Prevalence and predictors of potential drug–drug interactions in patients of internal medicine wards of a tertiary care hospital in India

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ABSTRACT

Background Drug–drug interactions are a major source of adverse drug events (ADEs). Polypharmacy, age and the number of comorbid conditions are important predictors of adverse drug interactions. ADEs account for up to 5% of hospital admissions per year and an increase in the length of hospital stay.

Objective To find the prevalence and predictors of potential drug–drug interactions (pDDIs) in patients admitted to the wards of an internal medicine department of a tertiary care hospital.

Method Patients admitted to internal medicine wards with prescriptions having more than one drug were selected. Demographic details including age, gender, number of comorbid conditions, number of drugs prescribed and the disease for which the patient was admitted were recorded in a case record form. Interactions were checked using Micromedex DrugReax software.

Results A total of 939 patients were recruited for this study based on inclusion criteria. 433 prescriptions (46%) had one or more pDDIs, with a range of 1–13 drug interactions per prescription. A total of 1395 drug interactions were found, with 866 moderate drug interactions (62%), 435 major interactions (31.1%) and 89 minor interactions (6.3%). During the study period only three contraindicated drug combinations (0.2%) were recorded. A significant association ($p < 0.01$) was found between the number of pDDIs and predictors, age and number of drugs.

Conclusion A total of 433 prescriptions (46%) had one or more pDDIs. Older patients and those prescribed >6 drugs are at major risk for occurrence of pDDIs. Moderate severity interactions were the highest number followed by major severity interactions.

INTRODUCTION

Adverse drug event (ADE)-related hospital admissions range from 0.37% to 27.4% and preventable ADEs are responsible for 17.5–85.7% of intensive care unit (ICU) admissions.¹ Drug–drug interactions (DDIs) are responsible for 6–30% of all adverse drug reactions (ADRs) and 2.8% of ADR-related hospital admissions are due to DDIs.² DDI-related ADRs are preventable. ADEs are responsible for up to 5% of hospital admissions every year, with an approximate cost of \$16 000 per hospitalisation.³ DDIs are preventable medication-related problems, which are the main cause of ADRs.⁴ Adverse drug interactions lead to an increase in patients' length of hospital stay and healthcare cost.⁵ A DDI is one

which alters the pharmacokinetic (PK) and/or pharmacodynamic (PD) profile of either drug when two drugs are administered together. The intensity of the harm may be severe or low depending on the patients' characteristics.²

Polypharmacy is a major concern since an increase in the number of drugs per prescription increases the risk of a DDI.⁶ The risk of pDDIs has been estimated at approximately 6% with two drugs, 50% with five drugs and 100% with eight drugs when used concomitantly. Interactions are labelled as potentially clinically significant when the combination of drugs leads to therapeutic failure or worsening of the patient's condition.⁷

In India the prevalence of pDDIs ranges from 8.3% to 63%.^{2, 7–10} Globally, the prevalence of pDDIs ranges from 2.8% to 63% depending on the study population and study setting.^{3, 5, 11–14}

Becker *et al* found that 0.54% of emergency visits, 0.57% of hospital admissions and 0.12% of patient re-hospitalisations were due to actual DDIs and 4.8% of the elderly admissions were due to drug interactions.¹⁵

In our study setting pDDIs have not previously been estimated so this study was undertaken to find the prevalence and predictors of pDDIs in patients admitted to internal medicine wards of a tertiary care hospital using Micromedex DrugReax software V2.0.

MATERIALS AND METHODS

Study setting

A cross-sectional observational study was conducted in the four wards of the internal medicine department of a tertiary care hospital in Pondicherry, India. Prescriptions were hand written. Electronic prescribing and online DDI checking system was not in force in the study wards. Wards did not have clinical pharmacy services to monitor pDDIs in inpatients. The study was carried out from July 2014 to May 2015 and was approved by the institute scientific advisory committee and institute ethics committee (JIP/IEC/SC/2013/3/404).

