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*Original Article*

# Incidence rate and pattern of clinically relevant potential drug-drug interactions in a large outpatient population of a developing country

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## *Abstract*

The objective of this study was to determine incidence rate, type, and pattern of clinically relevant potential drug-drug interactions (pDDIs) in a large outpatient population of a developing country. A retrospective, descriptive cross-sectional study was conducted on outpatients' prescriptions in Khorasan Razavi province, Iran, over 12 months. A list of 25 clinically relevant DDIs, which are likely to occur in the outpatient setting, was used as the reference. Most frequent clinically relevant pDDIs, most common drugs contributing to the pDDIs, and the pattern of pDDIs for each medical specialty were determined. Descriptive statistics were used to report the results. In total, out of 8,169,142 prescriptions, 6,096 clinically relevant pDDIs were identified. The most common identified pDDIs were theophyllines-quinolones, warfarin-nonsteroidal anti-inflammatory drugs, benzodiazepines-azole antifungal agents, and anticoagulants-thyroid hormones. The most common drugs contributing to the identified pDDIs were ciprofloxacin, theophylline, warfarin, aminophylline, alprazolam, levothyroxine, and selegiline. While the incidence rate of clinically relevant pDDIs in prescriptions of general practitioners, internists, and cardiologists was the highest, the average pDDI incidence per 10,000 prescriptions of pulmonologists, infectious disease specialists, and cardiologists was highest. Although a small proportion of the analyzed prescriptions contained drug pairs with potential for clinically relevant DDIs, a significant number of outpatients have been exposed to the adverse effects associated with these interactions. It is recommended that in addition to training physicians and pharmacists, other effective interventions such as computerized alerting systems and electronic prescribing systems be designed and implemented.

***Keywords:*** Drug-drug interactions; Drug utilization review; Patient safety; Developing countries

## INTRODUCTION

Drug-drug interactions (DDIs) are one of the major problems with medication therapy which occur due to the concomitant use of specific drugs. DDIs are often caused by errors that have occurred in prescription phase and can have devastating consequences for patients (1-3). Studies have shown that 2%-3% of hospital admissions are due to DDIs (4-6), and about 11% of patients experience adverse effects caused by DDIs (1). Due to the large number of available drugs, the number of drug pairs whose concomitant use could cause DDIs is high. However, from the perspective of physicians, some DDIs are not clinically relevant and they believe that the concomitant use of the two drugs is required to achieve suitable therapeutic activity (7,8). In such cases, in order to prevent adverse effects associated with DDIs, the laboratory and clinical parameters of the patient are carefully monitored. However, the co-prescription of some drugs is contraindicated and in case of concomitant use clinically relevant DDIs could occur and may have adverse effects for the patient. Drug interaction compendia are

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not in agreement regarding clinical relevance of most DDIs (9,10). That is why some researchers attempted to determine a finite number of clinically relevant DDIs with which drug interaction compendia and experts are in agreement about their importance. For example, Malone and colleagues using multiple well-known drug interaction compendia and experts' perspective determined a list of 25 clinically relevant (serious) DDIs that are likely to occur in outpatient setting and in case of occurrence would cause serious harm to the patients (11).

Several studies have attempted to determine the rate of co-prescription of drugs which in case of concomitant use; DDIs occur (i.e. potential DDIs (pDDIs)). However, there have been few studies on the incidence rate of clinically relevant pDDIs. A study on outpatient prescriptions in 2000-2002 in the United States showed that 0.63% of prescriptions contained clinically relevant pDDIs (12). Another study in 2005 in the United States reported that from a population of 46 million people, 374,000 people were exposed to clinically relevant DDIs (13). A similar study in 2005 in Italy concluded that a noticeably high number of patients had been at risk of clinically relevant DDIs (14).

To the best of our knowledge, no study has yet reported the incidence rate of clinically relevant pDDIs in outpatient prescriptions in developing countries including Iran. However, many studies in these countries have reported the incidence rate of pDDIs based on different drug interactions compendia (15-17). A recently published systematic review gathered the evidence related to DDIs in Iran and reported the incidence rate of DDIs is relatively high (18). If it is determined that clinically relevant pDDIs exist in the physicians' prescriptions, while determining the pattern of them, it is necessary to design and implement appropriate interventions to prevent the co-prescription of related drugs.

