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Evaluation of potential drug-drug interactions in medical wards of a referral university hospital in southern part of Iran: a retrospective observational study

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Abstract

Drug-drug interactions impose several financial and medical burden on medical system and can lead to various health problems. The aim of this study was to investigate the incidence of Potential Drug-Drug Interactions (PDDIs) and its related factors in patients admitted to a large university hospital in southern part of Iran. A retrospective observational study was conducted in neurology, infectious and endocrinology wards of a tertiary care teaching hospital, Shiraz, Iran. PDDIs were identified using Lexi-Interact™ Online database. The relationship betweenpatient's age, gender, comorbidity, number of medications,administration of high risk drugs, physician's university rank and scientific level, type of hospital wardand PDDIs has been studied using logistic regression analysis. Totally 600 patients were evaluated in our study. A total number of 5051 interactions were identified. 89.5% of patients experienced at least one interaction regardless of the severity. The most frequent interaction was reported to be class C (84.63%) interaction. According to our results, number of medications, administration of high risk drugs, and type of hospital ward were reported as significant risk factors for the incidence of PDDIs. This study suggest that the prevalence of PDDIs is still high even in a large university hospital.Using modern medical systems), regular monitoring of patients' medications,and paying special attention to patients who are elderly or have certain diseases could help to minimize drug interactions. Moreover, the role of pharmacist should not be ignored whom are the best professionals for preventing, monitoring and managing drug interactions.

Keywords: Drug-drug interactions, Potential drug-drug interactions, Lexi-Interact™ Online, University hospital, Pharmacist

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1. Introduction

Adverse drug events (ADEs) is a global concern and impose a great financial burden on medical system with an estimated cost of more than $16 000 per hospitalization. It can affect millions of patients each year and are responsible for up to 5% of hospital admissions (1). Drug interactions contribute to a major part of ADEs, especially in elderly. Although only about 10% of potential interactions result in clinically significant events, but death or serious clinical consequences are rare. However, low-grade and clinically unspectacular morbidity in the elderly may be much

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more common (1, 2). A review study suggests that about 0.05% of emergency referrals, 0.6% of hospitalizations and 0.1% of readmissions are due to the drug-drug interactions (DDIs) (3). In different studies, the rate of drug interactions in patients leading to adverse drug events and reduction in therapeutic effects varies from 0.63 to 56%, which can be due to differences in study design, study population or duration (4).

Some of the risk factors associated with potential drug-drug interaction (PDDIs) include: age of the patient, gender, number of drugs prescribed, administration of drugs with narrow therapeutic index, and the number of physicians involved in the patient's care (5). Most studies reported the number of administered drugs as a well-recognized and major risk factor for the development of PDDIs in patients. It has been reported that in patients with 5 drugs, the risk of developing PDDIs is about 40% while this risk is about 80% in patients with 7 or more drugs (6). By increasing the number of prescribed drugs to 8 drugs, PDDIs-can reach to 100% (7).

Although some ADEsare unpredictable, but most of them can be anticipated and avoided especially in the case of PDDIs. Previous reports, clinical studies, and an understanding of pharmacologic principles can be effective for anticipation of these interactions (8, 9). Pharmacodynamic interactions include synergistic, additive or antagonistic effects of drugs, while alternation in inhibition or induction of drug metabolism, absorption, distribution and excretion of drugs result in pharmacokinetic interactions (10). In some circumstances, PDDIs can be effective for the better management of patients for instance in the case of synergistic effects between drugs (4). Some of the effective strategies in decreasing the risk of PDDIs include: Limiting the number of drugs prescribed for each patient if possible, reviewing the prescribed drugs in a regularly basis and educating patients by responsible pharmacists and collaborative and professional relationship between pharmacists and physicians during patient care.

The importance of drug interactions in hospital settings is more than outpatient settings since hospitalized people are more often elder, polypharmacy, suffer from more than one disease and have kidney or liver disorders as well as electrolyte disturbances (11). The study of DDIs in different parts of the hospital is essential because by knowing the mechanisms and risk factors associated with drug interactions, it can be easier to reduce or even prevent the negative effects associated with them (12). Studies in this area can help health professionals identify and prevent these interactions.

Lexi-Interact is one of the reliable databases containing over 25 items, including different parts such as: monographs on prescription and over-the-counter drugs, herbal monographs, patient education for adult and pediatric populations, pregnancy and lactation, toxicology, drug allergies, lab and diagnostic tests, and pharmacogenomics. Interactive tools include a pill identifier, oral and topical drug interaction tool, more than 100 clinical calculators, and 2 intravenous-drug interactions tools (13).

