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Assessment of Potential drug-drug interactions among hospitalized patients

Mohammed Salem Al beladai[1], Inad Adel Alharbi[2], Fahad Abdullah Alharbi[3], Mohammed Kaseb Alanazi[4], Meshal Khaled Alawn[5], Mohammed Menahi Alshabi[6], Sami Dakhel Saad Almatrafi[7], Badr Hegy Abdullah Alakel[8], Kadhem Habib Kadhem Alsayafi[9]

[1]Omran General Hospital, Alahssa
[2]Pharmacist, UyunAljawa General Hospital, Al-Qassim Buraydah
[3]Clinical pharmacist, King Saud Hospital
[4]Pharmacist Technician, Primary Health Care Clinics Ishbiliyah
[5]Pharmacy technician, Imam Abdulrahman Al Faisal Hospital
[6]Pharmacist, Ayun Aljawa Hospital General
[7]Ghurab Primary Healthcare Center, Medinah, Assistant pharmacist
[8]Pharmacist Technician, Supply Chains - Medical Supply in Alhofuf, Alahsa
[9]Pharmacist Technician, Prince Saud Bin Jalawi Hospital, Alahsa

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ABSTRACT

Background: Drug-drug interactions (DDIs) are a significant contributor to preventable adverse drug events and associated health complications, especially in patients receiving polypharmacy. DDIs have been shown to contribute to hospital admissions and adverse drug reactions, making their identification and management crucial. This study aimed to assess the frequency, severity, and associated factors of potential DDIs (pDDIs) in patients admitted to internal medicine wards of a large teaching hospital.

Methods: A cross-sectional study was conducted at a large teaching hospital. Patients admitted to various internal medicine wards were included, and data on prescribed medications, patient demographics, and hospital stay were collected from medical records. The severity of potential DDIs was assessed using Lexi-Comp and Micromedex databases. Logistic regression was employed to analyze associations between pDDIs and factors such as age, gender, length of hospital stay, and the number of medications prescribed.

Results: A total of 448 patients were included, with 73.3% prescribed more than four medications. A total of 3,350 potential DDIs were identified, with moderate interactions being the most common (60.9%), followed by major interactions (48.8%) and minor interactions (28.8%). The average patient was exposed to 7.6 potential DDIs, and 11.8% of patients had at least one pDDI. A significant association was found between the occurrence of pDDIs and the prescription of seven or more medications (OR: 0.048, $p < 0.0001$). No significant associations were observed with age, gender, or length of hospital stay.

Conclusion: Polypharmacy is a key risk factor for potential DDIs in hospitalized patients, with moderate and major interactions being the most common. Efforts to reduce the prescription of multiple medications and implement clinical pharmacy systems are essential to mitigate the risk of DDIs and improve patient safety in hospital settings.

Keywords: pDDIs, DDIs, medications, risk.

INTRODUCTION

Drug-drug interactions (DDIs) are a significant contributor to preventable adverse drug events and related health complications (1). Polypharmacy is frequently used in the treatment of various medical conditions, which increases the potential for DDIs. Research has shown that DDIs account for 1% of all hospital admissions and represent 16% of all patients hospitalized due to adverse drug reactions (ADR) (2, 3). At least 15% of patients admitted to hospitals have at least one DDI at the time of admission (4). The clinical outcomes of potential DDIs are often unpredictable, and epidemiological data on this issue are limited. A study conducted in internal medicine wards found that 56.2% of patients were exposed to one or more major or moderate potential DDIs (pDDIs) (5). Another study identified 221 cases of interactions among 160 patients in an internal medicine ward, including 24 major interactions, 15 moderate ones, and 82 minor interactions. The likelihood of drug interactions increases with conditions such as renal failure or when more than six medications are prescribed (6). In many healthcare settings, professionals, including doctors, are often overburdened with patient care responsibilities (8). Medication therapy is one of the most common forms of treatment, with the number of items per prescription varying across specialties. For example, cardiologists may prescribe an average of 3.68 items, while dermatologists typically prescribe 2.06 items, which is higher than the global average (9).

In numerous hospitals, there is no established clinical pharmacy system to monitor and optimize medication use, leading to widespread irrational use of medicines. This has been identified as a significant issue in many healthcare systems, with several studies indicating that patients in these settings are at higher risk for potential DDIs (10-14). Despite the increasing recognition of this issue, data on the occurrence and consequences of DDIs, particularly in hospital inpatient settings, remains scarce.

The objective of this study was to assess the frequency and severity of potential DDIs in internal medicine wards of a large hospital and explore their association with patient age, length of hospital stay, and the number of prescribed medications.

