iran (SCI) in 2003, Iran possesses 730 medical establishments (e.g. hospitals, clinics) with a total of 110797 beds. The country is in an epidemiological transition and faces a double burden of diseases. In hospital settings, doctors and other health care professionals are mostly overburdened (8).

Medication therapy is the most common method of treatment in Iran. Average items per prescription ranged from 3.68 in cardiologists to 2.06 in dermatologist's prescriptions, which is higher as compared with other parts of the world (9).

In most of the hospitals, the established clinical pharmacy system does not exist to monitor and optimize medication use. Irrational use of medicines is a common and crucial problem in Iran. Several studies showed that the Iranian population is at higher risk to potential DDIs (10-14). Overall, data on the occurrence and consequences of DDIs within the hospital, especially in medical inpatients are scarce.

Therefore, the objective of this study was to identify the frequency and levels of potential DDIs in internal medicine wards in a large university hospital in Isfahan, Iran and found their association with patient's age, length of hospital stay and number of prescribed medications.

Methods

A cross-sectional study was conducted at the Alzahra Teaching Hospital of Isfahan, Iran. The hospital is an 850-bed teaching institution serving a population of approximately 1.7 million inhabitants. This study was approved by the Ethics Committee of the Pharmacy Faculty of Isfahan University of Medical Sciences. Between November 2014 to May 2015, patients admitted consecutively to all internal medicine wards (Pulmonary, Nephrology, Hematology, Cardiovascular, Gastrointestinal) were included in the study. Patients were admitted due to different diagnosis covering the entire field of internal medicine. Permission was obtained from hospital authorities to consult the patient's medical record for research purpose. Drugs prescribed during the hospital stay and discharge were retrieved from medical records and drug Kardex. The following information was collected: patient's age, gender, length of hospital stay, reasons for admission, detail of medication therapy provided in the hospital and severity and significance of drug interaction. All regular and PRN (pro-ra-nata, means as required) medications were included. All information was recorded on a standardized form. The severity and significance of drug interaction were analyzed using Lexi-Comp on desktop drug interaction software (Lexi-Comp, Inc., Ohio, USA). Significance of drug interactions was divided into 5 categories (A to X) which was presented in table 1.

Table 1. Significance of drug-drug interaction

Risk Degree	Necessary Measurement	Description
A	Undefined Interaction	Information has shown no pharmacokinetic or pharmacodynamics interaction between selected drugs.
B	No Measurement	Information has shown that the selected drugs may be interacting with each other. However, small evidence from clinical concerns exists about taking these medicines together.
C	Monitor therapy	Data has shown that certain components of selected medicines may interact with each other via a distinct clinical mechanism. The advantages of both drug consumptions should be more than risks.
D	Taking care reform	Data has shown that the two selected drugs may be interacting with each other through a specific physical mechanism. A patient-specific evaluation should be carried out to detect advantages of the dual consumption compared to hazards. Certain reactions to understand the advantages and minimize the use of two drugs together should be done. These actions include aggressive monitoring, experimental dose changes, and alternative medicine selection.
X	Avoidance of concomitant use of two drugs	Data has shown that certain components of the two drugs may interact with each other via a distinct clinical mechanism. Hazards associated with the combined use of two drugs are commonly more than the advantages. These drugs are usually considered together as contraindicated drugs.

Furthermore, Micromedex database ® (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, United states) (15), was used for DDIs analysis, which categorized interactions according to the degree of severity (contraindicated, major, moderate, minor). The program also provides information about the underlying mechanism and classifies onset of adverse drug reactions (rapid, delayed, unspecified), and potential adverse outcome of an interaction. Data were presented as proportions, means and standard deviations, or medians. Logistic regression was applied to identify the association of occurrence of pDDIs with patient's age, gender, length of hospital stay and number of prescribed medications.

