

A retrospective evaluation of drug–drug interactions in patients admitted to Internal Medicine Departments in Palestinian Hospitals

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Abstract

Objective: To measure the prevalence and identify risk factors associated with drug–drug interactions among patients admitted to internal medicine departments in Palestinian hospitals

Methods: A retrospective cross-sectional observational study was conducted. Data were obtained from patient files from the internal medicine departments in Palestinian hospitals from 1 September 2017, to 31 March 2018. The data collected included patient gender, age, length of hospitalization, medications prescribed, and the number of medications. The digital clinical decision support system IBM Micromedex[®] was used to assess potential drug–drug interactions.

Results: The number of patients included in this study is 513. The total number of potential drug–drug interactions detected in study participants is 1558. The average number of potential drug–drug interactions per patient was found to be 3 ± 3.9 . Among study participants, 66.1% (n = 339) were found to have potential drug–drug interactions in their current medications. The most commonly encountered drug–drug interactions type was “major” drug–drug interaction, which was encountered in 43.6% (n = 681) of total detected drug–drug interactions. Other types of drug–drug interactions were encountered in 42% (n = 647), 14% (n = 224), and 0.4% (n = 6) which were moderate, minor, and contraindicated drug–drug interactions, respectively. Patients’ age, number of medications, and length of hospitalization were associated with the increased risk of potential drug–drug interactions.

Conclusion: The results indicated a high prevalence of potential drug–drug interactions in Palestinian hospitals, associated with polypharmacy, increased age, and increased length of hospitalization. Therefore, managing patient medication by a drug expert such as a clinical pharmacist to identify and resolve potential drug–drug interactions will possibly decrease the high prevalence of drug–drug interactions, prevent patient harm, and decrease the cost of hospitalization.

Keywords

Drug–drug interaction, Internal medicine, Palestine hospitals

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Introduction

Many disease states and medical conditions require the use of multiple medications to manage symptoms, slow disease progression, or prevent future illnesses.¹ However, alongside their intended actions, medications may also induce illness and death due to adverse drug reactions or the misuse of drugs.²

The World Health Organization (WHO) defines adverse drug reactions as “noxious and unintended responses to drugs occurring at doses normally used in human for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.”¹

Drug–drug interactions (DDIs) are adverse drug reactions that occur when one drug’s pharmacological or clinical response is modified by co-administering a second drug.³ Hospitalized patients are more likely to be affected by DDIs because comorbidities, polypharmacy, and frequent therapy modifications are common in hospitalized patients.^{4,5}

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DDIs can be classified as pharmacodynamic, pharmacokinetic, or pharmaceutical, and can lead to increased or decreased response, or treatment failure.^{6–8}

Pharmacodynamic interactions occur when one drug alters the clinical effects of another drug resulting in synergistic or antagonistic pharmacological activity.^{9,10}

Pharmacokinetic interactions occur when a drug affects another drug's systemic concentration and bioavailability, changing the amount of time the drug is available at the site of action.⁹ This type of interaction occurs due to alteration of one of the pharmacokinetic processes: absorption, distribution, metabolism, or excretion of drugs.^{8,10}

Pharmaceutical interactions are DDIs that occur when two physically or chemically incompatible drugs are mixed. For example, this can happen when preparing mixtures or when a vehicle of a certain drug affects drug's pharmacokinetics or pharmacodynamics.⁸

Several published reports have demonstrated the effect of DDIs on hospitalization, length of hospital stay, morbidity, mortality, and financial costs; DDIs have been shown to cause an increase in all of those.^{11–14}

Different practical approaches have been considered to reduce the risk of adverse effects, decrease the possibility of having DDIs, improve drug treatment quality, and reduce healthcare costs, including managing polypharmacy and selecting drugs rationally.¹⁵ Furthermore, taking a complete medical history, correct diagnosis, choosing the correct drug, dosage, and evaluating each drug's risk versus benefit ratio are practical approaches in decreasing potential DDIs.^{1,16}

Several studies have been conducted on this subject. For example, Vonbach et al.² showed a mean of 1.11 potential DDI (pDDI) for each patient during hospitalization. Another study reported a potential DDI prevalence of 23%. Potential DDIs were associated with cardiovascular disease and four drugs or more on the chart.¹⁷ A cross-sectional study conducted in Iran revealed a significant association between the potential for DDIs and seven or more prescribed medications.¹⁸ In addition, in a Brazilian teaching hospital, the percentage of potential DDIs was 49.7%, and that increases with age and number of medications.¹⁹