Patients and data collection

Patients admitted to the internal medicine wards aged ≥ 13 years were the study participants. Patients were selected cross-sectionally by the convenient sampling method from four wards of internal medicine. Patients were chosen for the study if they were prescribed more than one drug. Participants' prescriptions were reviewed, scanned and kept for

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drug interaction evaluation. Patient characteristics including age, gender, diagnosis, number of comorbidities and length of hospital stay were taken from case sheets and recorded on a specially designed case record form (CRF). Drug interactions were checked using Micromedex Drug-Reax software V2.0 (Truven Health Analytics, USA), an online drug interaction database.¹⁶ Drugs prescribed to the patients were entered into the Micromedex software one by one. The software gave an output if any interaction was found between two concomitant drugs: level of severity, time of onset, level of scientific evidence for each interacting drug pair and clinical significance of each interaction. It also provides the drug–disease interaction. Drug interactions were categorised based on the severity as contraindicated, major, moderate and minor interactions. Patients' diagnoses and disease conditions were written by the respective clinicians in the patient case record and these were used to analyse the number of morbid and comorbid conditions. The patients' final diagnosis for which they were admitted to the wards was classified based on the World Health Organization International Classification of Diseases-10 (WHO-ICD-10) classification system.¹⁷ Data collection was done by a single author and duplication was avoided by careful selection.

Severity of drug interaction

Contraindicated

The combination of drugs should be avoided to prevent severe harm to the patient.

Major drug interaction

This interaction results in a serious reaction which requires medical intervention to prevent or minimise harm.

Moderate drug interaction

There may be harm so it should be monitored.

Minor drug interaction

No harm.

Onset of interaction

Rapid

The effect of interaction occurs within 24 hours of administration of the drug pair.

Delayed

The effect of interaction occurs after more than 24 hours (ie, days to weeks) when administered together.

Patients' demographic details were noted. Prescriptions were analysed for the number of drugs prescribed per prescription, the number of pDDIs and the number of morbid/comorbid conditions per patient. Correlation frequency of pDDIs with age, the number of morbid and comorbid conditions and the number of drugs prescribed were analysed. The possible mechanism of action for DDIs was also taken into consideration. Regression analysis was performed to check the association of exposure to pDDIs and predictor variables.

Statistical analysis

Age, number of male and female patients were expressed as mean±SD. Association of factors with pDDI was done using the Pearson correlation test. Logistic regression was undertaken to find the association of pDDIs with patients' age, gender, number of drugs prescribed, number of comorbid conditions and disease for which the patients were admitted. pDDI was the dependent variable in the model (0=absent, 1=present). Variables included

Table 1 Demographic details of patients

Variable	Value
Gender	n (%)
Men	552 (58.7)
Women	387 (41.3)
Age (years)	Mean±SD
Men	45.9±16.7
Women	42.4±17.1
Age in years	n (%)
13–45	490 (52.2)
46–60	278 (29.5)
≥61	171 (18.1)
Drugs per prescription	n (%)
<3	112 (12)
3–6	570 (60.6)
≥7	257 (27.3)

in the analysis were age (1=<60 years of age, 2=≥60 years of age), gender (male=1, female=2), number of drugs prescribed per prescription (1=<7 drugs, 2=≥7 drugs) and patients' disease ICD classification. Descriptive statistics were done using Microsoft Excel 2010 and logistic regression and correlation were done using SPSS v20 (SPSS, Chicago, Illinois, USA).

RESULTS

A total of 939 patients were recruited to the study, of which 552 (58.7%) were men and 387 (41.3%) were women. Patient demographic details are shown in [table 1](#). The incidence of pDDIs was 46% (433/939) with a total of 1395 interactions. The number of pDDIs per prescription ranged from 0 to 13. Nine prescriptions had a maximum number of drugs prescribed (12 drugs per prescription), 12% (n=112) had <3 drugs per prescription, 60.6% (n=570) had 3–6 drugs per prescription and 27.3% (n=257) prescriptions had >6 drugs. Of the 257 patients prescribed >6 drugs, 218 patients had a minimum of one pDDI and 39 patients had no pDDI. Of the 682 prescriptions (72.6%) with ≤6 drugs, only 215 patients (31.5%) experienced a pDDI and the majority of patients (n=467, 68.4%) had no pDDIs.