Exposure to pDDIs was the dependent variable in the model (0: absent, 1: present). The following variable was included in the model as predictors of pDDIs: patient's age (1=below 60 years, 2=60 years or older), gender (1=male, 2=female), hospital stay (1=less than 6 days, 2=6 days or above), and number of prescribed medications (1= less than 7, 2=7 or above). The odds ratio (OR) and respective confidence interval (CI) was calculated for each variable. A p-value of <0.05 was considered statistically significant. SPSS for windows Version 20 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Of the 448 patients, 263 (58.7%) were males and 185 (41.3%) were females. Most patients were between 61 and 80 years of age (35.7%; mean age 57.8±20.2 years). Median age was 61 years. The median hospital stay was 9 days (13.1±14.4, range 2-220 days). The number of concomitant prescription medications ranged from 1 to 28 (mean: 9.1±4.3) and 73.3% of patients took more than four drugs. Table 2 shows the general characteristics of patients in internal medicine wards. The number of potential DDIs found for each patient in the wards ranged from 0-61 interactions and the mean potential DDI for each patient was 7.6±8.8 interactions. In total, 3350 pDDIs were found in patients. Overall, 11.8% patients had at least one pDDIs regardless of type of severity. Moderate pDDIs were most prevalent (60.9%) followed by major pDDIs (48.8%) and minor pDDIs (28.8%). Contraindicated pDDIs were recorded only in 9.2% of patients. Table 3 shows the frequency of DDIs regarding the A to X category. The most type of interactions was C category (78.6%).

Table 2. General characteristics of patients in internal medicine wards.

Characteristics	Frequency
Gender	Patient: N(%)
Male	263 (58.7)
Female	185 (41.3)
Age (years)	
<20	15 (3.3)
21-40	82 (18.3)
41-60	126 (28.1)
61-80	160 (35.7)
81-100	65 (14.5)
Hospital stay (days)	
≤ 3	2 (0.4)
3-7	144 (23.1)
>7	302 (67.4)
Prescribed medications per patient	
< 3	15 (3.3)
3-6	130 (29)
> 7	303 (67.6)

Table 3. Prevalence of potential drug-drug interactions (pDDIs) in internal medicine wards.

Type of prevalence	Frequency
	Patient: N (%)
Overall prevalence *	386 (86.2)
Severity of pDDIs	
A	71 (15.8)
B	243 (54.2)
C	352 (78.6)
D	168 (42)
X	41 (9.2)
Major	217 (48.4)
Moderate	273 (60.9)
Minor	129 (28.8)
Rapid	188 (42)
Delayed	253 (65.5)
Unspecified	172 (38.4)
Number of pDDIs per patient	
1-2	100 (22.3)
3-5	89 (19.9)
6-9	82 (18.3)
≥ 10	115 (25.7)

* Overall prevalence means presence of at least one pDDI regardless of type of severity.

More than 25% of our patients were exposed to more than 10 pDDIs during their hospital stay. In 22.3% cases, patients were presented with one or two pDDIs. Of 386 identified pDDIs, most were delayed onset (56.5%) followed by rapid onset (42%). The onset of pDDIs in 38.4% of cases were unspecified. Table 4 shows the patient's characteristics and type of interactions in different internal medicine wards. More than 90% of patients in the pulmonary ward had pDDIs. Most frequently identified major or moderate interactions resulted in 27% of all pDDIs (907 out of 3350).

Their frequencies, levels of severity, onset and potential adverse outcomes were presented in table 5. In logistic regression analysis, there was a significant association of the occurrence of pDDIs with seven or more numbers of prescribed medications (OR: 0.048; 95% CI:0.02-012, p<0.0001). The association was not significant in case of the patient's gender (OR: 1.02; 95% CI=0.56-1.81, p=0.94), patient's age of 60 years less or more (OR: 0.94; 95% CI=0.51-1.7, P=0.85) and hospital stay of 6 days less or more (OR: 0.82; 95% CI:0.4-1.5, P=0.54).

Table 4. Patients' characteristics and prevalence of potential drug-drug interaction (DDI) in different internal medicine wards.