The aim of this study was to determine incidence rate, type, and pattern of clinically relevant pDDIs in the outpatient setting in Khorasan Razavi province, Iran.

## MATERIALS AND METHODS

This was a retrospective, descriptive cross-sectional study. In this study, a clinically relevant pDDI was defined as the presence of at least one of drug pairs associated with clinically relevant DDIs in one prescription.

### *Data source*

The study population was all drug prescription claims in Khorasan Razavi province, Iran (in the 12-month period from April 2013 through March 2014) which was obtained from the drug claims database of National Committee of Rational Drug Use. In this database, data on outpatients' prescriptions of two major insurance companies (i.e. the Social Security and Health Care Services) which cover over 80% of the population of six million people in the province are recorded. The unit of observation in this study was a prescription on a single visit. There were no exclusion criteria for the prescriptions. Data on each prescription included physician identification code and generic code and quantity of the dispensed drugs. Patients' demographic and clinical data were not available.

### *Clinically relevant DDI reference*

Twenty five serious DDI combinations, which have been determined previously in another study by a team of experts using a standard evaluation tool (Table 1), were used as reference in this study (11). First, the active ingredients in Table 1 have been searched in the official pharmacopeia of Iran and their generic drugs were determined. For each active ingredient, there is more than one generic drug. For example, for warfarin 32 generic drugs are available in the official pharmacopeia of Iran. Therefore, the serious DDIs between generic drugs in the official pharmacopeia of Iran were determined and they were used as the DDI reference in this study.

### *Data analysis*

After analyzing the prescriptions, the number of each clinically relevant pDDI was determined. Also, the most frequent clinically relevant pDDIs, the most common drugs contributing to the identified pDDIs, and the pattern of DDIs for each medical specialty were determined. Descriptive statistics such as frequency and percentage were used to report the results. The Microsoft SQL Server 2012 was used to analyze the prescriptions and generate reports.

**Table 1.** List of 25 clinically relevant DDIs.

| No. | Object drug or drug class | Precipitant drug or drug class |
|---|---|---|
| 1 | Anticoagulants | Thyroid hormones |
| 2 | Benzodiazepines | Azole antifungal agents |
| 3 | Carbamazepine | Propoxyphene |
| 4 | Cyclosporine | Rifamycins |
| 5 | Dextromethorphan | MAOIs |
| 6 | Digoxin | Clarithromycin |
| 7 | Ergot alkaloids | Macrolide antibiotics |
| 8 | Estrogen-progestin products | Rifampin |
| 9 | Ganciclovir | Zidovudine |
| 10 | MAOIs | Anorexiants |
| 11 | MAOIs | Sympathomimetics |
| 12 | Meperidine | MAOIs |
| 13 | Mathotrexate | Trimethoprim |
| 14 | Nitrates | Sildenafil |
| 15 | Pimozide | Macrolide antibiotics |
| 16 | Pimozide | Azole antifungal agents |
| 17 | SSRIs | MAOIs |
| 18 | Theophyllines | Quinolones |
| 19 | Theophyllines | Fluvoxamine |
| 20 | Theophyllines | Allopurinol |
| 21 | Warfarin | Sulfinpyrazone |
| 22 | Warfarin | NSAIDs |
| 23 | Warfarin | Cimetidine |
| 24 | Warfarin | Fibric acid derivatives |
| 25 | Warfarin | Barbiturates |

pDDIs; Potential drug-drug interactions, MAOIs; Monoamine oxidase inhibitors, SSRIs; Selective serotonin reuptake inhibitors, NSAIDs; Non-steroidal anti-inflammatory drugs.

## RESULTS

From 113 active ingredients in the table of clinically relevant DDIs (Table 1), 34 were not present in the official pharmacopeia of Iran. By extraction of generic drugs for each active ingredient, totally 2,100 generic drugs were present in the official pharmacopeia of Iran that contribute to the target DDIs. The number of 138 generic drugs were topical that did not contribute to the target DDIs, so they were removed. Therefore, 1,962 generic drugs were remained.