Few studies addressing the issue of DDIs in Palestinian hospitals have been previously published.^{20–22} One study explored DDIs among antihypertensive medication users and showed that DDIs are highly prevalent.²⁰ Another study addressed DDIs in patients on hemodialysis and showed a percentage of 89.1% drug interactions among hemodialysis patients.²¹ Finally, a third study conducted in surgery departments in Palestinian hospitals demonstrated that DDIs are prevalent in surgery departments in Palestine.²²

Internal medicine departments were chosen as the setting for this study since patients encountered are expected to have multimorbidities and polypharmacy. Patients admitted to the internal medicine departments are at higher risk for DDIs due to multimorbidities such as type 2 diabetes mellitus and cardiovascular diseases, which have been associated with increased risk for DDIs.²³

The objective of this study was to assess the prevalence and risk factors associated with DDIs among patients admitted to internal medicine departments in Palestinian hospitals. To the best of our knowledge, this topic has not been addressed in Palestinian hospitals in any published reports.

Methods

Study design and sample

An observational, retrospective, cross-sectional study was carried out among patients from internal departments of three major Palestinian hospitals in different areas of Palestine. Hospitals were included from three regions to obtain a representative sample. Palestine Medical Complex in Ramallah, Beit Jala Hospital in Bethlehem, and An-Najah National University Hospital in Nablus were included in this study. Patients included in this study were adult patients 18 years and above who were admitted to the internal departments between 1 September 2017 and 31 March 2018, and prescribed two or more medications. Patients prescribed less than two medications and patients not having records for the prescribed medications were excluded from the study.

Data collection and analysis

Data collected from patient files were anonymous and used solely for research purposes. Data extraction was done manually by two researchers and verified by a third researcher. Data collected included patient demographics (age, gender), medications they took in the hospital, and hospitalization length.

Analysis of DDIs

The prescribed medications were screened for interactions using the digital clinical decision support system IBM Micromedex[®]. The output of the system gives all potential interactions and presents information about the possible adverse effects of the interactions.²⁴ In addition, the system classifies the interactions according to severity, onset, and documentation. Micromedex[®] was shown to be among the best drug interaction screening tools in terms of performance.²⁵ Use of the digital clinical decision support system IBM Micromedex[®] was in agreement with the terms of use of the system available publicly at <https://www.ibm.com/legal>.

Statistical analysis

Data were statistically analyzed using Statistical Package for the Social Sciences (SPSS) version 23. Data are presented as percentages and frequencies of DDIs. Bivariate analysis using a chi-square test was done to test for the association between categorical variables and the dependent variable which is having or not having a potential drug interaction.

Table 1. General demographic characteristics of study participants (n = 513).

Characteristic:	n (%)	
Age (years)	18–39	105 (20.5%)
	40–59	150 (29.2%)
	60–79	192 (37.4%)
	≥80	66 (12.9%)
Gender	Male	294 (57.3%)
	Female	219 (42.7%)
Number of medications	≤5	169 (32.9%)
	6–10	193 (37.6%)
	11–15	104 (20.3%)
	≥16	47 (9.2%)
Length of hospital stay (days)	≤5	422 (82.3%)
	6–10	76 (14.8%)
	≥11	15 (2.9%)

Variables associated with *p* value less than 0.05 are considered statistically significant.

Results

Demographic information

Five hundred thirteen hospitalized patients in the internal department who met the inclusion criteria were analyzed for potential DDIs. The mean age was 57.54 (18–96), and 294 (57.3%) patients were males. The majority of the patients, 422 (82.3%) stayed less than 5 days at the hospital, and the mean length of hospital stay was 3.43 (1–16) days. The mean number of medications was 8.44 (2–32) drugs. Patient characteristics are shown in Table 1.

Prevalence of potential DDIs

Micromedex software output illustrated that the mean of the pDDIs for each patient was 3 (0–24) with a standard deviation of 3.9. A total of 1558 potential DDIs were identified from the software of the 513 patients. Of the 513 patients, 339 (66%) had potential DDIs.

Associated factors affecting DDIs

Several factors such as age, number of prescribed drugs, and length of hospital stay could be associated with increased potential DDIs. Table 3 presents the association between the occurrence of pDDIs and these factors. For example, the percentage of pDDIs among patients under 40 years of age was 44.8%, whereas it was 73.3% among patients over 60 years of age.

