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Original Article

Drug-Drug Interactions in Prescribing Practice: *The Challenge and Opportunity for Patient Safety*

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التفاعلات بين الأدوية في الوصفات الطبية التحدي والفرصة لسلامة المرضى

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قسم علم الأدوية و السموم و قسم صحة المجتمع وطب الحجيج* بكلية الطب جامعة أم القرى مكة المكرمة – المملكة العربية السعودية. ص. ب. : 7607

الملخص العربي

أهداف البحث: هدفت الدراسة إلى التعرف على التفاعلات المحتملة بين الأدوية التي تحدث للمرضى في بعض المستشفيات السعودية المختارة في مدينة مكة المكرمة بالمملكة العربية السعودية.

وسائل و طرق البحث: تم اختيار ثلاثمائة مريض عشوائياً من المستشفيات التعليمية بمدينة مكة المكرمة. تم تجميع بيانات المرضى وتضم الجنس، العمر، الجنسية، والأمراض المصاحبة لكل مريض. ولتحديد التفاعلات المحتملة بين الأدوية، تم تجميع وتحليل وصفات المرضى والتي تحتوي على دوائين أو أكثر وكذلك سجلاتهم الطبية في خلال فترة أربعة أشهر باستخدام برنامج Micromedex® لفحص التفاعلات بين الأدوية المدرجة الوصفات الطبية بالمرضى في أثناء إقامتهم بالمستشفى وكذلك عند خروجهم. تم تصنيف التفاعلات بين الأدوية في هذه الدراسة بالكبرى والمعتدلة والخفيفة.

النتائج: وُجدت الدراسة أن التفاعلات المحتملة بين الأدوية متكررة في الوصفات الطبية التي تحتوي على أدوية فالمرضى. فتعرضت هذه الدراسة معرضون لخطر إحتمال التفاعلات بين الأدوية خلال الإقامة في المستشفى أو بعد الخروج منها بنسبة 75% و45% على التوالي. وقد كان هناك ارتباط إيجابي بين التفاعلات المحتملة بين الأدوية وبين عدد الأدوية الموصوفة، وكانت الوصفات الطبية التي تحتوي على خمسة أدوية أو أقل والتي تحتوي على أكثر من خمسة أدوية بها تفاعلات محتملة بين الأدوية بنسبة 26.7% و 49% على التوالي. وحظ أن التفاعلات المحتملة بين الأدوية تزيد مع التقدم في العمر وكانت التفاعلات المحتملة بين الأدوية معظمها معتدلة (40%) كبرى (30.3%) بين المرضى البالغين، ، في حين أنها كانت معتدلة (50 ٪) بين المرضى كبار السن.

الخلاصة: إن البرامج المبرمجة على إكتشاف التفاعلات المحتملة بين الأدوية إلى جنب مع المعرفة والخبرة الدوائية، ومعرفة عوامل الخطورة الهامة ذات الصلة بالمريض لإضافة إلى التثقيف الوثيق بين الأطباء المعالجين والصيادلة السريريين، تكون ذات قيمة لخفض عدد التفاعلات الضارة المحتملة ومنع المخاطر المتصلة بالعلاج بالأدوية.

ABSTRACT

Aim:
To evaluate the prevalence of potential Drug-Drug Interactions (DDIs) that occur among patients in selected hospitals in Makkah city, Saudi Arabia.

Methods:
Three hundred (300) patients were randomly selected from two hospitals. Data collected included gender, age, nationality, and co-morbid diseases. To identify potential DDIs, patients' prescription forms with two or more drugs and their medical records were analyzed during a 4-month period. Prescriptions from each patient during hospitalization, and on discharge were included. DDIs were categorized as major, moderate and minor.

Results:
In our study, potential DDIs were found to be frequent among inpatients with multiple medication prescriptions. Around 75% and 45% of patients were exposed to drugs with the risk of potential interactions during hospital stay and on discharge, respectively. There was a positive correlation between total potential DDIs and number of drugs prescribed. Prescriptions with five drugs and less and those with more than five drugs produced a risk of DDIs in 26.7% and 49% of patients, respectively. As age increased, more DDIs were observed among the study population. DDIs were mostly moderate (40%) and major (30.3%) among adult patients, while it was moderate (50%) among senior age group in our study population.