Due to the lack of propoxyphene in the official pharmacopeia of Iran, we were sure that the combination of carbamazepine-propoxyphene does not exist in the prescriptions.

From 204 combinations of active ingredients in Table 1, 118 were related to drugs in the official pharmacopeia of Iran. By determining generic drugs, a list of 41,501 generic drug pairs was determined which was used as the reference of DDIs in this study.

### *Number of analyzed prescriptions and number of identified clinically relevant pDDIs*

Totally 8,169,142 prescriptions were obtained from drug claims database. 6096 clinically relevant pDDIs were found in the prescriptions. On average in every 10,000 prescriptions, 7.46 clinically relevant pDDIs existed. The average number of items per prescription in all of the analyzed prescriptions was 2.88 ± 1.96, while it was 4.90 ± 2.12 for the prescriptions containing clinically relevant pDDIs ($P<0.001$).

### *Incidence rate of each clinically relevant pDDI*

Table 2 shows incidence rate of each clinically relevant pDDI. From 25 DDIs, 16 were found in the analyzed prescriptions. PDDIs that did not exist in the analyzed prescriptions (i.e. carbamazepine-propoxyphene, cyclosporine-rifamycins, estrogen progestin products-rifampin, ganciclovir-zidovudine, monoamine oxidase inhibitors (MAOIs)-

anorexiants, meperidine-MAOIs, methotrexate-trimethoprim, pimozide-macrolide antibiotics, and warfarin- sulfinpyrazone) are not shown in the table. About 70% of the identified clinically relevant pDDIs were the combination of theophyllines-quinolones. More than 95% of the identified clinically relevant pDDIs were only related to five combinations (i.e. theophyllines-quinolones, warfarin-nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines-azole antifungal agents, anticoagulants-thyroid hormones, selective serotonin reuptake inhibitors (SSRIs)-MAOIs).

### *The most common drugs contributing to the identified clinically relevant pDDIs*

Overall, 69 generic drugs contributed to the identified clinically relevant pDDIs (3.5% of all drugs in the national pharmacopeia of Iran). The top 10 drugs contributing to the identified clinically relevant pDDIs are shown in Table 3.

### *The most frequent clinically relevant pDDIs*

From 41,501 drug pairs existing in the national pharmacopeia of Iran which contribute in clinically relevant DDIs, only 78 drug pairs (0.19%) were found in the analyzed prescriptions. Table 4 shows the most frequently identified drug pairs.

**Table 2.** Incidence rate of clinically relevant pDDIs.

| Clinically relevant DDI | N* (%**) |
|---|---|
| Theophylline-quinolones | 4,312 (70.73) |
| Warfarin-NSAIDs | 558 (9.15) |
| Benzodiazepines-azole antifungal agents | 341 (5.59) |
| Anticoagulants-thyroid hormones | 312 (5.12) |
| SSRIs-MAOIs | 301 (4.94) |
| Warfarin-fibric acid derivatives | 94 (1.54) |
| Theophylline-fluvoxamine | 83 (1.36) |
| Theophylline-allopurinol | 44 (0.72) |
| Warfarin-barbiturates | 33 (0.54) |
| Ergot alkaloids-macrolide antibiotics | 7 (0.11) |
| Other serious DDIs*** | 11 (0.18) |
| Overall | 6,096 (100) |

pDDIs; Potential drug-drug interactions; MAOIs; Monoamine oxidase inhibitors, SSRIs; Selective serotonin reuptake inhibitors, NSAIDs; Nonsteroidal anti-inflammatory drugs.
*Number of the clinically relevant pDDIs identified in the analyzed prescriptions, **The percentage of the identified clinically relevant pDDIs, ***Dextromethorphan-MAOIs, digoxin-clarithromycin, MAOIs-sympathomimetics, nitrates-sildenafil, pimozide-azole antifungal agents, warfarin-cimetidine.

