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Exposure to potential drug-antimicrobial agent interactions in primary health care

Izloženost potencijalnim lek-antimikrobni agens interakcijama u primarnoj zdravstvenoj zaštiti

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Abstract

Background/Aim. Drug-drug interactions involving antimicrobials present important and often unrecognized complications of pharmacotherapy which can be prevented. The aim of the present study was to identify the frequency and type of potential drug-antimicrobial agent interactions among outpatients and to define recommendations for their management. **Methods.** Cross-sectional prescription database study was conducted. The analysis randomly included 823 patients who visited Health Center Novi Sad over 1-month period (November 1–30, 2011) and had prescribed ≥ 2 drugs where at least one drug was antimicrobial agent for systemic use. All interacting drug combinations involving antimicrobials were identified according to Drug Interaction Facts. Additionally, based on the compendium, potential interactions were classified into categories: pharmacological mechanisms, potential clinical outcomes and management advice. **Results.** Overall, 88 potential clinically significant drug-antimicrobial agent interactions were identified among 69 (8.4%) exposed outpatients [the mean age 61.7 years (SD ± 15.4); the mean number of prescribed drugs 7.5 (SD ± 2.9); 56.5% females]. The most common identified potential interacting pairs were benzodiazepines undergoing oxidative metabolism and clarithromycin or erythromycin, and aminophylline and ciprofloxacin. In 83.0% of all cases underlying mechanism was pharmacokinetic involving primary inhibition of metabolic pathways mediated by CYP3A4 and CYP1A2 isoenzymes. Excessive sedation (22.7%), cardiotoxicity (20.5%), miscellaneous aminophylline adverse effects (13.6%), and bleeding (10.2%) were the most frequently implicated potential clinical outcomes. Risk for adverse interactions could be managed by close monitoring of simultaneous administration of drugs (37.5%), different risk-modifyng strategies (31.8%), and avoiding combinations (30.7%). **Conclusion.** Among outpatients, there was common potential for clinically significant interactions involving antimicrobials. Information based on the results of the present study could be integrated in existing computerized physician order entry system in the Health Center as a form of clinical support.

Key words:
drug therapy; anti-bacterial agents; drug interactions; outpatients; adverse drug reaction reporting systems; pharmacovigilance.

Apstrakt

Uvod/Cilj. Interakcije antimikrobnih lekova predstavljaju važne i često neprepoznate komplikacije farmakoterapije koje mogu biti prevenirane. Cilj prezentovane studije bio je da se identifikuje učestalost i tip potencijalnih interakcija antimikrobnih lekova kod ambulantnih bolesnika, i da se definišu preporuke za kontrolu istih. **Metode.** Sprovedena je studija preseka koristeći bazu podataka o propisanoj terapiji. U analizu je randomizacijom uključeno 823 bolesnika (propisana ≥ 2 leka a najmanje jedan lek bio je antimikrobni agens za sistemsku upotrebu) koji su posetili Dom zdravlja Novi Sad tokom jednomesečnog perioda (1–30. novembar 2011). Sve interakcije antimikrobnih lekova su identifikovane saglasno *Drug Interaction Facts*. Dodatno, bazirano na kompedijumu, potencijalne interakcije su klasifikovane u kategorije: farmakološki mehanizmi, potencijalni klinički ishodi, i preporuke za kontrolu. **Rezultati.** Ukupno, 88 potencijalnih, klinički značajnih lek-antimikrobni agens interakcija identifikovano je kod 69 (8,4%) izloženih bolesnika [prosečna starost 61,7

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godina (SD ± 15,4); prosečan broj propisanih lekova 7,5 (SD ± 2,9); 56,5% su bile žene]. Najzastupljeniji potencijalni interakcijski parovi bili su benzodiazepini koji se metabolizuju oksidacijom i klaritromicin ili eritromicin kao i aminofilin i ciprofloksacin. U 83% svih slučajeva u osnovi je bio farmakokinetski mehanizam interakcija uključujući primarno inhibiciju metaboličkih puteva posredovanu izoenzimima CYP3A4 i CYP1A2. Izražena sedacija (22,7%), kardiotoksičnost (20,5%), različite neželjene reakcije na aminofilin (13,6%), krvarenje (10,2%) bili su najčešće implicirani potencijalni klinički ishodi. Rizik za neželjene interakcije mogao je biti kontrolisan pažljivim monitoringom uporedne upotrebe lekova (37,5%), različitim strategijama za modifikaciju rizika (31,8%), i izbegavanjem kombinacija (30,7%). **Zaključak.** Kod ambulantnih bolesnika postojao je značajan potencijal za klinički važne interakcije antimikrobnih lekova. Informacije bazirane na rezultatima istraživanja mogle bi biti integrisane u postojeći sistem za elektronsko propisivanje kao vid kliničke podrške.