Conclusions:
Computerized programs for detection of DDIs, combined with pharmacological expertise, knowledge of important patient-related risk factors, and close collaboration between treating physicians and clinical pharmacists may be valuable for decreasing the number of potentially harmful drug combinations and preventing the risks related to drug therapy.

***Keywords*:** Soleus, calf, perforator, below-knee amputation.

INTRODUCTION

The expected therapeutic response might be affected by the presence of drug interactions. Although drug-drug interactions (DDIs) constitute only a small proportion of adverse drug reactions, which may cause health problems, they are often predictable and therefore avoidable or manageable.[1] This can be considered as an important risk factor specifically in hospitals, where patients are ill and multiple medications may be prescribed simultaneously.[2]

About 5% of all adverse drug reactions in hospitals are caused by DDI, the majority of which are avoidable.[3,4] Up to 10% of all hospitalized patients have at least one adverse drug reaction after being discharged.[5,6,7] A change of medication, an addition of new drugs duringa hospital stay and a lack of therapeutic or nursing care after discharge are among the most important risk factors for drug related problems. Some studies show that 40–70% of patients at discharge have a potential adverse drug interaction combination.[8,9,10]
Therefore, it is of agreat importance that discharge medication should have the lowest risk of potential DDIs and that doctors should be aware of possibly preventable, drug-related complications.[11]

Drug interaction is the phenomenon which occurs when the effects and/or toxicity of one drug are modified by the prior or concurrent administration of another drug(s). The effect may be an increase or a decrease in the action of either drug, or it may be an adverse effect that is not normally associated with either drug.[12,13,14] Although results may be positive (increased efficacy) or negative (decreased efficacy, toxicity or idiosyncrasy), in pharmacotherapy they are usually undesirable.[15]

Risk of occurrence and severity of potential clinically important DDIs rest upon several factors, including the number of drugs prescribed, duration of treatment, patient age and stages of disease. Patients who require a large number of drugs, longer duration of treatment, and those with physiological aging changes or certain diseases are considered at higher risk for severe drug-drug interactions.[16,17]

Information on the frequency of drug combinations with the potential to induce dangerous drug-drug interactions (DDIs) in patients discharged from the hospitals is scarce.[10]

MATERIAL AND METHODS

Study Population*:* Three hundred (300) patients of both genders at the age of 15 years and above were enrolled. In order to identify potential DDIs, patients' prescription forms that contain two or more drugs as well as their medical records were analyzed during a 4-month period. A written informed consent was obtained from each patient before participation.

Study Design*:* The study was performed using data from the patients' files of medical wards and ICU at Al-Noor and Al-Zaher hospitals in Makkah city, KSA. The hospitals are teaching public hospitals, which are also referral centres for hospital care.

Exposure to potential drug interactions: For each patient exposed to polypharmacy, all pair wise combinations of drugs were analyzed for potential drug interactions. Potential drug interactions were classified according to Hansten and Horn[18], standard drug interaction source using Micromedex® and drug interaction checker. Hansten and Horn classification is internationally accepted and used extensively throughout the world as drug interactions are updated regularly and the classification system gives detailed summaries of clinical outcome, mechanism of action and supporting references.[19]

Drug interactions are categorized as major, moderate and minor depending on the severity of the outcome and the quality of the documentation. Drug interactions that are either well documented with the potential of being harmful, or have a limited documentation with the potential of serious outcome, are classified as 'major drug interaction'. Drug interactions that are less likely to cause harm or less well documented are classified as 'moderate drug interaction'. Drug interactions, regardless of the degree of documentation, with only a limited risk are classified as 'minor drug interaction'.[17,19]

Variables, including main diagnoses, gender, age, polypharmacy and length of stay (LOS) were correlated with the frequency of potential DDIs.