**Table 3.** The top 10 drugs contributing to the identified clinically relevant pDDIs

| No. | Drug name | N* (%**) |
|---|---|---|
| 1 | Ciprofloxacin HCL 500 mg TAB | 4,034 (66.17) |
| 2 | Theophylline g 120 ml SYRUP | 2,970 (48.72) |
| 3 | Warfarin sodium 5 mg TAB | 1,001 (16.42) |
| 4 | Theophylline 200 mg RET TAB | 996 (16.34) |
| 5 | Aminophylline 250 mg/10 ml AMP | 353 (5.79) |
| 6 | Alprazolam 0.5 mg TAB | 323 (5.30) |
| 7 | Levothyroxine sodium 0.1 mg TAB | 309 (5.07) |
| 8 | Selegiline hcl 5 mg TAB | 301 (4.94) |
| 9 | Ciprofloxacin hcl 250 mg TAB | 275 (4.51) |
| 10 | Fluconazole 150 mg CAP | 187 (3.07) |

pDDIs; Potential drug-drug interactions.
*Number of the identified clinically relevant pDDIs in which the drug contributed, **The percentage of the identified clinically relevant pDDIs.

**Table 4.** The most frequently identified pDDIs.

| No. | Object Drug | Precipitant Drug | Clinically relevant DDI | N* (%**) |
|---|---|---|---|---|
| 1 | Theophylline G 120 ml SYRUP | Ciprofloxacin HCl 500 mg TAB | Theophyllines-quinolones | 2,728 (44.75) |
| 2 | Theophylline 200 mg RET TAB | Ciprofloxacin HCL 500 mg TAB | Theophyllines-quinolones | 906 (14.86) |
| 3 | Aminophylline 250 mg/10 ml AMP | Ciprofloxacin HCL 500 mg TAB | Theophyllines-quinolones | 333 (5.46) |
| 4 | Warfarin sodium 5 mg TAB | Levothyroxine sodium 0.1 mg TAB | Anticoagulants-thyroid hormones | 309 (5.07) |
| 5 | Theophylline G 120 ml SYRUP | Ciprofloxacin HCl 250 mg TAB | Theophyllines-quinolones | 199 (3.26) |
| 6 | Alprazolam 0.5 mg TAB | Fluconazole 150 mg CAP | Benzodiazepines-azole antifungal agents | 181 (2.97) |
| 7 | Citalopram HBR 20 mg FC TAB | Selegiline HCl 5 mg TAB | SSRIs-MAOIs | 171 (2.81) |
| 8 | Warfarin sodium 5 mg TAB | Diclofenac sodium 100 mg SUPP | Warfarin-NSAIDs | 97 (1.59) |
| 9 | Warfarin sodium 5 mg TAB | Diclofenac sodium 50 mg SUPP | Warfarin-NSAIDs | 81 (1.33) |
| 10 | Warfarin sodium 5 mg TAB | Gemfibrozil 300 mg CAP | Warfarin-fibric acid derivatives | 81 (1.33) |
| 11 | Citalopram HBR 40 mg FC TAB | Selegiline HCl 5 mg TAB | SSRIs-MAOIs | 68 (1.12) |
| 12 | Alprazolam 0.5 mg TAB | Fluconazole 100 mg CAP | Benzodiazepines-azole antifungal agents | 64 (1.05) |
| 13 | Warfarin sodium 5 mg TAB | Diclofenac sodium 25 mg EC TAB | Warfarin-NSAIDs | 64 (1.05) |
| 14 | Theophylline 200 mg RET TAB | Ciprofloxacin HCl 250 mg TAB | Theophyllines-quinolones | 57 (0.94) |
| 15 | Azathioprine 50 mg TAB | Allopurinol 100 mg TAB | Theophyllines-allopurinol | 44 (0.72) |
| 16 | Warfarin sodium 5 mg TAB | Diclofenac sodium SR 100 mg TAB | Warfarin-NSAIDs | 42 (0.69) |
| 17-78 | Other clinically relevant DDI combinations | | | 671 (11.01) |

pDDIs; Potential drug-drug interactions, MAOIs; Monoamine oxidase inhibitors, SSRIs; Selective serotonin reuptake inhibitors, NSAIDs; Nonsteroidal anti-inflammatory drugs. *Number of the clinically relevant pDDIs identified in the analyzed prescriptions, **The percentage of the identified clinically relevant pDDIs.