Ključne reči:
lečenje lekovima; antibiotici; lekovi, interakcije; ambulantno lečenje; lekovi, neželjeno dejstvo, sistemi za izveštavanje; farmakovigilanca.

Introduction

It is well known that adverse drug interactions (ADIs) involving antiinfective agents can be complication of pharmacotherapy. Thus, according to the World Health Organization Global Individual Case Safety Report (WHO Global ICSR) database, during the past 20 years, among the 15 most frequently reported adverse drug interacting combinations, 4 included antimicrobials [1]. Molden and Andersson [2] described two men with rhabdomyolysis, who received simvastatin 80 mg/day and who were hospitalized after the completion of short-term treatment with macrolide antibiotics (clarithromycin and erythromycin). Flockhart et al. [3] reported on the case of a 27-year-old man who experienced a prolonged QT interval and sudden cardiac death two days after coadministration of pimozide and clarithromycin. Additionally, reports on fatal *torsades de pointes* induced by terfenadine during its coadministration with ketoconazole or erythromycin contributed to the withdrawal of terfenadine from the United States market [4]. Also, antimicrobials can lead to a reduction or loss of therapeutic efficacy of concomitantly used drugs. Thus, ketoconazole affects formation of clopidogrel active metabolite causing reduced inhibition of platelet aggregation [5]. Also, bioavailability of tetracyclines and quinolones can be significantly reduced in presence of aluminium, magnesium or calcium-containing antacids [6, 7].

Besides safety aspect, interactions are important because they are often avoidable or preventable adverse drug events (ADEs). Thus, Juurlink et al. [8] estimated that at least 3.3% of hospital admissions due to hypoglycemia was caused by concomitant using of glibenclamide and cotrimoxazole, so as at least 2.3% of hospitalizations because of digoxin toxicity during its coadministration with clarithromycin could be prevented. The basis for the prevention of ADIs is possession of knowledge or possibility to predict situations when simultaneous administration of drugs presents risk for drug-mediated toxicity or therapeutic failure.

In literature a large number of interactions of antimicrobial drugs are listed and several reviews describe the ones which are clinically relevant [9, 10]. More specific, Spriet et al. [11] gave overview of significant CYP450-mediated interactions involving antiinfective agents and drugs frequently received in the Intensive Care Unit (ICU) and Becker [12, 13] described adverse interactions of antibiotics commonly used in dental practice while Tey et al. [14] reported on drug interactions with often prescribed antimicrobials in dermatological practice. However, differences in morbidity structure or complexity of healthcare contribute to specificity of study findings [15]. Hence, as intention to improve the safety of pharmacotherapy in the Health Center, the primary aim of this study was to identify the frequency and type of clinically significant potential drug-antimicrobial agent interactions among outpatients and to define recommendations for their control subsequently based on these local reports.

Methods

The Ethics Committee of the Health Center Novi Sad (HCNS), Novi Sad, Serbia approved the protocol of the present study.

Study design and data collection

The prevalence and type of potential drug-antimicrobial agent interactions among outpatients at the HCNS were analyzed in the cross-sectional, single-center study. HCNS provides primary health care for population of approximately 340,000 people living in Novi Sad, the administrative seat of the northern Serbian province Vojvodina. Medical care is offered to outpatients within 45 Basic Health Units (BHUs) involving health promotion and education, prevention and early management of health problems as well as curative care. The study was carried out using data from all BHUs.