Wards	Age Means±SD	Hospital stay (Days)	Prescribed medications per patient	PDDIs severity (N (%))					
				Total	A	B	C	D	X
Pulmonary	61.7±19.8	18.4±23	10.1±4.3	123 (97.6)	14 (10.3)	86 (63.2)	114 (83.8)	61 (44.9)	15 (11)
Cardiovascular	56.3±20.7	12.1±7.6	8.9±4.4	145 (87.3)	44 (26.5)	95 (57.2)	137 (82.5)	76 (45.8)	18 (10.8)
Gastroenterology	57.3±18.9	7.9±3.7	7.2±3.4	54 (76.4)	1 (1.4)	23 (32.4)	43 (60.6)	12 (16.9)	0
Nephrology/ hematology	54.8±20.3	10.2±5.9	9.5±3.9	64 (85.3)	12 (16)	39 (52)	58 (77.3)	39 (52)	9 (12)

Discussion

In the present study, we found that nearly all of the patients admitted to the internal medicine wards, experienced at least one potential DDIs, during their hospitalization. On average, this group of patients experienced 7.6 DDIs. Approximately, 67% of these patients were prescribed more than six drugs, which is the only factor that had significant association with the occurrence of pDDIs. Similar studies report a trend of increasing prevalence of potential DDIs with the increase in the number of drugs prescribed (16-19). Research worldwide has shown that polypharmacy (5 or more drugs) contributes to the increased risk of potential DDIs (20, 21). Overall, the mean number of prescription drugs in our study was more than similar studies conducted in similar settings (5, 16, 22). In our center, usually multiple physicians visit the patients and we do not have a system to alert about the potential DDI. Prescribing medicine with a computerized physician order entry (COPE) system with DDI alerts, may be promoted rational therapy in medical wards and decrease DDI occurrence (23, 24). A study by Rijkom et al., (25) shows that computerized DDI alerts may be a useful tool to prevent adverse drug events within

hospitals. Ismail et al., (22) reported the overall prevalence of 52.8% of at least one pDDIs in 400 medical inpatients. Major and moderate pDDIs were recorded in 23% and 63.6% of patients, respectively. In our study, the overall prevalence of pDDIs (86.2%) and also major pDDIs was higher as compared with the above report. The prevalence of moderate pDDIs (or C type) was similar to the aforementioned study. Rates ranging from 43% to 56.2% have been described in internal medicine wards for all potential DDIs. Despite variation in study design, these published reports suggest a high prevalence of pDDIs in internal medicine wards, which is even higher in our study.

The most prevalent type of interactions observed in our study was type C (78.6%). Type C drug interaction will not cause any serious and fatal consequences and need careful monitoring to avoid and minimize the negative outcomes of these interactions. However, we found that 41 (9.2%) patients have type X interactions, which could be harmful and life-threatening for patients. The rates of contraindicated or type X interactions were from 0.2-2.4% in other studies (12, 22, 25, 26).

Table 5. Most frequently identified major or moderate interactions, their levels and potential adverse outcomes.

Interaction	Frequency	Severity	Onset	Potential adverse outcome
Aspirin + heparin	51	Major	Rapid	Increase risk of bleeding
Aspirin + clopidogrel	33	Major	Delayed	Increase risk of bleeding
Enoxaparin + warfarin	28	Major	Unspecified	Increase risk of bleeding
Aspirin + warfarin	22	Major	Delayed	Increase risk of bleeding
Digoxin + furosemide	16	Major	Delayed	Risk of digoxin toxicity
Ciprofloxacin + insulin	14	Major	Rapid	Hypoglycemia
Clopidogrel + enoxaparin	13	Major	Unspecified	Increase risk of bleeding
Atorvastatin + azithromycin	9	Major	Delayed	Increase risk of myopathy
Midazolam + morphine	8	Major	Delayed	Increase sedation
Ceftazidim + warfarin	7	Major	Unspecified	Increase risk of bleeding
Clopidogrel + warfarin	6	Major	Unspecified	Increase risk of bleeding
Ciprofloxacin + warfarin	5	Major	Delayed	Increase risk of bleeding
Losartan + spironolactone	4	Major	Delayed	Hyperkalemia
Diazepam + morphine	4	Major	Unspecified	Increase sedation
Pantoprazole + warfarin	51	Moderate	Unspecified	Increase effect of warfarin
Atorvastatin + clopidogrel	33	Moderate	Delayed	Risk of blood clotting
Aspirin + enoxaparin	28	Moderate	Rapid	Increase risk of bleeding
Aspirin + captopril	25	Moderate	Rapid	Decrease effect of captopril
Digoxin + pantoprazole	22	Moderate	Delayed	Digoxin toxicity
Losartan + warfarin	18	Moderate	Delayed	Decrease effect of warfarin
Levofloxacin + prednisolone	17	Moderate	Delayed	Increase risk of tendon rupture
Atorvastatin + digoxin	16	Moderate	Delayed	Digoxin toxicity
Diazepam + valproic acid	14	Moderate	Delayed	Excessive sedation
Digoxin + spironolactone	12	Moderate	Rapid	Digoxin toxicity
Captopril + furosemide	11	Moderate	Rapid	Acute hypotension, renal insufficiency
Levothyroxine + warfarin	8	Moderate	Delayed	Increase risk of bleeding
Phenytoin + valproic acid	7	Moderate	Delayed	increase effect of phenytoin
Cyclosporine + diltiazem	7	Moderate	Delayed	Increase cyclosporine toxicity
Ciprofloxacin + prednisolone	6	Moderate	Delayed	Increase risk of tendon rupture
Ciprofloxacin + methadone	5	Moderate	Delayed	Increase QTc interval
Meropenem + valproic acid	5	Moderate	Delayed	Decrease level of valproic acid
Ciprofloxacin +Magnesium Oxide	4	Moderate	Rapid	Decrease level of ciprofloxacin
Lamotrigin + valproic acid	4	Moderate	Delayed	Increase level of lamotrigin
Gentamycin+ vancomycin	4	Moderate	Delayed	Nephrotoxicity, ototoxicity