The Lexi-Interact Database contains a wide range of information resources provided by Lexicomp®. This set of information is designed to provide a large part of the pharmaceutical information needed by medical staff and consumers. Some of the benefits of this database includes: Possibility to add unlimited medicines, possibility to add plant products and foods to check for interactions, ability to add a specific dosage form of a drug, possibility of adding alcohol and tobacco to check for drug interactions, provide suggestions for managing and treating interference, Complete information on plant product interactions, *etc*.

Little information is available about the epidemiology of PDDIs, and most of the evidence is derived from case reports and volunteer studies. The goal of the present study is to identify the frequency and levels of PDDIs in three wards of a university hospital in southern part of Iran. The determinants of PDDIs were investigated as a second endpoint.

2. Materail and Methods

2.1. Study design and study sample

A retrospective observational study was carried out in Namazi hospital, which is the largest referral and tertiary care hospital of southern part of Iran located in Shiraz, Iran. The popula-

tion study were selected from three wards including neurology, infectious and adult endocrinology wards. 600 patients were recruited into the study after applying inclusion and exclusion criteria in a period of 6 months from July 2020 to February 2021. All patients who were hospitalized in the mentioned wards for at least 48 hours during this period and received at least 2 drugs during the hospitalization period were included in the study. This study was approved by the Ethics Committee of the Shiraz University of Medical Sciences (SUMS) (ethics code: IR.SUMS.REC.1398.910).

The information required for this study was obtained from the medical charts of patients. Demographic and clinical data including patient's age, gender, length of hospital stay, reasons for admission, comorbidity, the treatment provided, and administration of high risk drugs were collected. It should be noted that after reviewing the history of the underlying disease, only diseases such as diabetes, hypertension, hyperlipidemia, chronic kidney disease, asthma, chronic obstruction pulmonary disease that could have a greater impact on the interactions were considered as comorbidities.

The APINCHS (Antimicrobials, Potassium and other electrolytes, Insulin, Narcotics, Chemotherapeutic agents,Heparin and other anticoagulants) system was used to evaluate high risk drugs and the presence or absence of these drugs and its number for patients was assessed (14).

2.2. Assessment of PDDIs

Lexi-Interact™ Online (15) was used to evaluate the occurrence of PDDIs. The Lexi-Interact software categorized each identified PDDIs according to clinical significance level into 5 categories (A, B, C, D, X). We considered potential interactions of level C, D, and X to be clinically significant.

As per classification of the Lexi-Interact software, all identified PDDIs were classified on the basis of their levels of severity, onset, reliability, and mechanism of interactions. Moreover, the mechanism of each interaction was divided into three categories: Pharmacokinetic, pharmacodynamics and unknown.

2.3. Statistical analysis

The data was analyzed using SPSS version 21 (SPSS, Inc., Chicago, IL, USA). Quantitative variable were presented as Mean±SD and categorical data were presented as frequencies and percentages. Logistic regression analysis was applied to determine the association between the occurrences of PDDIs with relate risk factors such as patients' characteristics including age, number of prescribed Medications, length of hospital stay, and physicians' characteristics including university rank and scientific level.

3. Results

Totally 600 patients were enrolled into the study. Of these, 309 (51.5 %) were male and 291 (48.5%) were female. Most patients were between 50 and 75 years of age (41.3%). The median age of patients were 54.82±19.11, 49.25±18.01 and 58.11±18.73 for neurology, endocrine and infectious wards, respectively. Most of the patients were hospitalized less than 5 days (46.1%). 535 patients (89.1%) were finally discharged, 50 patients (8.3%) were expired and 15 patients (2.5%) were transferred to other wards. Out of 600 patients 477 ones (79.5 %) received 5 drugs and more, 537 ones (89.5%) used high risk drugs and 378 ones (63%) had comorbidities. The most frequent comorbidity was Hypertension (132 patients) in the neurology ward and diabetes in the endocrine (111 patients) and infectious (63 patients) wards. The most frequent diagnosis were cerebrovascular accident (160 patients), Diabetic ketoacidosis (58 patients) and sepsis (26 patients) for neurology, endocrine and infectious wards, respectively. Demographic characteristics of studied patients were showed in table 1.

Anticoagulant agents were the most frequent class of drugs administered in the neurology (20.07%) and infectious (10.46%) wards. Insulin was the most frequent drug (17.71%) in the endocrine ward.