Methods

A cross-sectional study was conducted at a large teaching hospital with 850 beds, serving a population of approximately 1.7 million people. The study was approved by the Ethics Committee of the affiliated university's Pharmacy Faculty. patients admitted consecutively to various internal medicine wards (including Pulmonary, Nephrology, Hematology, Cardiovascular, and Gastrointestinal departments) were included in the study. These patients were admitted with a range of diagnoses across the field of internal medicine. Permission was obtained from hospital authorities to review patients' medical records for research purposes.

Medications prescribed during the hospital stay and at discharge were retrieved from the medical records and drug Kardex. The data collected included patient age, gender, length of hospital stay, reasons for admission, details of the medication therapy provided during hospitalization, and the severity and significance of any drug interactions. Both regular and as-needed (PRN) medications were included. All data were recorded on a standardized form.

The severity and significance of drug interactions were assessed using Lexi-Comp's desktop drug interaction software (Lexi-Comp, Inc., Ohio, USA), which classifies interactions into five categories (A to X) . Additionally, the Micromedex database® (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, USA) was used to analyze DDIs, categorizing interactions based on severity (contraindicated, major, moderate, or minor). The database also provided information on the mechanism of the interaction, the onset of adverse drug reactions (rapid, delayed, or unspecified), and the potential adverse outcomes of the interaction.

Data were presented as proportions, means, standard deviations, or medians. Logistic regression was used to identify associations between the occurrence of potential DDIs (pDDIs) and variables such as age, gender, length of hospital stay, and the number of prescribed medications.

Exposure to pDDIs was the dependent variable in the model (0 = absent, 1 = present). Predictor variables included patient age (1 = below 60 years, 2 = 60 years or older), gender (1 = male, 2 = female), hospital stay (1 = less than 6 days, 2 = 6 days or more), and number of prescribed medications (1 = fewer than 7, 2 = 7 or more). Odds ratios (OR) and respective confidence intervals (CI) were calculated for each predictor. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows Version 20 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Among the 448 patients included in the study, 263 (58.7%) were male and 185 (41.3%) were female. The majority of patients were between 61 and 80 years old (35.7%), with a mean age of 57.8 ± 20.2 years. The median age was 61 years. The median duration of hospital stay was 9 days (mean: 13.1 ± 14.4, range: 2-220 days). The number of medications prescribed concurrently ranged from 1 to 28 (mean: 9.1 ± 4.3), and 73.3% of patients were prescribed more than four medications. Table 1 provides a summary of the general characteristics of patients in the internal medicine wards. The number of potential DDIs for each patient ranged from 0 to 61, with the average patient having 7.6 ± 8.8 potential DDIs. In total, 3,350 potential DDIs were identified. Overall, 11.8% of patients experienced at least one potential DDI, regardless of severity. Moderate interactions were the most common (60.9%), followed by major interactions (48.8%) and minor interactions (28.8%). Only 9.2% of patients had contraindicated potential DDIs. Table 2 shows the distribution of DDIs by severity category (A to X). The most frequent category of interactions was category C (78.6%).

Over 25% of patients were exposed to more than 10 potential DDIs during their hospital stay. In 22.3% of cases, patients had one or two potential DDIs. Among the 386 identified potential DDIs, most had a delayed onset (56.5%), followed by rapid onset (42%), with 38.4% having an unspecified onset. Table 3 outlines the characteristics of patients and the type of interactions in different internal medicine wards. More than 90% of patients in the pulmonary ward were exposed to at least one potential DDI. Major and moderate interactions accounted for 27% of all potential DDIs (907 out of 3,350). Table4 provides details on the frequency, severity, onset, and potential adverse outcomes of these interactions.

In the logistic regression analysis, a significant association was found between the occurrence of potential DDIs and the prescription of seven or more medications (OR: 0.048; 95% CI: 0.02-0.12, p < 0.0001). However, no significant association was found with patient gender (OR: 1.02; 95% CI: 0.56-1.81, p = 0.94), age (under or over 60 years) (OR: 0.94; 95% CI: 0.51-1.7, p = 0.85), or length of hospital stay (less than or more than 6 days) (OR: 0.82; 95% CI: 0.4-1.5, p = 0.54).