Although this result is much lower than the frequency found in this study, the difference may partially be explained by the study design and characteristics of the population. As this type of interactions could be harmful for patients, physicians and pharmacists should be aware of them and keep patients under close surveillance. No statistically significant differences were found between age, gender and length of hospital stay regarding DDIs in our study, which is in agreement with a number of studies about gender (17, 27),

but in disagreement with other studies that report a positive association between older age and length of hospital stay and potential DDIs (19, 28). Some of these studies conducted in different settings. Ismail et al., (22) found a significant association of the occurrence of pDDIs with patient age 60 years or more (OR: 2.1, P: 0.003), hospital stay of 6 days or longer (OR: 2.6, P: 0.001) and seven or more numbers of prescribed medications (OR: 5.9, P<0.001). Finding of our study suggests that patients on polypharmacy are exposed to

pDDIs. The two most active substances involved in potentially clinically significant interactions were ciprofloxacin and aspirin. Ciprofloxacin is an antibiotic from quinolones class which has two important DDIs: decreased absorption with magnesium, calcium, iron and zinc and inhibit specific cytochrome p-450 isozymes responsible for metabolism of many drugs including methylxanthines. The consequence of interaction could be an increase in the plasma concentrations of some drugs, which in the case of theophylline could be life-threatening (29). The most frequent DDI of oral ciprofloxacin was with insulin. Ciprofloxacin increases the effect of insulin and may increase or decrease blood sugar. Careful monitoring of blood glucose is important. Potential DDIs have also been described with aspirin. The most important is the DDI with other antiplatelet or anticoagulant drugs (such as heparin, warfarin, enoxaparin, and clopidogrel) which may increase the risk of bleeding (30). These combinations are sometimes necessary during treatment. As a consequence, patients should always be carefully monitored.

Following are the potential limitations of this study. We did not investigate the actual effects of the identified pDDIs. Studies are needed to identify actual clinical consequences of these interactions. The present study was carried out in one hospital, so its exact external validity is not known. Yet, we anticipate a similar pattern in internal medicine wards of other hospitals, particularly in the developing world. We identified the association of pDDIs with specific risk factors. Studies can be designed to investigate the contribution of other factors such as use of a specific class of drugs, multiple prescribers, a specific diagnosis and type and number of comorbid illnesses.

In conclusion the findings of the present study showed a high prevalence of DDIs in internal medicine wards. Most of the interaction was of moderate severity, nonetheless, major pDDIs were also recorded in substantial numbers and similar to other international studies show an exponential growth in major DDIs. Exposing patients to a greater number of prescription drugs, four or more, proved to be a significant predictor of DDIs. Prescription of drugs with a low risk for DDIs and careful monitoring for possible adverse drug reactions (ADR) are measures to minimize harm associated with DDIs. We also recommend the development and use of computerized DDI alerts tool to prevent ADRs events within the hospital.