In this study, a total of 6617 drugs were administered to 600 patients during the study period, of which 5051 interactions were identified. 537 patients (89.5%), experienced at least one interaction regardless of the severity. Table 2 showed the

Table 1. Demographic and clinical characteristics of study patients (n=600).

Characteristics	Hospital wards		
	Infectious, n(%), n=150	Endocrine, n(%), n=150	Neurology, n(%), n=300
Age, years			
<25	17(5.7)	16(10.7)	6(4)
25-49	110(36.7)	63(42)	45(30)
50-74	121(40.3)	60(40)	67(44.7)
≥75	52(17.3)	11(7.3)	32(21.3)
Mean ± SD (year)	54.82 ± 19.11	49.25 ± 18.01	58.11 ± 18.73
range (year)	18-95	17-92	19-94
Gender			
Male	156(52)	75(50)	78(52)
Female	144(48)	75(50)	72(48)
Length of hospital stay(day)			
Less than 5	159(53)	73(48.7)	45(30)
5-10	85(28.3)	37(24.7)	43(28.7)
More than 10	56(18.7)	40(26.7)	62(41.3)
Mean ± SD (day)	6.54 ± 4.80	7.85 ± 6.50	11.12 ± 7.86
range (day)	2-29	2-29	2-31
Outcome of hospitalization			
Discharge	284(94.7)	132(88)	119(79.3)
Expired	10(3.3)	13(8.7)	27(18)
Transfer	6(2)	5(3.3)	4(2.7)
Number of prescribed medications			
2-4	73(24.3)	34(22.7)	16(10.7)
≥5	227(75.7)	116(77.3)	134(89.3)
Mean ± SD (number)	10.09 ± 4.934	10.87 ± 5.336	13.05 ± 5.203
range (number)	2-31	2-31	3-32
High risk drugs			
Yes	250(83.3)	141(94)	146(97.3)
No	50(16.7)	9(6)	4(2.7)
Comorbidity			
Yes	163(54.3)	122(81.3)	93(62)
No	137(45.7)	28(18.7)	57(38)

DDIs parameters including risk rating, reliability, severity, on set and mechanism of action. The most frequent interaction based on risk rating was class C (84.63%). 83.19% interactions were moderate followed by major (16.11%) and minor (0.69%) interactions. Based on reliability, most of the interactions were fair (72.38%). In addition, the onset of most of interactions were unknown (95.88%). Moreover, pharmacodynamic interactions were responsible for 78.53% of interactions.

Some of the most frequent class X interactions observed in this study includes:diazepam /metronidazole (7 cases), acetazolamide/topiramate (6 cases), quetiapine /methadone (4 cases), salbutamol/labetalol (4 cases), sodium polystyrene sulfonate /magnesium hydroxide (4 cases), rivaroxaban/heparin (3 cases), salbutamol /carvedilol (3 cases). Moreover, the most frequent major in-

Table 2. Prevalence and levels of PDDIs in study patients.

DDI Parameters		All patients	
		Interactions, n(%), n=5051	patients with at least one interaction, n(%), n=600
Risk Rating	C	4275(84.63)	524 (87.33)
	D	685(13.56)	319 (53.17)
	X	91(1.81)	67 (11.16)
Severity	Major	814 (16.11)	346 (57.66)
	Moderate	4202 (83.19)	526 (87.66)
	Minor	35 (0.69)	50 (8.33)
Reliability Rating	Excellent	78 (1.54)	52 (8.66)
	Good	1299 (25.7)	386 (64.33)
	Fair	3656 (72.38)	516 (86)
	Poor	18 (0.35)	18 (3)
Onset	Immediate	7 (0.13)	4 (0.66)
	rapid	166 (3.28)	162 (27)
	delay	35 (0.69)	29 (4.83)
	unknown	4843 (95.88)	537 (89.5)
Mechanism	pharmacokinetic	625 (12.37)	282 (47)
	pharmacodynamic	3967 (78.53)	521 (86.83)
	Unknown	459 (9.08)	576 (96)

teractions include:Heparin / Aspirin (175 cases), Clopidogrel / Pantoprazole (156 cases), valproic acid & derivatives/meropenem (13 cases), diazepam/phenytoin (8 cases) and atorvastatin /nicotinamide (8 cases).

