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Study of Potential Drug-Drug Interactions in Prescriptions of University-Based Pharmacies

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ABSTRACT

***Background*:** Drug-Drug Interactions (DDIs) are adverse reactions caused by a combination of drugs; they are often predictable and therefore avoidable or manageable. The objective of this study was to evaluate the nature, type and prevalence of potential DDIs in prescriptions dispensed in university-based community pharmacies in Tehran, Iran.

Methods: From July 2012 to February 2014, sample of 1260 prescriptions were collected from community and outpatient hospital pharmacies affiliated to Tehran University of Medical Sciences (TUMS), Iran. The prescriptions were assessed using the reference text "drug interaction facts". The identified DDIs were categorized according to their level of significance into three classes (minor, moderate, major).

Results: At least one drug-drug interaction was present in 339 (26.9%) of prescriptions and a total of 751 cases of interactions were found in prescriptions. Major DDIs represented 7.3% of all DDIs detected, whereas moderate DDIs were 75% of all DDIs. The mean number of drugs per prescriptions was 3.2, with a median of 4 (range, 2-10).There was a positive association between number of prescribed drugs and occurrence of DDIs (OR: 2.14, 95% CI: 1.9-2.4). The prescriptions of medical specialist had greater risk of occurrence of moderate severity DDIs than general practitioners (OR: 1.52, 95%CI: 1.08-2.15).

Conclusion: Despite the prescriptions were collected from university-based pharmacies, but the overall prevalence of potential DDIs were high among patients. Physicians should be aware of potentially harmful DDIs. Meanwhile Pharmacists can contribute to the detection and prevention of drug-related injuries. Appropriate education, collaborating drug selection and pharmaceutical care are strongly recommended for physicians and pharmacists.

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Introduction

Treatment of a disease with multiple symptoms usually requires prescribing more than one drug. The possibility of Drug- Drug Interactions (DDI) should be considered by health care professionals in this case (1). DDIs account for 5-26% of all adverse drug events (2) and causing roughly 2.8% of all hospitalizations especially in elderly and representing an estimated cost of more than one billion USD per year to health care systems (3-5). Thus, handling DDIs could enhance patient safety and reduce costs.

Different factors are associated with the occurrence of potential DDIs. Polypharmacy is now common and carries a high risk of DDIs and drug-disease interactions (6). Several studies were performed in Iran regarding the potential DDI especially on physician prescriptions. These studies were carried out in different settings. Study by Ahmadizar et al.,(7) on 28956638 prescriptions in 2007 revealed that 0.77% of prescriptions had DDIs, out of them 0.67% had significant clinical importance. Other studies, usually in community setting reported a prevalence rate of 8.5-42% for potential DDIs (4, 8-12). The purpose of this study was to gain an overview of the frequency and nature of DDI in university based pharmacies which were affiliated to Tehran University of Medical Sciences (TUMS). These pharmacies distributed in different region of Tehran city and provide patient's medication needs.

Methods

A prospective descriptive cross-sectional study was conducted on overall 1260 prescriptions of six community pharmacies and two outpatient hospital pharmacies (Shariati and Imam Khomeini hospital), affiliated to Tehran University of Medical Sciences (TUMS). All prescriptions from July 2012 to February 2014 were analyzed.We performed one month pilot study on prescriptions, from 270 of analyzed prescriptions, 56 of them had potential DDIs, and so we calculated a sample size of 1260 prescriptions for this study.

Prescriptions with two or more prescribed drugs were selected and data were extracted on predesigned forms including patient characteristics (age, gender), the number of prescribed drugs, physician specialty (General Practitioners (GPs) or medical specialist) and severity and significance of drug interactions.