### *Pattern of the clinically relevant pDDIs*

The number of clinically relevant pDDIs in prescriptions of each medical specialty is shown in Table 5. The pDDIs that did not exist in the analyzed prescriptions and those which their occurrence in the prescriptions of each specialty was very small (DDIs with less than 10 case findings) are not shown in the table. The incidence rate of clinically relevant pDDIs in prescriptions of general practitioners, internists, and cardiologists was more than the others. As shown in Fig. 1, the average incidence of clinically relevant pDDIs per 10,000 prescriptions of pulmonologists, infectious disease specialists, and cardiologists was more than the others.

**Table 5.** Pattern of the clinically relevant pDDIs in prescriptions of each medical specialty.

| **Medical specialty** | **N* (%**)** | **Clinically relevant pDDIs with incidence rate more than 10 in the analyzed prescriptions** |
|---|---|---|
| General medicine | 3,584 (58.79) | Anticoagulants-thyroid hormones, benzodiazepines-azole antifungal agents, SSRIs-MAOIs, theophyllines-quinolones, theophyllines-fluvoxamine, warfarin-NSAIDs, warfarin-fibric acid derivatives, warfarin-barbiturates |
| Internal medicine | 668 (10.96) | Anticoagulants-thyroid hormones, benzodiazepines-azole antifungal agents, theophyllines-quinolones, theophyllines-allopurinol, warfarin-NSAIDs, warfarin-fibric acid derivatives |
| Unknown specialty | 399 (6.55) | Anticoagulants-thyroid hormones, benzodiazepines-azole antifungal agents, theophyllines-quinolones, theophyllines-fluvoxamine, warfarin-NSAIDs |
| Cardiology | 317 (5.20) | Anticoagulants-thyroid hormones, theophyllines-quinolones, warfarin-NSAIDs, warfarin-fibric acid derivatives |
| Otorhinolaryngology | 179 (2.94) | Theophyllines-quinolones |
| Infectious diseases | 162 (2.66) | Theophyllines-quinolones |
| Surgery, general | 155 (2.54) | Anticoagulants-thyroid hormones, theophyllines-quinolones, warfarin-NSAIDs |
| Psychiatry | 145 (2.38) | SSRIs-MAOIs |
| Neurology | 108 (1.77) | SSRIs-MAOIs, theophyllines-quinolones, warfarin-NSAIDs |
| Other specialties | 71 (1.16) | Benzodiazepines-azole antifungal agents, theophyllines-quinolones |
| Pulmonary disease | 55 (0.90) | Theophyllines-quinolones |
| Pediatrics | 54 (0.89) | Theophyllines-quinolones |
| Nephrology | 48 (0.79) | Theophyllines-quinolones |
| Neurological surgery | 47 (0.77) | SSRIs-MAOIs |
| Obstetrics and gynecology | 41 (0.67) | Benzodiazepines-azole antifungal agents |
| Orthopedic surgery | 40 (0.66) | Theophyllines-quinolones, warfarin-NSAIDs |
| Surgery, vascular | 23 (0.38) | Anticoagulants-thyroid hormones |

pDDIs; Potential drug-drug interactions, MAOIs; Monoamine oxidase inhibitors, SSRIs; Selective serotonin reuptake inhibitors, NSAIDs; Nonsteroidal anti-inflammatory drugs.
*Number of clinically relevant pDDIs identified in the analyzed prescriptions of each specialty, **The percentage of the identified clinically relevant pDDIs.