HCNS possesses a health information system certified by the European Institute for Health Records. Computerized medical record contains all relevant facts about patient and his/her therapy. Hence, study data were obtained from the electronic prescription database and their collection was done automatically by the computer server administrator. Data collection was described in detail by Nikolic et al [16]. In brief, there was no access as well as direct manipulation of the healthcare data by researchers, and strict registration routines and access controls support the security and accuracy of information involved in the electronic dataset. Prescription records referred to all reimbursed drugs by National Health Service, according to the List of drugs prescribed and dis-

pensed under the mandatory health insurance scheme, and database did not include information on *over-the-counter* (OTC) drugs. For the purpose of the study, the following data were selected from medical documentation: year of birth and patient's sex, prescribed drugs and date of their prescribing, dose regimen, quantity (number of prescribed packs) and route of the administration. Drugs were coded according to Anatomical Therapeutic Chemical (ATC) classification system as recommended by the WHO [17].

Medical records of drug users in the HCNS during one-month observed period (November 1–30, 2011) were recruited to the study if patients had been prescribed two or more than two drugs where at least one of medicines was antibacterial for systemic use. Two researchers (BN and DR) were responsible for determination of subjects eligible for inclusion in the study. For each outpatient was assumed that using of medicines started at the same day when the medicine was prescribed and the duration of therapy for each medicine was calculated in days by multiplying a daily dose by the number of daily doses contained in the prescribed packs. Potential for the drug-antiinfective agent interactions was studied when the exposure period for two medicines overlapped. Overlapping was defined as the presence of at least a day of co-prescription of two medicines. This definition is consistent with previous studies using administrative claims databases, evaluating the exposure of patients to potential drug-drug interactions (DDIs) rather than clinically manifest DDIs and their relative severity [18, 19]. Furthermore, monitoring of one-day overlap in therapy is beneficial in the cases when clinical effects are evident within 24 hours of administration of the interacting drugs (e.g. diazepam and clarithromycin, ciprofloxacin and iron salts) and when immediate action is necessary to avoid the effects of the interaction [20].

Interacting combinations not involving antibacterial agents were not considered in the study.

Identification and analysis of potential drug-antimicrobial agent interactions

Potential drug-antimicrobial agent interactions were identified and classified according to the *Drug Interaction Facts* (DIFs) [20]. In the compendium, based on the Editorial Group's assessment of interaction severity (the magnitude of the effect of a drug interaction) and documentation (the quality and clinical relevance of the primary literature supporting the occurrence of an interaction), significance rating was assigned by number 1 through 5 to each interaction monograph. In the current study, interactions ranked as 1 and 2 were considered as potentially harmful and therefore clinically relevant. According to the compendium, these interactions have a reasonable probability of occurrence (proven to occur in well-controlled studies; or, very likely but not proven clinically; or may occur, they are some good data, but more studies are needed); their effects are potentially life-threatening or capable to cause permanent damage (significance rating 1); or, may cause a deterioration in patient's clinical status, hence additional treatment, hospitalization, or an extended hospital stay may be necessary (significance rating 2) [20]. For each subject exposed to overlapping prescriptions, all pairs of drug combinations were analysed for interacting potential by two independent researchers (BN and DR). In the case of disagreement among assessors, evaluation of potential drug-antiinfective agent interaction was discussed until consensus view was achieved. The assessment of interrater agreement (determined before a consensus was reached) indicated acceptable consistency among observational ratings (kappa, 0.76; 95% confidence interval – 0.50 to 1.00).

Additionally, the drug-antimicrobial agent interactions were classified in "pharmacological mechanisms", "potential clinical outcomes" and "management advice" categories. The DIFs provide textual information about these parameters for each interaction. The compendium text was converted into aforementioned categories by three researchers (BN, JP, MB). Differences in classification were resolved by discussion. Interrater agreement (based on the estimation before a consensus was reached) was substantial for "pharmacological mechanisms" (kappa, 0.82; 95% confidence interval – 0.73 to 0.91), "potential clinical outcomes" (kappa, 0.95; 95% confidence interval – 0.91 to 0.99) as well as "management advice" (kappa, 0.76; 95% confidence interval – 0.66 to 0.86).