In this study the extent of occurrence and frequency of potential drug interactions were analyzed based on the reference text "Drug Interaction Facts ". This particular reference was used because of its extensive and unique classifications of drug interactions. Whenever the data were not found in Drug Interaction Facts, we used Lexicomp on desktop drug interaction software (Lexicomp, Inc., Ohio, USA). DDIs were sorted by clinical relevance. Drug interactions are rated mild when they are not of clinical importance, or the effect of the interaction has not yet been established. Moderate interactions can cause possible changes in the therapeutic effects, or may cause adverse effects, but can be avoided adjusting the individual drug doses. A major DDI is defined as drug interactions, which can cause potential adverse effects; individual dose adjustment is difficult in these cases. Potential DDIs are defined as the moderate and major drug interactions.

Statistical analysis

Demographic data of patients and other data of prescriptions were presented as mean± standard deviation and percentage. Independent sample t-test and chi-square were applied to assess differences among groups. In the multivariate analysis, all variables with a p-value <0.05 and all confounding variables were incorporated into the model. The data were controlled for gender, age and number of drugs. The odd ratio (OR) and respective confidence interval (CI) was calculated in the multivariate analysis for each variable. A P-value <0.05 was considered statistically significant. The data were processed using SPSS software version 18.0.

Results

From July 2012 to February 2014, 1260 prescriptions were investigated for the identification of potential drug-drug interactions. Of total prescriptions, 160 of them (12.7%) were collected from outpatient hospital pharmacies and the remaining from community pharmacies (87.3%). Most patients were between 28 and 97 years old of age (mean age: 43.11±21.5) and female (56.1%). No statistically significant differences were found between men and women regarding DDIs (P: 0.18). There was a significant association between age and potential DDIs (P<0.001), for every five years increment in age, risk of DDIs increase 1.014 (OR: 1.014; 95% CI: 1.008-1.020).The number of concomitant prescription medications ranged from 2 to 10 (mean: 3.2) and 34.1% of patients took more than four drugs.

Among the prescriptions analyzed, 339 (26.9%) of them had at least one drug interaction case. A total of 751 cases of interactions were found in prescriptions. The prevalence of major DDIs was 7.3% (55/751 cases). Table 1 represents the frequency of interaction severity.

From 160 prescriptions retrieved from outpatient hospital pharmacies, 142 of them had DDIs, which 74.6% were moderate severity interactions. Out of 609 DDIs in community pharmacies, 457 (75%) of them were moderate DDIs based on Table 2.

No statistically significant differences were found regarding the presence/ absence of potential DDIs between community pharmacies and hospital pharmacies (P: 0.07); however, community pharmacies prescriptions had greater risk of potential DDIs compared to hospital

Table 1. Frequency of interaction severity in prescriptions retrieved from all pharmacies.

Interactions Type	Number of interactions	Percentage of interactions
Minor	133	17.7%
Moderate	563	75%
Major	55	7.3%
Sum	751	100

Table 2. Frequencies of drug interactions in community and hospital pharmacies.

Setting	Community pharmacies		Outpatient hospital pharmacies	
Interactions	Number	Percentage	Number	Percentage
Minor	103	16.9	30	21.1
Moderate	257	75	106	74.6
Major	49	8	6	4.2
Sum	609	100	142	100

pharmacies (OR: 1.78; 95% CI: 1.27-2.51).

Figure 1 show the prevalence of drug interactions between GPs and medical specialists. A total of 286 prescriptions belonged to GPs and 931 prescriptions to medical specialists. 72 cases (25.2%) of GPs prescriptions and 291 cases (31.3%) of medical specialist had at least one drug interactions. The difference between groups was not significant regarding major and minor DDIs (P: 0.1, P: 0.9 respectively), but prescriptions of medical specialist had statistically significant more moderate DDIs than GPs (P: 0.009).

The percentage of moderate severity DDIs was 16% in GP's prescriptions compared to 23% in medical specialist, the difference was significant (P: 0.018). The prescriptions of medical specialist had greater risk of occurrence of moderate severity DDIs (OR: 1.52; 95% CI: 1.08-2.15).

Figure 2 shows the frequency number of drug items per prescriptions, 2 drugs per prescription were most prevalent (n=445, 35.3%); average number of item per prescriptions was 3.2. In both univariate and multivariate analyses, the number of drugs prescribed was significantly associated with potential DDIs (OR: 2.14; 95% CI: 1.9-2.4) (P<0.001).