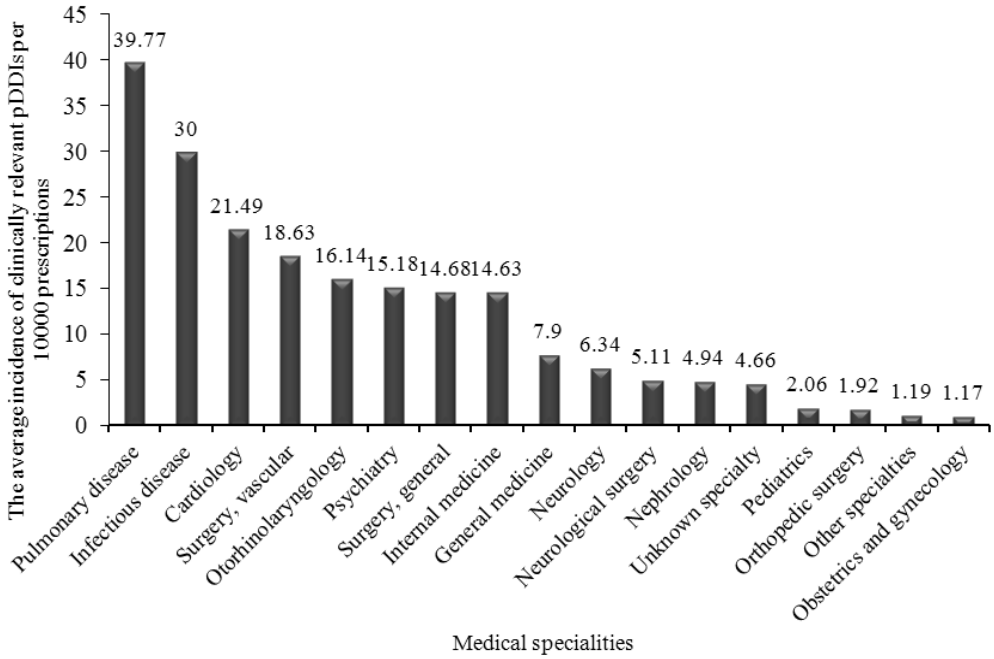


**Fig. 1.** The average incidence of clinically relevant pDDIs per 10,000 prescriptions of each medical specialty, (pDDIs; potential drug-drug interactions).

## DISCUSSION

In total, in the 8,169,142 analyzed prescriptions, which were received from drug claims database, 6,096 clinically relevant pDDIs were found (on average in every 10,000 prescriptions, 7.46 pDDIs existed). The most frequently identified clinically relevant pDDIs was the combination of theophyllines-quinolones (70% of the total). Ciprofloxacin and theophylline contributed more than other drugs in the identified clinically relevant pDDIs, and the interaction between them was more frequent than others. The incidence rate of clinically relevant pDDIs in 10,000 prescriptions of pulmonologists, infectious disease specialists, and cardiologists were the highest.

Although some studies exist that have determined the incidence rate of clinically relevant pDDIs (12-14), due to different study methods used, different types of reporting results, and various drug interaction references used, the direct comparison of the incidence rate in our study with the results of those studies is difficult. Although our results, similar to previous studies, showed that a small proportion of outpatient prescriptions contains drug combinations with potential for clinically relevant DDIs, due to the occurrence of more than 6,000 identified clinically relevant pDDIs, a significant number of patients have been exposed to adverse effects caused by DDIs.

Researchers have warned that in case of the occurrence, clinically relevant DDIs would cause great harm to patients. For example, concomitant use of theophylline and ciprofloxacin (which in our study was more frequent than other pDDIs) increases (up to two-fold) the risk of theophylline toxicity compared to lack of concomitant use (19). Some of the adverse effects of the interaction between these two drugs include: cardiac arrest, seizure, status epilepticus, respiratory failure, and even death (20,21). According to drug interaction compendia, the combination of warfarin-levothyroxine, which frequently prescribed in the analyzed prescriptions, leads to serious DDI that increases the risk of bleeding (22,23). Also, some pharmacodynamic changes associated with the interaction between fluconazole and alprazolam are increased and prolonged sedation, enhanced benzodiazepine-related electroencephalogram (EEG) effects, and increased impairment of psychomotor performance (24).

The combination of theophylline-ciprofloxacin occurred more than other drug combinations. Some of the adverse effects of concomitant use of these two drugs were mentioned above. The results of a knowledge assessment study which was conducted at the same time with this study in Mashhad, Iran, found that almost half of the physicians were unaware of interaction between these two drugs (unpublished study). Therefore, it is necessary to give physicians education related to this serious DDI, in the form of continuing medical education.