Table 1. General characteristics of patients in internal medicine wards

Characteristics	**Frequency**
Gender Male Female	Patient: N(%) 263 (58.7) 185 (41.3)
Age (years)	
<20 21-40 41-60 61-80 81-100	15 (3.3) 82 (18.3) 126 (28.1) 160 (35.7) 65 (14.5)
Hospital stay (days)	
≤3 3-7 >7	2 (0.4) 144 (23.1) 302 (67.4)
Prescribed medications per patient	
<3 3-6 > 7	15 (3.3) 130 (29) 303 (67.6)

Table 2. Prevalence of potential drug-drug interactions (pDDIs) in internal medicine wards

Type of prevalence	**Frequency**
Overall prevalence *	Patient: N(%) 386 (86.2)
Severity of pDDIs	
A B C D X	71 (15.8) 243 (54.2) 352 (78.6) 168 (42) 41 (9.2)
Major Moderate Minor Rapid Delayed Unspecified	217 (48.4) 273 (60.9) 129 (28.8) 188 (42) 253 (65.5) 172 (38.4)
Number of pDDIs per patient	
1-2 3-5 6-9 ≥ 10	100 (22.3) 89 (19.9) 82 (18.3) 115 (25.7)

*Overall prevalence means presence of at least one pDDI regardless of type of severity.

Table 3. Patients' characteristics and prevalence of potential drug-drug interaction (DDI) in different internal medicine wards

Wards	**Age Means±SD**	**Hospital stay (Days)**	**Prescribed medications per patient**	**PDDIs severity (N (%))**					
				Total	**A**	**B**	**C**	**D**	**X**
Pulmonary	61.7±19.8	18.4±23	10.1±4.3	123 (97.6)	14 (10.3)	86 (63.2)	114 (83.8)	61 (44.9)	15 (11)
Cardiovascular	56.3±20.7	12.1±7.6	8.9±4.4	145	44	95	137	76	18

				(87.3)	(26.5)	(57.2)	(82.5)	(45.8)	(10.8)
Gastroenterology	57.3±18.9	7.9±3.7	7.2±3.4	54 (76.4)	1 (1.4)	23 (32.4)	43 (60.6)	12 (16.9)	0
Nephrology/ hematology	54.8±20.3	10.2±5.9	9.5±3.9	64 (85.3)	12 (16)	39 (52)	58 (77.3)	39 (52)	9 (12)

Table 4. Most frequently identified major or moderate interactions, their levels and potential adverse outcomes.

Interaction	Frequency	Severity	Onset	Potential adverse outcome
Aspirin + heparin	51	Major	Rapid	Increase risk of bleeding
Aspirin + clopidogrel	33	Major	Delayed	Increase risk of bleeding
Enoxaparin + warfarin	28	Major	Unspecified	Increase risk of bleeding
Aspirin + warfarin	22	Major	Delayed	Increase risk of bleeding
Digoxin + furosemide	16	Major	Delayed	Risk of digoxin toxicity
Ciprofloxacin + insulin	14	Major	Rapid	Hypoglycemia
Clopidogrel + enoxaparin	13	Major	Unspecified	Increase risk of bleeding
Atorvastatin + azithromycin	9	Major	Delayed	Increase risk of myopathy
Midazolam + morphine	8	Major	Delayed	Increase sedation
Ceftazidim + warfarin	7	Major	Unspecified	Increase risk of bleeding
Clopidogrel + warfarin	6	Major	Unspecified	Increase risk of bleeding
Ciprofloxacin + warfarin	5	Major	Delayed	Increase risk of bleeding
Losartan + spironolactone	4	Major	Delayed	Hyperkalemia
Diazepam + morphine	4	Major	Unspecified	Increase sedation
Pantoprazole + warfarin	51	Moderate	Unspecified	Increase effect of warfarin
Atorvastatin + clopidogrel	33	Moderate	Delayed	Risk of blood clotting
Aspirin + enoxaparin	28	Moderate	Rapid	Increase risk of bleeding
Aspirin + captopril	25	Moderate	Rapid	Decrease effect of captopril
Digoxin + pantoprazole	22	Moderate	Delayed	Digoxin toxicity
Losartan + warfarin	18	Moderate	Delayed	Decrease effect of warfarin
Levofloxacin + prednisolone	17	Moderate	Delayed	Increase risk of tendon rupture
Atorvastatin + digoxin	16	Moderate	Delayed	Digoxin toxicity
Diazepam + valproic acid	14	Moderate	Delayed	Excessive sedation
Digoxin + spironolactone	12	Moderate	Rapid	Digoxin toxicity
Captopril + furosemide	11	Moderate	Rapid	Acute hypotension, renal insufficiency
Levothyroxine + warfarin	8	Moderate	Delayed	Increase risk of bleeding
Phenytoin + valproic acid	7	Moderate	Delayed	increase effect of phenytoin
Cyclosporine + diltiazem	7	Moderate	Delayed	Increase cyclosporine toxicity
Ciprofloxacin + prednisolone	6	Moderate	Delayed	Increase risk of tendon rupture
Ciprofloxacin + methadone	5	Moderate	Delayed	Increase QTc interval
Meropenem + valproic acid	5	Moderate	Delayed	Decrease level of valproic acid
Ciprofloxacin +Magnesium Oxide	4	Moderate	Rapid	Decrease level of ciprofloxacin
Lamotrigin + valproic acid	4	Moderate	Delayed	Increase level of lamotrigin
Gentamycin+ vancomycin	4	Moderate	Delayed	Nephrotoxicity, ototoxicity