Fifty nine (59) active substances accounted for 53 pairs of major potential DDIs, classified on drug A and drug B. The drugs of group A most involved in major potential DDIs were nortriptyline (13.2%), methotrexate (9.5%) and bupropione (7.5%). Drugs acting on the Central Nervous System (CNS) account for 43.4% of potential major DDIs, those acting on cardiovascular system (CVS) accounted for 14.1% and Non-Steroidal Anti Inflammatory Drugs (NSAIDs) accounted for 12.2% of major DDIs.

Discussion

In the present study, the prevalence of DDIs in prescriptions was almost 30%. This finding is in agreement with some studies which reported a rate of 30-40% of DDIs (13-15), but higher than the frequency of other studies in Iran (10, 12) and also in other countries (16, 17). This broad range of prevalence value may be partially explained by factors such as study design, methodology, definitions, and characteristics of the population, number of medications prescribed, and compendium of drug interactions (18, 19).

The mean number of prescription drugs was 3.2, which is in consistent with the National Committee of Rational Use of Drugs (NCRUD) report of 3.2 items per prescription (in 2007) (20); however, the number of items per prescription is still higher than the standard average of 1.3-2.1 items per prescriptions(21-23). There is a positive association between potential DDIs and increasing number of drugs prescribed. Approximately 34% of the patients were prescribed more than four drugs, which is similar to the frequencies reported in previous studies (30.4% to 50.5%) (24). An association between the number of drugs prescribed and the occurrence of potential DDIs was observed in Italy (25). The adjusted OR rose from 2.71 [95% CI 2.63-2.80] in patients using 3-5 drugs for chronic disease to 5.59 [95% CI 5.39-5.80] in those using six or more drugs. Based on our results, risk of potential DDIs has been increased 2.1 times with the addition of every drug. A strong association between the number of dispensed drugs and the probability of potential DDIs was also reported among outpatients in Sweden after adjustment for age and sex (26).

The majority of DDIs in our study had moderate

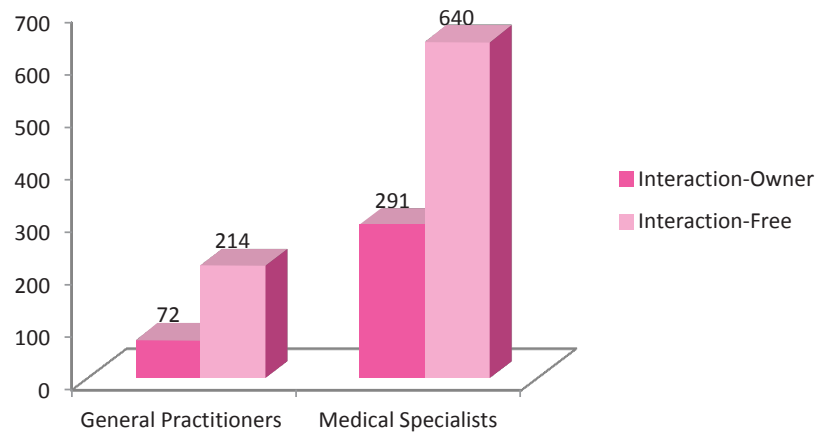

Figure 1. Frequency of prescribed drugs divided by physician's specialty.