The second most frequent identified clinically relevant pDDI was the combination of warfarin-NSAIDs. Studies have shown that concomitant use of warfarin and an NSAID increases the risk of bleeding (25,26). Another study also showed that the risk of serious gastrointestinal bleeding in patients who used NSAIDs during coumarin therapy has been more than five times higher than those who used warfarin alone (27). Similar to the results of the two studies conducted in the United States (12,13), our results showed that the most commonly prescribed drug classes that had potential interaction with warfarin were NSAIDs, thyroid hormones, and fibric acid derivatives. In case of co-prescription of warfarin and one of these drug classes, to avoid the risks associated with the interaction, it was recommended that, in addition to dose adjustment, patients' clinical and laboratory parameters should be carefully monitored.

Given that theophylline, ciprofloxacin, and warfarin contributed more than others in the identified clinically relevant pDDIs in this study, physicians should be aware that using these drugs in the therapeutic regimen increases the risk of adverse drug interactions for patients. Therefore, physicians should be careful when prescribing them concomitantly with other drugs particularly those mentioned in this study.

In this study, clinically relevant pDDIs which existed in prescriptions of each medical specialty were determined. It is necessary that physicians of each specialty, based on the identified pDDIs in the prescriptions of the same specialty, prescribe the related drug with caution. Although the incidence rate of clinically relevant pDDIs in the prescriptions of general practitioners, internists, and cardiologists were highest, the average incidence of clinically relevant pDDIs per 10,000 prescriptions of pulmonologists, infectious disease specialists, and cardiologists was highest. The clinically relevant pDDIs identified in the prescriptions of infectious disease specialists and pulmonologists were only related to the combination of theophyllines-quinolones. These specialists should note that, as mentioned above, the concomitant use of these two drugs can cause theophylline toxicity. Cardiologists also need to pay more attention to the co-prescription of anticoagulants and thyroid hormones, theophyllines and quinolones, and also warfarin and two drug groups of NSAIDs and fibric acid derivatives. The adverse effects of these interactions were mentioned above. Note that the concomitant use of warfarin and fibric acid derivatives increases bleeding episodes (28).

To our knowledge, this is the first study in a developing country that investigated the incidence rate and pattern of clinically relevant pDDIs. In this study we analyzed all prescriptions of a large population in a period of one year. Since the study population was large and diverse, it may be representative of the population of Iran as a developing country. However, our study has several limitations. First, the study was conducted only on prescription claims of the two main insurance companies (more than 80% of all prescriptions) and prescription claims of other insurance companies and uninsured ones were not available. Second, the unit of analysis was prescription. Regarding the fragmentation of the healthcare system in Iran, some patients are managed by multiple physicians who prescribe drugs independently of each other. Hence, our estimates are probably optimistic. Third, this study was conducted based on a limited number of clinically relevant DDIs. It is possible that there may be other clinically relevant DDIs which were not included in this study. Finally, due to the lack of access to patients' demographic and clinical data, clinical consequences of DDIs for different groups of patients were not measured. It is

recommended that future studies measure incidence rate of clinical outcomes of clinically relevant DDIs for different groups of patients and identify factors (e.g. age and type of disease) that have the potential to increase the risk of harm.

Given the significant number of clinically relevant pDDIs in the analyzed prescriptions, the design and implementation of interventions including computerized alerting systems and electronic prescribing systems for physicians and pharmacists to improve medication safety is necessary. These systems based on pharmaceutical knowledge and patients' medication history provide alerts about the possibility of DDI occurrence. It is suggested that researchers design such systems and evaluate their effectiveness in real clinical environments. Due to the large number of possible DDIs, physicians are not expected to remember all of them, but measures should be taken by healthcare authorities for implementation of effective interventions. The results of this study on the pattern of clinically relevant pDDIs for each medical specialty have important implications for researchers who plan to design and implement educational interventions for physicians.

## CONCLUSION

A significant number of outpatients have been exposed to the adverse effects associated with these interactions (more than 6,000 clinically relevant potential DDIs). To improve medication safety, it is necessary that the prescription of drug combinations which their concomitant use may lead to clinically relevant DDIs is prevented. Therefore, it is recommended that in addition to training physicians and pharmacists, other effective interventions such as computerized alerting systems be designed and implemented.

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