Inclusion Criteria*:* Prescriptions with two or more drugs prescribed were selected once a week, from January to April 2011. All drug groups were accepted. Patients of both genders and aged 15 years and above were included in this study. Prescription forms of all patients during hospitalization and on discharge from hospitals were included.

Statistics:

All analyses were performed by means of the statistical SPSS® program version 16.

RESULTS

The study population was equally chosen from two major hospitals in Makkah city, Kingdom of Saudi Arabia, (150 patients from each hospital). Females constituted 63% (n = 189) and males 37% (n = 111). Moreover, 91.7% (n = 275) of patients were from medical wards and 8.3% (n = 25) were from ICU. Around 20.3% (n = 61) of the study population were from the youth group (from 15 to 24 years old), 51.7% (n = 155) were within the adult age group (between 25 and 64 years old), and 28% (n = 84) were within the senior group (65 years and above) (Table 1, Fig. 1).

Table 1: Demographic data of the study population

300 patients	Nationality		Gender		Department		Age groups (years)		
	Saudi	Non-Saudi	Males	Females	Medical	ICU	Youth 15-24	Adult 25-64	Senior > 65
No. of Participants	203	97	111	189	275	25	61	155	84
% of	67.7	32.3	37	63	91.7	8.3	20.3	51.7	28

Participants

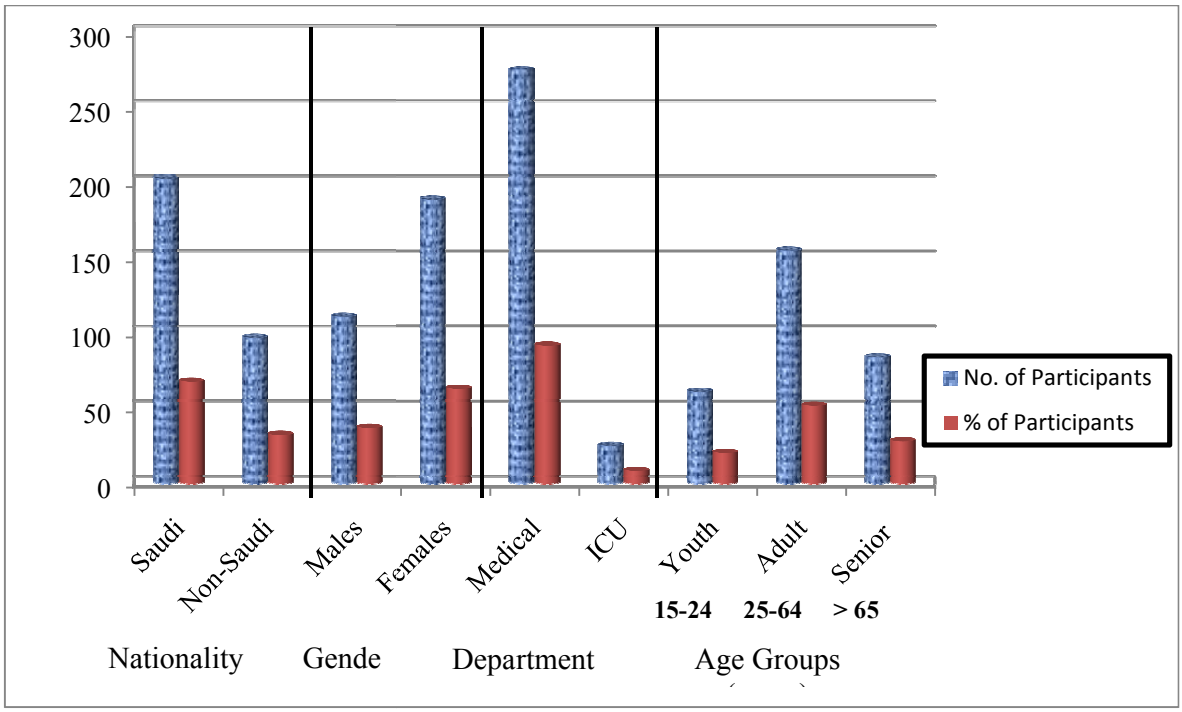

Figure 1. Summary of demographic data of the study population

Psychiatric diseases, acute infections and cardiovascular diseases were among the most frequent medical disorders among the study population (Table 2).