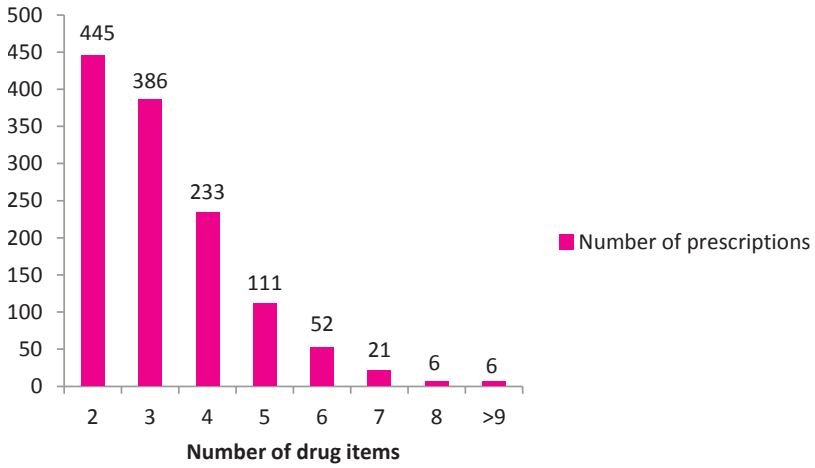

Figure 2. Number of drug items per prescriptions.

severity, accounting for 75% of all interactions observed regarding the settings. The prevalence of potential major DDIs was 7.3%. This finding is in agreement with other studies, which report values ranging from 3.8% to 16% for major DDIs (27, 28). Most of the moderate interactions need patient monitoring and can be avoided by adjusting the individual drug doses. But major DDIs are considered clinically important and should be avoided by health care professionals, especially physicians and pharmacists. Pharmacists in particular, should avoid dispensing combinations of drugs that may have serious DDIs (29).

Medical specialist's prescriptions in comparison with GPs had significantly more moderate severity interactions; the risk of occurrence of moderate DDIs was 1.52 in medical specialists' prescriptions. As we discussed, most of these type of interactions could be avoided by dose adjustment, medical specialist usually deal with more severe diseases and more efficacious drugs with lower therapeutic index, regular education of health care professionals about the importance of these type of interactions and prevention of them could be effective in reducing the prevalence of them.

No statistically significant differences were found between community pharmacies and outpatient hospital pharmacies, which is because of eight locations of sampling, only two of them were hospital pharmacies; therefore the risk of potential DDIs was higher in community pharmacies (OR:1.78). This result is not in consistent with the findings of other studies which reported a higher rate of interactions in hospital pharmacies than community pharmacies (30-32).

In the present study, no statistically significant differences were found between gender and DDIs, which is similar to findings of other studies (33) in different settings. The positive association between age and potential DDIs was consistent with other studies report; also we found a weak association between age and number of prescribed drugs, even though the correlation was significant (r= 0.096, P: 0.01).

The large number of active substances prescribed with potential DDIs, were those acting on the CNS (SSRIs, TCAs) (43.3%) which is in consistent with the finding described in previous studies (34, 35). The second class of drugs most involved were those acting on the cardiovascular system (diuretics, ACEI, beta blocker, calcium channel blockers), which is similar to findings described in studies carried out in different settings (14, 36). Nortriptyline and bupropione not only used as antidepressants, but also have other therapeutic indications and so are one of the most wildly CNS prescribed drugs. Most of the interaction of these two drugs in our study occurred in combination with other CNS drugs which increased the risk of toxicity and CNS side effects. Patients at high risk for developing serious adverse effects with these drugs should be closely monitored for signs and symptoms of the disease. Among CVS class, captopril in combination with allopurinol may increase the risk of hypersensitivity reaction (37). Aspirin interacting with warfarin increase the risk of bleeding (38). The prescriptions of these drugs in combination should always be analyzed according to risk/benefit ratio.

Facing the results of the current study, we can assume that the prevalence of potential DDIs among adults was high, whereas major DDIs occurred in a smaller proportion and within the rates reported in the literature. As the rate of moderate DDIs is relatively high in this study and considering this fact that this type of DDIs are preventable, providing strategies such as regular educational classes and workshop for physicians, adhering to correct policies of writing prescriptions, and being up to date on drug information may significantly reduce this type of interaction. Exposing patients to a greater number of prescription drugs, three or more, proved to be a significant predictor of DDIs. Therefore, reducing the number of prescribed drugs for patients whenever possible, or make a careful selection of therapeutic alternatives and close monitoring of patients could reduce the frequency of DDIs. Finally, collaboration of health care professionals with the pharmacist can contribute in early detection and prevention of DDIs and its related hazardous consequence.

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