It also shows that an increase in the number of medications increases the risk of pDDIs. The percentage of potential DDIs was 36.1% for patients in whom the number of prescribed drugs was less than or equal to 5. The potential DDIs increased to 68.2% and 97.9% when the medications were from 6 to 10 and more than 16 medications, respectively.

Regarding the length of hospitalization, Table 2 shows that the pDDIs were 61.4% when the length of hospitalization was less than or equal to 5 days. pDDIs were 86.8% in patients hospitalized from 6 to 10 days and 93.3% in patients hospitalized for 11 days or more.

No significant differences or associations were found between males and females regarding DDIs with a *p*-value of 0.1. The percentages of pDDIs were 63.6% and 69.4% for males and females, respectively.

Types of potential DDIs. The types of pDDIs according to the level of severity are contraindicated, major, moderate, and minor. In the present study, the majority were major DDIs, with 43.6% (681 DDIs), 42% (647 DDIs) moderate, and 14% (224 DDIs) minor DDIs. Only 0.4% (6 DDIs) were classified as a contraindication.

Common examples of pDDIs. Table 3 shows some of the pDDIs found in our study and the interaction mechanisms. These interactions were classified according to severity.

Discussion

The prevalence of DDIs in patients admitted to internal medicine departments in Palestinian hospitals is successfully assessed in this study using the digital clinical decision support system IBM Micromedex®. This drug interaction screening tool was previously used to assess DDI prevalence²² and was shown to be among the best performance DDI screening tools.²⁵

DDIs result in an increased burden on the healthcare system, and the factors associated with DDIs were studied in a few hospitals in Palestine. This study revealed that the total percentage of interactions among patients hospitalized in medical wards in Palestinian hospitals is more than half (66.10%), which is much higher than in other countries where the prevalence of DDIs was much lower with the prevalence 47%,⁷ 49.7%,²¹ and 23%.⁸ At the same time, some studies in different countries reported higher prevalence values of 78.2%²⁶ and 78.03%.²⁷ This wide variation in the prevalence of potential DDIs might be explained by factors such as the availability of an alternative drug, drug resource, drug information, information, and not employing a clinical pharmacist in the medical ward, which has shown to decrease the prevalence of DDIs among hospitalized patients' medication significantly.^{26,28}

Concerning the severity of the interactions, the vast majority of the potential DDIs were of major or moderate severity (43.6% (n=681), 42% (n=647), respectively), while only 14% (n=224) were minor interactions. Each DDI has a different ability to cause harm, and each has a specific mechanism of interaction. These findings disagree with numerous previous investigations in other countries such as Italy,²⁹ Denmark,³⁰ and Ethiopia.²⁶

The results of the current study reported that no statistically significant differences were found between males and

Table 2. Bivariate analysis of possible variables associated with potential DDIs (n = 513).

Variable		Percentage of cases having pDDIs (n)	Percentage of cases not having pDDIs (n)	p-value	Significance
Age category (years)	18–39	44.8% (47)	55.2% (58)	<0.001	Significant
	40–59	68.7% (103)	31.3% (47)		
	≥60	73.3% (189)	26.7% (69)		
Gender	Male	63.6% (187)	36.4% (107)	0.1	Not significant
	Female	69.4% (152)	30.6% (67)		
Medication number	≤5	36.1% (61)	63.9% (108)	<0.001	Significant
	6–10	68.4% (132)	31.6% (61)		
	11–15	96.2% (100)	3.8% (4)		
	≥16	97.9% (46)	2.1% (1)		
Length of hospitalization (days)	≤5	61.4% (259)	38.6% (163)	<0.001	Significant
	6–10	86.8% (66)	13.2% (10)		
	≥11	93.3% (14)	6.7% (1)		

DDI: drug–drug interaction.

Table 3. The most frequent DDIs in patients admitted to Palestinian internal medicine wards in 513 patients.