Table 2: Frequency of medical disorders among study population

Medical Disorders	Frequency	%
Rheumatic diseases	1	0.33
Malignancies	1	0.33
Liver diseases	6	2.00
Renal diseases	8	2.67
Epilepsy	11	3.67
Gastrointestinal disorders	17	5.67
Hypertensive heart disease	18	6.00
Diabetes mellitus	21	7.00
Sickle cell disease	22	7.33
Respiratory diseases	26	8.67
Cerebrovascular diseases	54	18.00
Acute infections	56	18.67
Psychiatric diseases	59	19.67

Patients with disturbed liver function tests (LFT) constituted 10.7% (n = 32) of the study population. Whereas, 14.7% (n = 44) of patients had impaired renal function tests (RFT) (Table 3).

Table 3: Distribution and percentage of the LFT and RFT results among study population

300 patients	Liver functions		Renal functions	
	Normal	Disturbed	Normal	Impaired
No. of cases	268	32	256	44
% of cases	89.3	10.7	85.3	14.7

LFT = Liver function tests RFT = Renal function tests

The current study revealed that total number of DDIs increased with the number of prescribed drugs. Prescriptions of five drugs or less carried a potential total DDIs risk in 26.7% (n = 80) of the patients. On the other hand, prescriptions of five drugs or more, showed a risk of potential total DDIs in 49% (n = 147) of patients, most of those DDIs were of moderate and major types (Table 4, Fig. 2).

Table 4: Frequency of individuals at risk of potential DDIs according to the number of drugs prescribed

	Number of patients				
Number of Drugs	No DDIs	Minor	Moderate	Major	Total DDIs (%)
5 drugs and less	56	18	43	19	80 (26.7)
Drugs more than 5	17	10	77	60	147 (49)

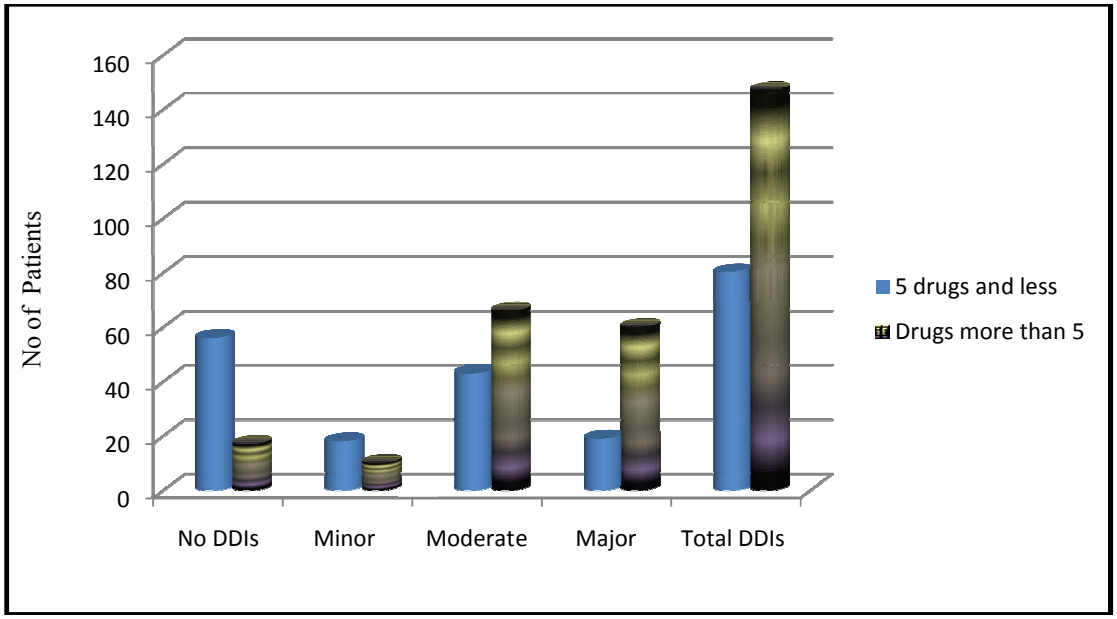

Figure 2. Frequency of individuals at risk of potential DDIs according to the number of drugs prescribed