Statistical analysis

Descriptive statistics was used to describe patient characteristics. The mean and standard deviation were calculated for age and number of prescribed drugs, while proportion was calculated for sex. The selected sample for analysis was divided into two different groups, thus subjects with ≥ 1 potential drug-antimicrobial agent interaction were in the exposed group and those without potential drug-antimicrobial agent interaction were in the unexposed group. Intergroup differences in the continuous variables, age and number of drugs, were assessed applying nonparametric Mann-Whitney U test because they failed to show a normal distribution. A categorial variable, sex, was compared using χ^2 test of independence. Parameters of potential interactions (pIs) ("pharmacological mechanisms","potential clinical outcomes", and "management advice") were evaluated by absolute and relative frequencies. For all of tests, p value < 0.05 was considered as statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) 20.0 software.

Sample size calculation was based on assumption on 10% exposure to pIs (variable derived from a small pilot study conducted within our population). Standard tabular values of 95% confidence limit factors for estimate of a Poisson-distributed variable were used to assist in carrying out this computation [21]. Thus, 800 outpatients (95% confidence interval, 384 to 1472) were needed for study to be confident. Additionally, calculated size was increased by 3% to account for potential losses.

Results

During the study period medication records for 823 patients were analysed, the mean age of subjects was 50.8 years (SD ± 23.3) ranged from 1 to 94 years, 520 (63.2%) were

females, and the average number of prescribed drugs was 4.7 (SD ± 2.6). Overall, 88 clinically significant potential drug-antiinfective agent interactions were identified among 69 (8.4%) outpatients. Exposed subjects were significantly older ($p < 0.01$) and they had more complex therapeutic regimen ($p < 0.01$), while risk for occurrence of pIs was not in line with patient sex ($p = 0.285$), (Table 1). The average number of interactions involving antibacterials per exposed patients was 1.3 (ranged 1–5), and 56 subjects had 1, and 13 subjects ≥ 2 pIs.

Potential drug-antimicrobial interactions

In total, 31 different interacting combinations were identified, the most common pIs were benzodiazepines undergoing oxidation and clarithromycin or erythromycin and aminophylline and ciprofloxacin (Table 2). The proportion of pIs involving antimicrobials was 44.3% for macrolides, 33.0% for quinolones, 9.1% for azole antifungals, 5.7% for aminoglycosides, 4.5% for penicillins, 3.4% for cephalosporins, and 2.3% for tetracyclines.

Pharmacological mechanisms

The reported mechanisms for pIs were classified as pharmacodynamic (11.4%), pharmacokinetic (83.0%), a combination of both types (2.3%) and unknown (3.4%). Pharmacodynamic pIs were in line with potentiation of pharmacological effects while pharmacokinetic pIs were associated primarily with inhibition of metabolic pathways mediated by CYP3A4 and CYP1A2 isoenzymes (Table 3).

Potential clinical outcomes

In 89.8% of cases there was an increased risk for ADEs including excessive sedation (22.7%), cardiotoxicity (20.5%), miscellaneous adverse effects of aminophylline (13.6%), bleeding risk (10.2%), miscellaneous adverse effects of corticosteroids (8.0%), etc. (Table 4). The potential for decreased effectiveness of antiinfective agents was reported in the 12.5% of cases (Table 4).

Table 1

Patient general characteristics according to exposure to potential drug-antimicrobial agent interactions

Characteristics	Exposed (n = 69)	Unexposed (n = 754)	*p* value
Age (years), median (IQR)	67.0 (19.0)	56.0 (33.0)	< 0.001
Female, n (%)	39 (56.5)	481 (63.8)	0.285
Number of prescribed drugs, median (IQR)	7.0 (4.0)	4.0 (3.0)	< 0.001

IQR – interquartile range; *p* value < 0.05 was considered as statistically significant.

Table 2

The most common potential drug-antimicrobial agent interactions

Drug combination	pIs, n (%)
BZs (diazepam, alprazolam)/clarithromycin or erythromycin	17 (19.3)
Aminophylline/ciprofloxacin	12 (13.6)
CCBs (verapamil, diltiazem)/ clarithromycin	7 (8.0)
Digoxin/clarithromycin or azithromycin	5 (5.7)
Iron salts/ciprofloxacin or norfloxacin or levofloxacin	5 (5.7)
Antiarrhythmic agents (amiodarone, sotalol)/levofloxacin	5 (5.7)
Methylprednisolone/clarithromycin	4 (4.5)

pIs – potential interactions; BZs – benzodiazepines; CCBs – calcium channel blockers.