DISCUSSION

This study showed that almost all the patients admitted to internal medicine wards developed at least one potential drug-drug interaction during their stay in the hospital, and an average of 7.6 pDDIs per patient. Also, about 67% of the studied patients took a prescription of more than six drugs, which was the sole factor that had significant relation with the occurrence of pDDIs. Other studies similarly showed this trend in that the prevalence of potential DDIs increases with an increase in the number of medications prescribed (16-19). Global studies have reported that polypharmacy, or the use of five or more drugs, contributes to the heightened risk for potential DDIs (20, 21). The mean number of prescribed drugs in our study was higher compared to other studies that were carried out in similar settings (5, 16, 22). This is partly because of the practice at our center where the same patients are being managed by many physicians and also, we do not have a system to alert healthcare providers about the potential DDIs.

The implementation of COPE systems with DDI alerts could foster rational prescribing and help reduce the actual incidence of DDIs in medical wards (23, 24). Rijkom et al., identified that the computerized DDI alerts might be an effective tool in preventing adverse drug events in hospitals. Ismail et al., showed that among 400 medical inpatients, 52.8% had at least one pDDI, whereas major and moderate pDDIs were determined among 23% and 63.6% of patients respectively. Our study demonstrated a higher overall prevalence of pDDIs, 86.2%, particularly major pDDIs. The prevalence of moderate pDDIs, category C, in our study was in agreement with findings in a study by Ismail. Other studies in the internal medicine wards also reported prevalence rates of pDDIs that ranged from 43% to 56.2%, consistent with high prevalence in this study.

The most frequent category in our study was Category C interactions with 78.6% of the total. Generally, these interactions usually do not lead to toxic or life-threatening situations but require rigorous monitoring to prevent any possible adverse outcomes. However, type X interactions, demonstrating a risk to potential harm or life threat, were observed in 41 patients representing 9.2% of the patients. The prevalence of type X interactions in the literature ranges between 0.2 and 2.4% (12, 22, 25, 26). Although in our study the frequency of type X interactions was higher, the difference might be due to differences in study design and population characteristics. As mentioned above, type X interactions can be harmful; therefore, physicians and pharmacists should show caution and closely monitor the patients for the risk of such interaction types. Age, gender, and length of stay were not significantly associated with the occurrence of DDIs, confirming several studies on gender (17, 27) but differing from other findings where a positive association between older age, longer length of stay, and DDIs was shown (19, 28). For instance, one study reported that Ismail et al. identified pDDIs significantly associated with the age of the patient ≥ 60 years [OR: 2.1, P value: 0.003], duration of hospitalization ≥ 6 days [OR: 2.6, P value: 0.001], and taking ≥ 7 medications [OR: 5.9, P value < 0.001]. Our research indicates that polypharmacy is significantly associated with increased exposure to pDDIs.

The two most common drugs implicated in clinically significant DDIs were ciprofloxacin and aspirin. Ciprofloxacin, a quinolone antibiotic, exhibits two important DDIs: impairment of the absorption of magnesium, calcium, iron, and zinc; and inhibition of certain cytochrome P-450 enzymes involved in metabolizing a large number of drugs, including methylxanthines. The latter interaction increases the plasma levels of these drugs, which can be life-threatening for theophylline. One of the common interactions of ciprofloxacin is with insulin either by raising or lowering the blood sugar levels; hence, it is essential to monitor the blood glucose closely. Aspirin also has some well-documented DDIs, especially with antiplatelet or other anticoagulant medications. Examples include heparin, warfarin, enoxaparin, and clopidogrel, which raise the risk of bleeding (30). These combinations of medicines are commonly used; however, the patients need close follow-up.

Conclusion: Our study determined a high prevalence of DDIs in internal medicine wards; moderate severity was the most prevalent class, though major pDDIs were also frequently seen. These data are in concordance with international studies that showed a progressive and significant increase of major DDIs. Taking four or more prescription drugs was found to be a significant predictor for DDIs. Thus, in order to minimize DDIs-related harm, drugs with lower risks of interactions have to be prescribed, and having careful ADR monitoring is advised. Further, we recommend the development and implementation of computerized DDI alert systems to avoid ADRs within the hospital setting.

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