The types and frequency of pDDI are presented in [table 2](#). Interactions of moderate severity were higher than those of major or minor severity. Three combinations of contraindicated DDIs (0.2%) were found (see [table 3](#)) and a list of the top 10 drug interactions is shown in [table 4](#). The frequency of patients admitted with different disease conditions, patients exposed to pDDIs and the total number of drug interactions related to each disease condition are presented in [table 5](#). Regression analysis showed that patients aged >59 years with cardiovascular disease and prescribed ≥7 drugs were significantly associated with drug

Table 2 Types and frequency of potential drug–drug interactions (pDDIs)

Severity of interaction	Number of drug pairs	Number of interactions (%)	Number of patients exposed to pDDI (n=433) (%)
Contraindicated	3	3 (0.2%)	3 (0.3%)
Major	85	435 (31.1%)	254 (27%)
Moderate	152	866 (62%)	352 (37.4%)
Minor	23	89 (6.3%)	83 (8.8%)
Total	263	1395	

Table 3 Contraindicated drug combinations

Interacting drug combination	Inference
Fluconazole/ondansetron	Increased risk of QT interval prolongation
Amitriptyline hydrochloride/ metoclopramide hydrochloride	Increased risk of extrapyramidal reactions or neuroleptic malignant syndrome
Medroxyprogesterone acetate/ tranexamic acid	Increased risk of thrombotic events

interactions. A positive correlation was found between exposure to pDDIs and the number of medications, age and the number of comorbid conditions. The correlation analysis showed a positive association between age and number of comorbid conditions ($r=0.15$, $p<0.01$), age and number of drugs per prescription ($r=0.22$, $p<0.01$), age and pDDIs ($r=0.25$, $p<0.01$), number of comorbid conditions and pDDIs ($r=0.12$, $p<0.01$) and number of drugs and pDDIs ($r=0.61$, $p<0.01$).

Regression analysis was performed to find a strong association between pDDIs and their factors. The results of the univariate and multivariate analysis are shown in table 6. A total of 221 patients had more than one comorbid condition. Univariate analysis shows that patients with more than one comorbid condition were significantly at risk to exposure to pDDIs with a significance of $p<0.01$, OR 2.21 (95% CI 1.6 to 2.9), but it was not significant in multivariate analysis. Patients aged >59 years, those prescribed >6 drugs and patients admitted with cardiovascular diseases were at a significantly higher risk for pDDIs both in univariate and multivariate analysis. Aspirin was the substrate for 31.6% of patients ($n=441$), atorvastatin for 10.3% ($n=144$) and clopidogrel for 6.2% ($n=87$) in all the pDDIs identified in the study participants.

DISCUSSION

This study highlights the prevalence, types and predictors of pDDIs in internal medicine wards of a tertiary care hospital in India. In this study, 46% ($n=433$) of prescriptions had one or more pDDIs, ranging from 1 to 13 pDDIs per prescription. The prevalence of pDDIs is 46%, which is within the range reported in other studies (8.3–63%).^{2–10} Compared with another study, the prevalence of pDDIs was less due to fewer prescriptions having >6 drugs (27.3%), but in a similar study it was 55.2%.¹⁸

The average number of pDDIs per prescription was 1.4, which is similar to 1.6 reported by Ismail *et al.*¹⁸ The incidence of major pDDIs was 31.1% (435/1395), moderate pDDIs was 62% (866/1395) and minor pDDIs was 6.3% (89/1395). Contraindicated drug combinations were very few ($n=3$, 0.2%). There

were more pDDIs of moderate severity than major pDDIs, which is similar to other studies.^{12–19} There was a significant association between the number of drugs and the frequency of pDDIs, which is also similar to other studies.^{9–20} The association of pDDIs was significantly linear in proportion to the number of drugs, age and morbid condition.

Eleven of the admissions (1.1%) were related to ADEs, similar to a study reported by the Australian Institute of Health and Welfare which found that 1.3% of hospital admissions were due to ADEs.²¹ Patients admitted due to cardiovascular disease had the highest number of ADEs ($n=246$, 26%), followed by patients with infectious diseases ($n=128$, 13.6%) and those with genitourinary disorders ($n=102$, 10.8%). This is similar to a study by Egger *et al* which found that cardiovascular disease was the main disease for patient admission to hospital (35.4%).²² Age >59 years and prescriptions with >6 drugs were significantly associated with exposure to pDDIs. Patients admitted due to cardiovascular disease were also at a higher risk for drug interactions ($p=0.001$, OR 4.1 (95% CI 2.8 to 6.2)).