Interactions	Severity	Effect	Mechanism of interaction	Occurrence in % of cases
Ciprofloxacin: Metronidazole	Major	Increase risk of QT prolongation	Additive effect	4.27
Clopidogrel: Omeprazole	Major	Reduced Clopidogrel activity	CYP2C19 inhibition	4.27
Aspirin: Furosemide	Major	Reduced Furosemide effectiveness & nephrotoxicity	Decreased renal prostaglandin synthesis	18.38
Clopidogrel: Atorvastatin	Moderate	Reduced Clopidogrel activity	Competition on CYP3A4 & inhibition of P-gp	12.39
Bisoprolol: Aspirin	Moderate	Increased blood pressure	Decreased production of renal prostagland-ins	14.10
Ranitidine: Aspirin	Minor	Decreased Aspirin anti-platelet effect	Reduced absorption of Aspirin	25.64
Tacrolimus: Fluconazole	Contraindicated	Tacrolimus toxicity	CYP3A4 inhibition by Fluconazole	0.04
Salmeterol: Fluconazole	Contraindicated	Increased risk of QT prolongation	CYP3A4 inhibition by Salmeterol	0.04

DDI: drug–drug interaction.

females regarding the appearance of potential DDIs. The Cruciol-Souza et al. study results were not the same. They found that the risk for pDDIs was higher in females than males,¹⁹ whereas another study—Gagne et al.³¹—showed the odds in males were higher than those in females, but this study was done among ambulatory patients. These differences could be due to differences in patient profiles and the way the drugs are prescribed by different doctors.¹³

Age is another significant variable to consider in association with DDIs. In this study, an increased prevalence of pDDIs with increasing age with a significant relationship (p -value < 0.001). Older patients are prone to polypharmacy due to treatment with multiple comorbidities.¹¹

The potential for DDIs increases significantly as the total number of patient medications increases; furthermore, the length of hospital stay is significantly linked to pDDIs. An increase in

hospital stay is associated with the administration of more drugs to patients, increasing the chance for pDDIs.¹³ It could also be that the pDDI are the reason for the increased length of stay.¹⁹

One of the most common interactions that we found in our study is clopidogrel with atorvastatin, which is a moderate interaction caused by the inhibition of CYP3A4 activation of clopidogrel, which in turn causes decreased antiplatelet activity.³² This interaction can be avoided by utilizing a different statin not metabolized by CYP3A4, such as rosuvastatin. Another frequently recurring interaction is between ciprofloxacin and metronidazole, a major DDIs that increases the risk of QT-interval prolongation when the two medications are used concurrently. Therefore, ECG changes monitoring is recommended for patients on high doses of the interacting drugs and patients at high risk for hyperkalemia.³³

Another interaction due to the inhibition of CYP3A4 was between tacrolimus and fluconazole. Fluconazole is an azole antifungal that inhibits the metabolism of tacrolimus and subsequently increases nephrotoxicity.³⁴ This interaction requires reducing the tacrolimus dose by half when using up to 200 mg/day and closely monitoring the renal function.³⁴ An example of a frequently repeated minor interaction is ranitidine with aspirin, which causes a reduced antiplatelet effect of aspirin due to the changes in absorption of this drug.³⁵

Limitations

In this retrospective study, DDIs were measured and classified based on Micromedex analysis and were done by profile reviews and assessment of patient medication lists. Therefore, it lacks the clinical significance of the interaction and the patient outcome associated with the interaction. No sample size calculation was performed for this study. Screening for DDIs was carried out using one screening tool (Micromedex), other available screening tools could have been used.

Conclusion

The results showed a high prevalence of pDDIs among patients admitted to the internal medicine units in Palestinian hospitals. Potential DDIs are associated with polypharmacy, increased age, and increased length of hospitalization. This finding supports the need to manage patient medication by a drug expert such as a clinical pharmacist to prevent, identify and resolve potential DDI, prevent patient harm, and decrease the cost of hospitalization

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Author contributions

A. K. R.: study design, project supervision, data analysis, and drafting of manuscript. W. O. A., A. N. N., and A. A. I.: Data collection, data analysis, and manuscript drafting. H. A. N. and A. D. A.: Data analysis, manuscript drafting, and interpretation of findings. All authors approved the final version of the manuscript.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Before conducting the study, approval was obtained from the Research and Ethics Committee at Birzeit University (Approval

code BZUPNH1801), the Ministry of Health, and the three hospitals. Data obtained were used only for research purpose, and patient identity was not revealed.

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Consent for publication

All authors read and approved the final manuscript.

Informed consent

Informed consent was not sought for the present study because Research and Ethics Committee waived the need to obtain individual informed consent as the study was a retrospective investigation of anonymous patient records.

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