Table 3

Overview of pharmacological mechanisms for identified drug combinations

Overall mechanism	Mechanisms	pIs, n (%)
Pharmacodynamic	Additive pharmacological effect	10 (11.4)
Pharmacokinetic	Drug absorption[a]	7 (8.0)
	Drug metabolism[b]	55 (62.5)
	Drug excretion[c]	8 (9.1)
	Other[d]	3 (3.4)
	Pharmacokinetic (total)	73 (83.0)
Pharmacodynamic/pharmacokinetic		2 (2.3)
Unknown		3 (3.4)

pIs – potential interactions; [a]Drug absorption: chelation (6 pIs), high gastric pH (1 pIs); [b]Drug metabolism: CYP3A4 inhibition (36 pIs), CYP3A4 induction (1 pIs), CYP1A2 inhibition (17 pIs), CYP2C9 inhibition (1 pIs); [c]Drug excretion: P-glycoprotein (Pgp) inhibition (5 pIs), glomerular filtration reduction (2 pIs), competition for organic anion transporter (1 pIs); [d]Drug absorption/drug metabolism combination:Pgp/CYP3A4 inhibition (3 pIs).

Table 4

Potential clinical outcomes for drug-antimicrobial agent interactions

Overall risk	Risks	pIs, n (%)
Increased risk for ADEs	Bleeding risk	9 (10.2)
	Cardiotoxicity	18 (20.5)
	Excessive sedation	20 (22.7)
	Corticosteroids adverse effects	7 (8.0)
	Aminophylline adverse effects	12 (13.6)
	ABs adverse effects	3 (3.4)
	Antipsychotics adverse effects	3 (3.4)
	Other	7 (8.0)
	Increased risk for ADEs (total)	79 (89.8)
Risk for decreased effectiveness	Failure of ABs effectiveness	11 (12.5)

pIs – potential interactions; ADEs – adverse drug events; ABs – antimicrobials; * Percentages do not add up to 100% because one pI could have multiple clinical outcomes.

Table 5

Advised management strategies for drug-antimicrobial agent interactions

Overall recommendation	Recommendations	pIs, n (%)
Monitoring	Clinical monitoring of toxicity	22 (25.0)
	Monitoring of physiological markers[a]	11 (12.5)
	Monitoring (total)	33 (37.5)
Adjust dose as needed		33 (37.5)
Avoid combination		27 (30.7)
Risk-modifying strategy	Separate administration	6 (6.8)
	Therapeutic alternative	20 (22.7)
	Supplements	2 (2.3)
	Risk-modifying strategy (total)	28 (31.8)
Contraindicated combination		1 (1.1)

pIs – potential interactions; [a]Monitoring of physiological markers: serum creatinine (2 pIs), coagulation parameters (9 pIs); *Percentages do not add up to 100% because one pI could have multiple management advice.

Management advice

To control the ADI risk, common recommendation was monitoring of simultaneous administration of drugs (37.5%) and in that case advice also included dose adjustment as needed (37.5%). Additionally, frequent advice were to avoid combination (30.7%) as well as different risk-modifying strategies (31.8%), and as a part of latter, significant proportion related to the choice of therapeutic alternative (22.7%) (Table 5).

Discussion

In the study, of the 823 patients included, 69 (8.4%) were exposed to a risk for the clinically significant ADIs involving antimicrobial agents. In the literature there is a lack of reports about frequency of these type of pIs. One study was conducted in the Netherlands among home-dwelling patients aged ≥ 75 years who used ≥ 4 drugs and the prevalence of pIs involving antiinfectives for systemic use was 14.3% [22]. Lower prevalence of pIs in our study could be explained by general characteristics of study population, given that outpatients in the HCNS were younger (50.8 *vs* 81 years in the Dutch study) and had less number of prescribed drugs on average (4.7 *vs* 6.8 medicines, respectively). According to the results of previous studies, both variables contribute to a greater risk for exposure to pIs [23–25]. Further comparison is difficult with regard that the primary aim of the Dutch study was to determine the nature, volume and clinical relevance of prescription-related points of attention in the main ATC groups and there were no more information in line with prescriptions of anti-infectives for systemic use.