The highest number of prescriptions having pDDI were seen for patients with cardiovascular morbidities and is in concordance with other studies.^{3–23} Patients with cardiac failure and myocardial infarction received the highest number of drugs, which favours a high potential for drug interactions, but those drugs are crucial in relieving disease symptoms.¹⁴

Cardiovascular drugs contribute to the most frequent drug interactions. Aspirin and atorvastatin are at the top of the list. The most frequently seen major severity drug interaction was aspirin/clopidogrel combination (7.6%, $n=106$) and atorvastatin/clopidogrel also had the highest moderate severity interactions (8.3%, $n=117$). The frequency of pDDIs with digoxin/furosemide (1%, $n=15$) and enalapril/furosemide (1.9%, $n=27$) were lower than in an Iranian study which reported pDDIs in 5.9% ($n=12$) and 13.3% ($n=27$), respectively.³ A total of 276 drug pairs were observed, 41.3% ($n=114$) were PD interactions, 38.7% ($n=107$) were (PK interactions and 19.9% ($n=55$) had an unknown mechanism. This observation is similar to Kapadia *et al* who also reported a higher number of PD interactions than PK interactions.⁷ The onset of drug interactions in 46.3% ($n=128$) of drug pairs was of a delayed type, 13.7% ($n=38$) rapid and 39.8% ($n=110$) of drug combinations were not of any specified type.

This study found three contraindicated drug interactions (3/1395), which is similar to Kapadia *et al* who reported 5/3405 interactions⁷ and Teixeira *et al* who found contraindicated drug interactions in 0.4% (3/827) of patients.¹²

Our study has found a statistically significant positive association between age and the number of drug interactions, which

Table 4 List of top 10 major and moderate severity potential drug–drug interactions (pDDIs), their frequency and clinical significance ($n=1395$)

Drug combination	Severity	Frequency (%)	Type of DDI	Significance of interaction
Atorvastatin/clopidogrel	Moderate	117 (8.3%)	PK	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity
Aspirin/clopidogrel	Major	106 (7.6%)	PD	Increased risk of bleeding
Aspirin/enalapril	Moderate	80 (5.7%)	PD	Decreased effectiveness of enalapril
Aspirin/metoprolol	Moderate	58 (4.1%)	PD	Decreased antihypertensive effect
Aspirin/insulin	Moderate	46 (3.2%)	PD	Increased risk of hypoglycaemia
Aspirin/heparin	Major	43 (3.0%)	PD	Increased risk of bleeding
Clopidogrel/heparin	Major	41 (2.9%)	PD	Increased risk of bleeding
Aspirin/furosemide	Moderate	34 (2.4%)	PD	Decreased diuretic and antihypertensive efficacy of furosemide
Amlodipine/aspirin	Moderate	30 (2.1%)	PD	Increased risk of gastrointestinal haemorrhage and/ or antagonism of hypotensive effect
Enalapril/furosemide	Moderate	27 (1.9%)	PD	Postural hypotension (first dose)

PK, pharmacokinetic interaction; PD, pharmacodynamic interaction.

Table 5 Frequency of patients admitted based on the ICD-10 disease classification and their exposure to potential drug–drug interactions (pDDIs)

ICD-10 disease classification	No. of patients admitted, n (%)	No. of patients with pDDIs, n (%)	Total no. of pDDIs, n (%)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D89)	61 (6.4)	11 (2.5)	18 (1.2)
Diseases of the circulatory system (I00–I99)	245 (26)	184 (42.4)	793 (56.8)
Congenital malformations, deformations and chromosomal abnormalities (Q00–Q99)	5 (0.5)	2 (0.4)	4 (0.2)
Diseases of the digestive system (K00–K93)	70 (7.4)	28 (6.4)	43 (3)
Endocrine, nutritional and metabolic diseases (E00–E90)	65 (6.9)	34 (7.8)	109 (7.8)
External causes of morbidity and mortality (V01–Y98)	2 (0.2)	1 (0.2)	1 (0.07)
Diseases of the eye and adnexa (H00–H59)	2 (0.2)	1 (0.2)	1 (0.07)
Diseases of the genitourinary system (N00–N99)	102 (10.8)	46 (10.6)	121 (8.6)
Certain infectious and parasitic diseases (A00–B99)	127 (13.5)	38 (8.7)	79 (5.6)
Diseases of the musculoskeletal system and connective tissue (M00–M99)	22 (2.3)	11 (2.5)	29 (2)
Neoplasms (C00–D48)	67 (7.1)	18 (4.1)	40 (2.8)
Diseases of the nervous system (G00–G99)	65 (6.9)	30 (6.9)	84 (6)
Injury, poisoning and certain other consequences of external causes (S00–T98)	30 (3.1)	4 (0.9)	9 (0.6)
Diseases of the respiratory system (J00–J99)	46 (4.8)	16 (3.6)	44 (3.1)
Diseases of the skin and subcutaneous tissue (L00–L99)	6 (0.6)	4 (0.9)	9 (0.6)
Others	24 (2.5)	5 (1.1)	11 (0.7)
Total	939	433	1395