Up to 75% (n = 225) of patients could have developed or were at risk of developing DDIs during their hospital stay. 82% of cases with potential DDIs were found among Al-Zaher hospital (n = 123/150) as compared to 68% of patients admitted to Al-Noor hospital (n = 102/150). This difference of total DDIs between the two hospitals was statistically significant ($p = 0.005$) (Table 5, Fig. 3).

Table 5: Frequency of individuals at risk of potential DDIs during hospital stay

During stay	DDIs				
	No DDIs	Minor	Moderate	Major	Total DDIs (%)
Al-Noor	48	19	61	22	102 (68)
Al-Zaher	27	9	58	56	123(82)
P-value		0.047*	0.637	0.000***	0.005**

*$P < 0.05$

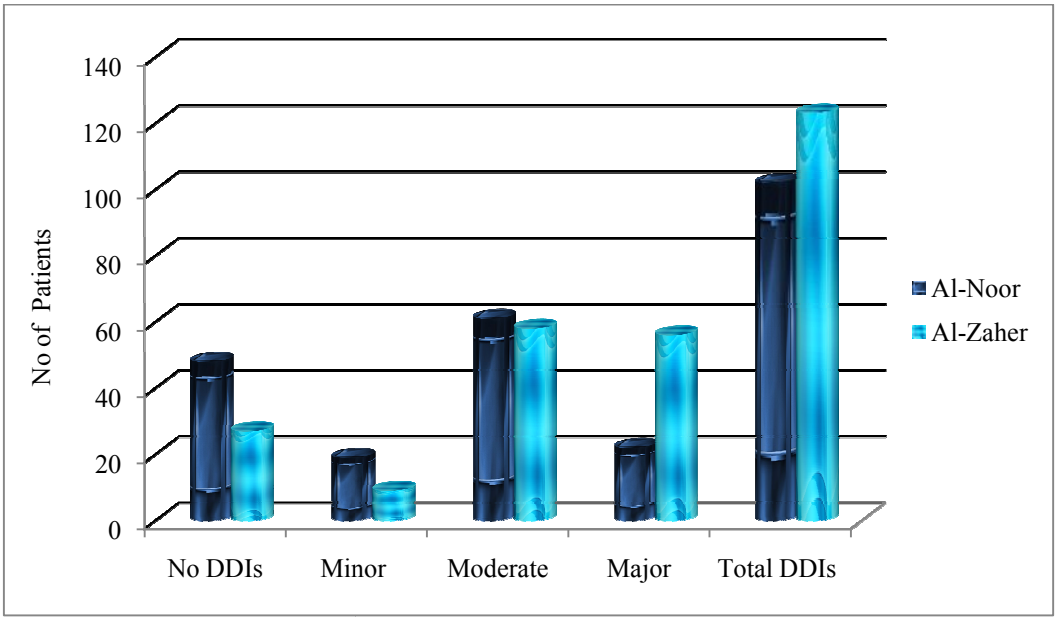

Figure 3. Frequency of individuals at risk of potential DDIs during hospital stay

Meanwhile, up to 45% (n = 135) of patients could have developed or were at risk of developing DDIs on discharge. 69.3% (n = 104/150) of cases with potential DDIs were discharged from Al-Zaher hospital as compared to the 20.7% of patients discharged from Al-Noor hospital (n = 31/150). This difference of total DDIs between the two hospitals was highly statistically significant ($p = 0.000$) (Table 6, Fig. 4).