In the present study, the proportion of potential benzodiazepine and macrolide interactions was the most frequent (17 cases), thus co-administration of diazepam and clarithromycin, alprazolam and clarithromycin, and diazepam and erythromycin represented an increased risk for excessive sedation. Reis' et al. [26] study showed that excessive sedation was ADE which was most frequently related to clinical manifestations of DDIs in the ICU, and among others, it was caused by administration of the interacting pair midazolam and clarithromycin. Benzodiazepines metabolized by oxidation were recognized as substrates of CYP3A4 isoenzyme, and macrolide antibiotics can inhibit their metabolism [20]. However, Yeates et al. [27] reported that azithromycin did not affect midazolam metabolism. Hence, to prevent the risk, it is necessary to caution patients about over-sedation and to reduce the benzodiazepine dose as needed, or, to consider the use of benzodiazepines metabolized by conjugation (e.g.

lorazepam), which are unlikely to interact, or, to take into consideration azithromycin as therapeutic alternative for erythromycin and clarithromycin. To facilitate health professionals detection of pharmacokinetic interactions as well as interventions for reducing adverse events, numerous information about CYP450 substrates, inhibitors and inductors could be implemented in CYP450-based software [28].

In the study, among commonly reported pIs, there was the interaction between aminophylline and ciprofloxacin (12 cases). The inhibitory effects of quinolones on aminophylline metabolism were mediated by CYP1A2 isoenzyme [20]. But, among quinolones there were significant differences in pharmacokinetic features. Thus, enoxacin was the most potent inhibitor of theophylline metabolism (reduced clearance by more than 50%), pipemidic acid, ciprofloxacin and pefloxacin reduced theophylline clearance to a smaller extent (approximately 20% to 30%), norfloxacin, ofloxacin and nalidixic acid had minimal effects [29]. Finally, there was no pharmacokinetic interaction between orally administered levofloxacin and intravenously administered theophylline [30]. When theophylline toxicity was studied in a 19-year period concomitant drug and/or substance exposure was positive in 87.8% of patients admitted to the Department of Emergency Medicine, and antimicrobials were among commonly co-administered medicines [31]. The choice of therapeutic alternative without or with a limited potential for interaction with theophylline as well as monitoring its plasma concentration and clinical response can prevent adverse effects. However, considering an intermittent contact and an infrequent communication between clinicians and patients in primary health settings, it is very important to advise patients to report unexplained abdominal pain, nausea, vomiting, tachycardia, palpitations, headache or insomnia.

In the current study, antimicrobial drugs (benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, and fluconazole) had potential for interactions with warfarin (9 cases; 10.2% of all pIs) increasing the risk of bleeding. Thus, co-administration of specified antibiotics or oral azole antifungals and warfarin were considered as indicator of a high risk when prescribed in primary care patients because of the consistency in article reportings about clinically significant bleeding [32]. Macrolides, quinolones and metronidazole were defined as interacting antibiotics. Furthermore, according to the data on spontaneous reported ADEs to the WHO Global ICSR database decreased prothrombin level, increased International Normalized Ratio (INR), and haematuria, there were commonly noted adverse events during administration of interacting combinations involving warfarin and antimicrobials [1]. There were several pharmacodynamic and pharmacokinetic factors which may potentiate warfarin's effect. Thus, beta-lactams modifying gut flora reduced endogenous vitamin K production, additionally penicillins induced inhibition of adenosine diphosphate-mediated platelet aggregation [20, 33]. Fluconazole was identified as an inhibitor of CYP2C9 isoenzyme which mediated in oxidative biotransformation of S-enantiomer of warfarin [20, 34]. The R-enantiomer of warfarin was metabolised by CYP1A2 and CYP3A4 and quinolones (ciprofloxacin, enoxacin, norfloxacin) inhibited CYP1A2 while macrolides (clarithromycin, erythromycin) and azoles (fluconazole, itraconazole, ketoconazole, miconazole) inhibited CYP3A4 activity [20]. Hence, if combined using of interacting drugs cannot be avoided, it is necessary to monitor anticoagulant activity more frequently when starting or discontinuing antiinfective agent, and to adjust the warfarin dose accordingly. The reported fact should be taken into account. One of the most common reasons for preventable drug related hospital admissions was overdosing of oral anticoagulants due to the lack of the INR monitoring at patients known to be hard to control or following introduction of an antibiotic [35].