The association between related risk factors and the incidence of PDDIs (C, D,X) and the incidence of PDDIs (D, X) has been shown in table 3 and 4, respectively. The possible variables affecting the incidence of drug interactions were examined once with total interactions and once with D and X category interactions, taking into account all risk factors simultaneously.According to logistic regression analysis, It has been shown that ages 75 years and older, underlying disease, number of prescription 5 drugs and more, prescribing high-risk drugs and type of ward (endocrine and infectious) have a significant relationship with the incidence of DX interactions (p-value <0.05). While there was no correlation between gender, length of hospitalization, physician's university rank and scientific level of physicians (p-value> 0.05). On the other hand, ages 75 years and older, underlying disease, and endocrine ward only affect significant interactions (DX), and no significant relationship was found between the roles of these risk factors in the incidence of all interactions (CDX).

It has been shown that the incidence of DX interactions in the neurology ward is less than the infectious and endocrine wards.Regarding the relationship between the type of ward and the amount of CDX interactions, it was found that in the infectious ward, the probability of interactions is higher than in the neurology ward. No significant relationship was observed in the endocrinology and neurology ward. These results may be due to the different nature of the wards and their patients lead to administration of different medication. All of these differences may result in a different level of interaction.

4. Discussion

In recent years, studies on ADEs have become more prevalent and particularly more important due to the effect of these errors in increasing patient mortality, hospital cost, duration of hospitalization and decreasing medication safety (16, 17). The American Medical Institute reports on medication errors have increased the awareness of medical care staffs about this issue (18).

Table 3. Predictors of PDDIs (C, D, X) in study patients.

Variables	PDDI CDX		p-value	OR (95% CI)
	Absent, n(%)	Present, n(%)		
Age, years				
<25	11(17.5)	28(5.2)	-	1.00
25-49	37(58.7)	181(33.7)	0.55	1.4(0.47-4.09)
50-74	12(19)	236(43.9)	0.18	2.33(0.67-8.10)
≥75	3(4.8)	92(17.1)	0.64	1.48(0.28-7.96)
Gender (female)	34(54)	257(47.9)	0.5	0.77(0.37-1.63)
Comorbidity	17(27)	361(67.2)	0.09	1.99(0.89-4.47)
Length of hospital stay				
Less than 5	32(50.8)	245(45.6)	-	1.00
5-10	23(36.5)	142(26.4)	0.12	0.39(0.17-0.92)
More than 10	8(12.7)	150(27.9)	0.14	0.41(0.13-1.35)
Number of prescribed medications				
2-4	28(44.4)	16(3)	-	1.00
≥5	35(55.6)	521(97)	<0.001	29.22(10.78-79.21)
Administration of high risk medications	32(50.8)	505(94)	<0.001	8.84(3.65-21.41)
Ward				
Neurology	36(57.1)	264(49.2)	-	1.00
Endocrine	8(12.7)	142(26.4)	0.54	1.5(0.41-5.51)
Infectious	19(30.2)	131(24.4)	0.03	0.2(0.05-0.82)
Physician's university rank				
Full Professor	4(69.8)	353(65.7)	-	1.00
Associate professor	11(17.5)	103(19.2)	0.69	1.24(0.43-3.53)
Assistant professor	8(12.7)	81(15.1)	0.6	1.39(0.4-4.9)
Scientific level of Doctors				
Specialist	25(39.7)	183(34.1)	-	1.00
Sub-specialist	38(60.3)	354(65.9)	0.51	0.67(0.2-2.21)

The main findings of our study were as follows: 1. about 89.5% of patients have experienced at least one PDDI regardless of its type while 55.33% of patients have encountered at least one significant PDDI (D or X) 2. Most of PDDIs were class C and moderate in severity 3. Factors such as number of prescribed medications, administration of high risk drugs, and types of hospital wards had significant relationship with the incidence of CDX interactions, while ages 75 years and older, number of prescribed mediation, administration of high risk drugs, patient comorbidity, and types of hospital wards were considered as risk factors for the incidence of DX interactions.

Most of our patients were categorized at the age of above 50 years old. These patients are more sensitized to DDIs due to age-related changes in pharmacokinetics and pharmacodynamics In addition, elder individuals have higher number of medications in their drug list that may make them more vulnerable to DDIs (19). The lack of relationship between gender and the incidence of interactions has been shown in previous studies (20, 21). Our results also showed similar finding.

According to our study, administration of 5 drugs and more could significantly increase the incidence and the amount of interactions. The possibility of PDDIs will be increased with the increment in the number of drugs used by the patients based on several other studies (19, 22).