Table 6: Frequency of individuals at risk of potential DDIs on discharge

On discharge	DDIs				
	No DDIs	Minor	Moderate	Major	Total DDIs (%)
Al-Noor	119	6	23	2	31(20.7)
Al-Zaher	46	6	53	45	104 (69.3)
P-value		0.09	0.000***	0.000***	0.000***

*$P < 0.05$

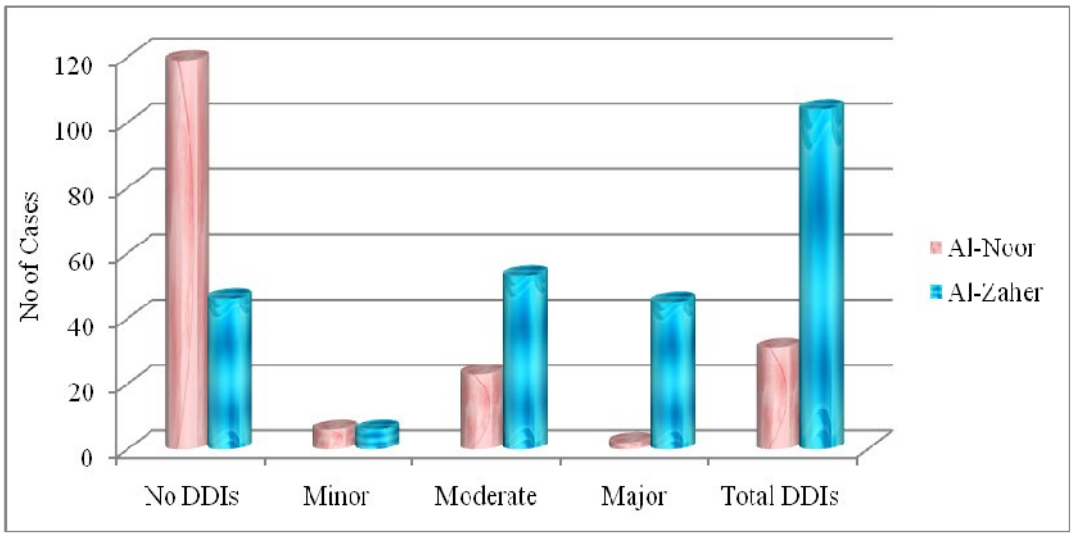

Figure 4. Frequency of individuals at risk of potential DDIs on discharge

As age increased, more potential DDIs were observed among the study population. More cases at risk of moderate and major DDIs were observed among the adult and senior age groups as compared to the young age group (*p*-value of 0.015) (Table 7, Fig. 5). The youth group (15-24 years), accounting for 20.3% of our study population (n = 61), showed equal number of patients (n = 16) with the risk of developing moderate and major DDIs (26.25%). Around 51.7% (n = 155) of patients from the adult group were at risk of developing moderate 40% (n = 62) and major 30.3% (n = 47) DDIs. Meanwhile, 28% (n = 84) of patients belonging to the senior group were at risk of developing 50% (n = 42) moderate DDIs. Contrary to the age, gender showed no significant effect on DDIs among our study population.

Table 7: Frequency of individuals at risk of potential drug interactions DDIs among study population

Number and % of patients					
Age groups (years)	Total of 300 patients	No DDIs	Minor DDIs	Moderate DDIs	Major DDIs
Youth (15-24)	61	18	11	16	16
%	20.3 %	29.5	18	26.25	26.25
Adults (25-64)	155	37	9	62*	47*
%	51.7 %	23.9	5.8	40	30.3
Seniors (65 and above)	84	18	8	42*	16
%	28 %	21.4	9.5	50	19.1
Total No of Patients		73	28	120	79
%		24.3	9.3	40	26.3

*$P < 0.05$ from youth group

Tables 8, 9 and 10 show drug combinations involved in potential major, moderate and minor drug interactions, respectively.