References

1. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255-9.

2. Ayvaz S, Horn J, Hassanzadeh O, et al. Toward a complete dataset of drug–drug interaction information from publicly available sources. J Biomed Inform 2015; 55: 206-17.

3. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug–drug interactions. Expert Opin Drug Saf 2012; 11: 83-94.

4. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993; 9: 51-9.

5. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug–drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med 2008; 19: 413-20.

6. Patel VK, Acharya LD, Rajakannan T, et al. Potential drug interactions in patients admitted to cardiology wards of a south Indian teaching hospital. Australas Med J 2011; 4: 9-14.

7. World Health Organization. The world health report 2000: health systems: improving performance: World Health Organization 2000.

8. Mehrdad R. Health system in Iran. JMAJ 2009; 52: 69-73.

9. Karimi A, Haerizadeh M, Soleymani F, Haerizadeh M, Taheri F. Evaluation of medicine prescription pattern using World Health Organization prescribing indicators in Iran: A cross-sectional study. J Res Pharm Pract 2014; 3: 39-45.

10. Ahmadizar F, Soleymani F, Abdollahi M. Study of drug-drug interactions in prescriptions of general practitioners and specialists in Iran 2007-2009. Iran J Pharm Res 2011; 10: 921-31.

11. Moradi Dirin M, Mousavi S, Afshari AR, Tabrizian K, Ashrafi MH. Potential drug-drug interactions in prescriptions dispensed in community and hospital pharmacies in East of Iran. J Res Pharm Pract 2014; 3: 104-7.

12. Pourseyed S, Fattahi F, Pourpak Z, et al. Adverse drug reactions in patients in an Iranian department of internal medicine. Pharmacoepidemiol Drug Saf 2009; 18: 104-10.

13. Rafieii H, Arab M, Ranjbar H, et al. The prevalence of potential drug interactions in Intensive Care Units. J Crit Care Nursing 2012; 4: 191-6.

14. Sepehri G, Khazaelli P, Dahooie FA, Sepehri E, Dehghani MR. Prevalence of potential drug interactions in an Iranian general hospital. Indian J Pharm Sci 2012; 74: 75-9.

15. DRUG-REAX® System. (n.d.). Retrieved on January 20, 2015, from http://thomsonhc.com. Greenwood Village, CO: Thomson Micromedex. Available at: http://truvenhealth.com/products/ micromedex

16. Bhagavathula AS, Berhanie A, Tigistu H, et al. Prevalence of potential drug–drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. Asian Pac J Trop Biomed 2014; 4: S204-8.

17. Cruciol-Souza JM, Thomson JC. Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. J Pharm Pharm Sci 2006; 9: 427-33.

18. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish prescribed drug register. Drug Saf 2007; 30: 911-8.

19. Köhler G, Bode-Böger S, Busse R, et al. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 2000; 38: 504-13.

20. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med 2015; 13: 74.

21. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ 2015; 350: h1059.

22. Ismail M, Iqbal Z, Khattak MB, et al. Potential drug–drug interactions in internal medicine wards in hospital setting in Pakistan. Int J Clin Pharm 2013; 35: 455-62.

23. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 2003; 163: 1409-16.

24. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005; 293: 1197-203.

25. Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. Frequency and nature of drug–drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009; 68: 187-93.

26. Glintborg B, Andersen SE, Dalhoff K. Drug-drug interactions among recently hospitalised patients–frequent but mostly clinically insignificant. Eur J Clin Pharmacol 2005; 61: 675-81.

27. Fokter N, Možina M, Brvar M. Potential drug-drug interactions and admissions due to drug-drug interactions in patients treated in medical departments. Wien Klin Wochenschr 2010; 122: 81-8.

28. Egger SS, Drewe J, Schlienger RG. Potential drug–drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58: 773-8.

29. Polk RE. Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med 1989; 87: S76-81.

30. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Int J Cardiol 2005; 98: 1-14.