In the HCNS, increased risk for cardiotoxicity was among the most prevalent potential clinical outcomes (20.5% of all cases), adverse interacting combinations were digoxin and clarithromycin, digoxin and azithromycin, amiodarone and levofloxacin, sotalol and levofloxacin, verapamil and clarithromycin, and diltiazem and clarithromycin. Just, interacting drug pair digoxin and clarithromycin was the second most frequently reported combination with adverse effects to the WHO Collaborating Center for International Drug Monitoring, the study covered reports from January 1990 to February 2010 [1]. To control the ADIs, if possible, the administration of these drug pairs should be avoided or patients should be monitored more frequently and guidance about possible adverse effects should be provided. Generally, in ambulatory care, cardiovascular events are among the most frequent type of ADEs and among the most preventable or ameliorable events, 18% and 18% (the denominator is the total number of patients taking the medications), respectively [36].

Besides increased risk for the ADEs among outpatients, there was a risk of decreased effectiveness of antibiotics, mainly because of potential for the formation insoluble chelates of quinolones and iron salts as well as tetracyclines and calcium salts. Iron reduced the mean bioavailability of ciprofloxacin 64% in 12 healthy men [37]. Similarly, a study of 8 volunteers demonstrated 55% of a decrease in urinary excretion of norfloxacin 400 mg taken with ferrous sulfate 300 mg, suggesting a reduction in norfloxacin bioavailability [38]. Tetracycline absorption may be decreased by more than 90% by its chelation with calcium salts [6]. Hence, separate administration of these agents is recommended as long as possible, at least 2 hours.

The present study has some limitations. Using outpatient prescription database which did not include information on OTC product prescriptions (e.g. iron salts, zinc salts, antacids, ibuprofen) could contribute to underestimating the prevalence of pIs. Additionally, in relation to the methodology, one source of drug interaction checking was used, and it could lead to a less sensitive identification of drug pairs minimizing the possibility for detection DDIs. For example, combination of the ACE inhibitors or angiotensin receptor blockers and co-trimoxazole was not listed in the compendia and therefore it was not considered in the present study, but it elevates a risk for hospitalization in older adults [39]. On the other hand, the lack of information about compliance could lead to the overestimation of the prevalence of pIs. In addition, information on physician advice for the ADIs control was not captured. For example, the risk for exposure could

be avoided in case when it was recommended to separate administration of iron salts and fluoroquinolones.

Authors did not focus on clinically manifested drug-antimicrobial interactions. It would be interesting for further research to consider common percentage of outpatients exposed to pIs involving antiinfective agents. Additionally, in the present study frequently reported interacting combinations (benzodiazepines and clarithromycin, digoxin and clarithromycin, aminophylline and ciprofloxacin, calcium channel blockers and clarithromycin, warfarin and antimicrobials) were listed in recent literature as risk factors associated with pharmacotherapy problems. Considerable frequency of pIs as well as strong epidemiological evidence about risk co-prescription of antimicrobials pointed out the importance of interactions with this drug class using for short-term intercurrent diseases.

In spite of its limitations, our study discussed the prevalence and type of potential drug-antimicrobial agent interactions in primary medical care which could cause a deterioration in a patient's clinical status. For assessment of interacting combinations, the parameters as quality of evidence, rating of clinical significance, pharmacological mechanisms, clinical outcomes and management strategies were considered. By evaluation of these features for each potential interaction, we got the set of information which could be the base for taking measures to their prevention and consequently reduction of harming the patient.

Conclusion

The current study showed that among outpatients there was a common potential for clinically significant interactions involving antimicrobials. Antiinfective agents could contribute to overdosing of co-administered drugs frequently used in primary health care (benzodiazepines, calcium channel blockers, digoxin, corticosteroids, aminophylline), primarily by inhibition of their metabolic pathways mediated by CYP3A4 and CYP1A2 isoenzymes. On the other hand, the efficacy of certain antibiotics (quinolones, tetracyclines) could be compromised. From a clinical perspective, there are opportunities to improve primary care prescribing associated with drug-antimicrobial interactions related to close monitoring of simultaneous administration of drugs, different risk-modifying strategies and avoiding hazardous combinations. Information based on the results of the present study could be integrated into existing computerized physician order entry system in the Health Center as a form of clinical support.

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