Table 8: Drug combinations involved in potential major drug interactions

Drug Combinations	Potential adverse effect	Frequency (%)
Haloperidol-Promethazine	Prolongation of QT interval	12 (9%)
Aspirin-Enoxaprin	Bleeding	12 (9%)
Rifampin-Isoniazid	Hepatotoxicity	11 (8.3%)
Rifampin-Pyrazinamide	Hepatotoxicity	9 (7%)
Clopidogrel-Omeprazole	Decrease Cardio protection	9 (7%)
Haloperidol-Risperidone	Prolongation of QT interval	9 (7%)
Enoxaprin-Clopidogrel	Bleeding	7 (5.3%)
Lorazepam-Olanzapine	Hypotension , bradycardia, and respiratory or CNS depression	5 (4%)
Morphine-Tramadol	Seizures	5 (4%)
Captopril-Spironolactone	Hyperkalaemia	4 (3%)
Captopril-Potassium Chloride	Hyperkalaemia	4 (3%)

Table 9: Drug combinations involved in potential moderate drug interactions

Drugs Combination	Potential adverse effect	Frequency (%)
Aspirin-Perindopril (ACEI)	Decrease antihypertensive effect	30 (3.9%)
Aspirin-Clopidogrel	Bleeding	29 (3.8%)
Insulin-Aspirin	Hypoglycaemia	28 (3.7%)
Insulin-Captopril	Hypoglycaemia	24 (3.1%)
Aspirin-Amlodipine(CCB)	Decrease antihypertensive effect	19 (2.5%)
Simvastatin-Omeprazole	Myopathy	17 (2.2%)
Aspirin-Heparin	Bleeding	16 (2.1%)
Haloperidol-Benztropine	Anti-cholinergic intoxication	12 (1.6%)
Insulin-Atenolol	Mask physiological response of hypoglycaemia	12 (1.6%)
Perindopril-Enoxaparin	Hyperkalaemia	11 (1.4%)
Phenytoin-Omeprazole	Phenytoin toxicity	10 (1.3%)

Table 10: Drug combinations involved in potential minor drug interactions.

Drugs Combination	Potential adverse effect	Frequency (%)
Aspirin-Omeprazol	Decrease anticoagulants	22 (9.2%)
Aspirin-Atenolol	Decrease antihypertensive effect	15 (6.3%)
Aspirin-Furosemide	Decrease diuretics concentration	15 (6.3%)
Heparin-Clopidogrel	Increase probability of bleeding	13 (5.4%)
Captopril-Amlodipine	Additive hypotensive effect	13 (5.4%)
Ranitidine-Acetaminophen	Potentiate hepatotoxicity	12 (5%)
Clarythromycin-Omeprazol	Increase antibiotic concentration	12 (5%)
Amlodipin-Perindopril	Additive hypotensive effect	11 (4.6%)
Amoxicillin-Clarythromycin	Decrease antibiotic concentration	11 (4.6%)
Ranitidine-Sodium Bicarbonate/ Ca Carbonate	Decrease H_2 blocker concentration	10 (4.2%)
Perindopril/Ca Carbonate	Decrease ACEI level	8 (3.3%)

DISCUSSION

In the current study, three hundred patients have randomly and equally been selected from two hospitals in Makkah city, KSA, of both genders, different age groups and different nationalities. Of the three hundred patients, 75.7% (n = 227) were found to be at risk of developing DDIs. These findings are consistent with the results of previous studies, in which potential DDI were estimated in 40–70% of patients. [9,10,20]

The drug interactions that were established in this study were only potential. This means, it was not known whether these interactions were harmful to the exposed patients or not. Generally, only a small number of patients receiving potentially interacting drugs show clinical signs of a drug interaction.[21] However, individuals respond differently, in which major potential interactions may not produce adverse effects in some patients whereas minor interactions may cause significant adverse effects in others. Drugs with a steep dose-response curve and/or a narrow therapeutic index, and those are metabolized by enzymes susceptible to induction or inhibition are most likely to result in clinically significant interactions.[19,21]

Our data revealed a positive correlation between the number of the prescribed drugs and the increasing age of the patients on one hand, and number of potential DDIs on the other hand. Prescriptions contained five or less drugs produced a risk of DDIs in 26.7% (n = 80) of patients, while 49% (n = 147) of patients having prescriptions enclosed more than five drugs were at risk of developing DDIs. As age increased, more DDIs were observed among the study population, and DDIs were mostly moderate and major in the adult group (40% and 30.3%), and moderate in the senior group (50%).