Table 4. Predictors of PDDIs (C, D, X) in study patients.

Variables	PDDI CDX		p-value	OR (95% CI)
	Absent, n(%)	Present, n(%)		
Age, years				
<25	28(10.4)	11(3.3)	-	1.00
25-49	113(42.2)	105(31.6)	0.23	1.73(0.71-4.2)
50-74	99(36.9)	149(44.9)	0.11	2.1(0.85-5.18)
≥75	28(10.4)	67(20.2)	0.04	2.78(1.03-7.51)
Gender (female)	137(51.1)	154(46.4)	0.6	0.9(0.62 -1.32)
Comorbidity	167(62.3)	211(63.6)	0.03	0.6(0.38-0.95)
Length of hospital stay				
Less than 5	139(51.9)	138(41.6)	-	1.00
5-10	75(28)	90(27.1)	0.92	1.02(0.64-1.62)
More than 10	54(20.1)	104(31.3)	0.24	1.33(0.83-2.13)
Number of prescribed medications				
2-4	42(15.6)	2(0.6)	-	1.00
≥5	228(84.4)	328(99.4)	<0.001	10.22(5.52-18.91)
Administration of high risk drugs	218(81.3)	319(96.1)	<0.001	3.47(1.64-7.36)
Ward				
Neurology	111(41.4)	189(56.9)	-	1.00
Endocrine	86(32.1)	64(19.3)	<0.001	0.41(0.22-0.76)
Infectious	71(26.5)	79(23.8)	0.01	0.39(0.19-0.82)
Physician's university rank				
Full Professor	181(67.5)	216(65.1)	-	1.00
Associate professor	46(17.2)	68(20.5)	0.73	1.11(0.63-1.94)
Assistant professor	41(15.3)	48(14.5)	0.97	1.01(0.51-1.99)
Scientific level of Doctors				
Specialist	78(29.1)	130(39.2)	-	1.00
Sub-specialist	190(70.9)	202(60.8)	0.58	0.84(0.44-1.59)

High risk medications, also mentioned as high-alert medication classes in studies, were identified as a major risk factor for medication errors and can cause serious health problems or even death to patients if use inappropriately. These medications have a greater risk of causing adverse events compared to ordinary drugs (23) and sometimes were administered improperly (24) Therefore, in this study, the relationship between the administration of these drugs and PDDIs was investigated. Insulin and anticoagulant agents were the most frequent medications used in studied wards in our study, both of which categorized as high-alert medication classes. According to our analysis, there was a direct association between administration of high risk medications and the incidence of PDDIs which was incongruent with the report of other studies (25). In addition, there was a significant association between admission in infectious ward and the incidence of PDDIs in our study. This observation can be illustrated by the higher number of medications prescribed in patients admitted to infectious ward and also higher rate of administration of high risk drugs in these patients.

As it has been reported in previous studies, lack of sufficient information and poor training of medical staffs is the main reason for the

high prevalence of drug interactions (26, 27). Therefore, it is necessary for healthcare provider to have adequate information toward drug interactions and ways to prevent and control them (28). Many studies have highlighted the role of clinical pharmacists in reducing medicinal errors (29, 30). Leape et al. showed that the presence of a clinical pharmacist in medical rounds prevents the occurrence of adverse drug events by 66% and plays an important role in preventing adverse drug consequences due to medication errors (31). Therefore it should be noted that Clinical pharmacists along with other health care professionals can play an essential role in the prevention or management of PDDIs and improvement of medicinal therapy in hospitalized patients.

5. Study limitation

In this study the patients were examined only for the presence of drug interactions and the clinical consequences associated with PDDIs were not investigated. On the other hand, among all resources and softwares available for identifying drug interactions, Lexi-Interact was selected in this study. Although selecting a specific software prevents bias in results, it can also causes limitation as some interactions might be missed or some clinically unimportant interactions might be highlighted.

6. Conclusion

Drug interactions are still very prevalent in hospitalized patients even in large university hospitals. Minimizing the number of drugs prescribed for each patient,Using modern medical systems such as CPOE (Computerized physician order entry), regular and accurate monitoring of patients' medications,paying special attention to patients who are elderly or have certain diseases such as liver and kidney failure and performing medication review by pharmacist are some of the suggested strategies to reduce drug interactions.

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Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional research Committee of Shiraz University of Medical Sciences and with the 1964 Helsinki declaration and its later amendments. All participants signed the written informed consent.

Conflict of Interest

All authors declared that they have no conflict of interest

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