These results are similar to those of previous studies that showed number of prescribed medications and age of the patients were the major, if not the most important, risk factors for DDIs.[10,22,23] Doubova et al.,[24] found that patients at age of 60 years or older, who were receiving five or more drugs, were at high risk to develop such potential interactions. In addition, various studies have revealed that potential DDIs are frequent when patients received multiple medications prescribed by different physicians,[25,26,27] therefore, prescriptions by a single physician would decrease the risk of inappropriate DDIs.[28] Cruciol-Souza and Thomson[20] reported that along with prescription size, medical specialty and number of prescribers are also clear predictors of potential DDIs.

The present study revealed that the prevalence of total moderate and major potential DDIs among the study population were 40% (n = 120), and 26.3% (n = 79) respectively. These results are higher than those reported by Langdorf et al.,[29] and Cruciol-Souza and Thomson [20] in that the prevalence of the potentially major drug interactions judged to be clinically significant in 25% and 10% of patients respectively.

The most frequent classes of medications that could produce a risk of potential DDIs in our study were NSAIDs, ACE inhibitors, anticoagulants, antipsychotics, hypoglycemic, anticonvulsants, antibiotics and calcium channel blockers. These finding are similar to previous reports which also implicated antibiotics, diuretics, hypoglycemics, calcium-channel blockers,[30] NSAIDs, beta-blockers, steroids, ACE inhibitors, anticoagulants, and anticonvulsants[23,31] in potential drug-drug interactions. Although a number of potential interactions have been identified, not all of them are clinically relevant. It is important for the

expert systems to alert the physicians only to the most important interactions; otherwise they will run the risk of showing too many alerts for the patients on multiple medications.[31]

Basically the clinical management of potential DDIs implies monitoring of symptoms related to possible side effects and laboratory parameters, in order to prevent potentially serious adverse outcomes. In modern medicine, complex therapeutic schemes with multiple drug combinations have become the rule. Therefore, the collaboration between clinicians and clinical pharmacists in the evaluation of drug-drug interactions and getting information that may lead to treatment modification or, at least, to specific patient monitoring in order to identify early potential harmful DDIs, are of paramount importance.[11]

The limitations in this study include the sample size which was not large enough, and that the study focused on potential DDIs while it did not address the question of how many of the detected potential DDIs were known by the physician and if some of the patients were already under close clinical monitoring. Also, the study was not designed to determine how often the potential DDIs identified actually resulted in adverse clinical consequences for patients.

Finally, the present study recommends an essential collaboration between treating physicians and clinical pharmacists to help to prevent and manage the risks related to drug therapy, and a close monitoring of the impact of every given drug or drug combination on each patient.

CONCLUSION

In the present study, the potential drug-drug interactions were frequent among inpatients prescribed multiple medications, as 75% of patients were exposed to drugs with the risk of potential interactions during their hospital stay, while 45% of patients were exposed to drugs with the risk of potential interactions upon discharge. There was a positive correlation between total potential DDIs and the number of drugs prescribed. As age increased, more DDIs were observed among the study population, and DDIs were mostly moderate and major among adult age group, whereas moderate DDIs were observe among the senior age group. Development of alert guidelines and computer-based screening would help physicians to recognize and prevent potentially dangerous drug-drug interactions. This should be combined with pharmacological expertise, as well as the knowledge of important patient-related risk factors to decrease the number of potentially harmful drug combinations. However, in order to appraise the real relevance of such pharmacological expertise, it is necessary to monitor the impact of every given recommendation on each patient. Consequently, adverse outcomes resulting from DDIs can be prevented by making patient- and situation-specific assessments and, whenever appropriate, avoiding concomitant administration by implementing alternative therapeutic strategies or taking precautionary measures such as dosage adjustments and increased monitoring. This may be valuable for decreasing the number of potentially harmful drug combinations, and contribute to an increase in patient safety. A successful DDIs evaluation and prevention will have a positive impact on the medication-use system to improve the quality of patient care and in reducing the occurrence of devastating DDIs in medical inpatients. Finally, population-based studies are needed to assess the prevalence of "real" drug-drug interactions and their clinical consequences to report and avoid them for patient safety.

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