is in agreement with other studies.¹² The prevalence of pDDI increases with a rise in the number of drugs prescribed. Many studies have reported that polypharmacy contributes to an increased risk of drug interactions.^{5, 24} Cardiovascular patients were at an increased risk for pDDIs; this may be due to patients being older and prescribed multiple drugs.²⁵

We could not find any significant association between gender and frequency of pDDIs, which is similar to another study.¹⁸ Age >59 years is a significant risk factor for drug interactions. Patients with >6 drugs are at a higher risk for drug interactions. Patients admitted with more than one comorbidity had a 1.7 times higher risk of a drug interaction. Patients admitted due to cardiovascular disease had the highest number of interactions (56.8% (793/1395) of all interactions). This is similar to other studies reported worldwide.^{3, 13, 14}

Clopidogrel is a prodrug which acts by inhibiting platelet activation via ADP receptors. It is metabolised by the CYP3A4 enzyme to an active metabolite. Only a minimal amount of the clopidogrel prodrug converts into an active form. Other CYP3A4 substrates like atorvastatin can alter the metabolism of clopidogrel and formation of active thiol metabolite. The anti-platelet activity of clopidogrel depends on the extent of active

metabolite available in the system. This will be influenced by the individual CYP3A4 activity or presence of the other CYP3A4 substrates.^{26, 27} In our study, clopidogrel and atorvastatin (both CYP3A4 substrates) were prescribed together, and this was the maximally prescribed moderate type of pDDI. Prescribing these drugs together reduces the activity of clopidogrel and attenuates the platelet inhibitory activity.²⁸

The combination of clopidogrel and aspirin has a significant risk reduction in stroke but may increase the risk of bleeding, intracranial haemorrhage and major bleeding.^{29, 30} Of the interactions found in our study, 7.6% were with clopidogrel and aspirin. This is the major drug–drug interaction seen frequently.

The drug interaction and clinical significance depends on the drug dosage, duration of concomitant use of drugs, patient factors like hepatic metabolism and renal clearance. Besides the prescribed potentially interacting drugs, other drugs are also prescribed to counteract the adverse effect of the drug combination, but those may not be considered by the drug interaction software. Patient factors also were not considered in this while checking the drug interactions using software. Timing and sequence of drug administration and patient factors can play a significant role in the outcome of ADEs. Since these are not included in the drug interaction

Table 6 Logistic regression analysis for frequency of potential drug–drug interactions (pDDIs)

Variable	No. of patients (n=939)	No. of patients with pDDIs	Univariate analysis		Multivariate analysis	
			p Value	OR (95% CI)	p Value	OR (95% CI)
Male gender	552	270	0.04	1.3 (1.0 to 1.7)	0.10	1.3 (0.9 to 1.8)
Age ≥60 years	211	128	<0.01*	2.1 (1.5 to 2.9)	0.01*	1.6 (1.1 to 2.4)
Patients with ≥7 drugs	257	217	<0.01*	12.1 (8.3 to 17.7)	<0.01*	11.4 (7.5 to 17.3)
>1 comorbidity	221	150	<0.01	2.2 (1.6 to 2.9)	0.02	1.5 (1.0 to 2.3)
Main disease for admission						
Blood	61	11	<0.01	0.2 (0.1 to 0.4)	0.01	0.3 (0.1 to 0.7)
Cardiovascular	245	184	<0.01*	5.4 (3.9 to 7.5)	<0.01*	4.1 (2.8 to 6.2)
Infectious	127	38	<0.01	0.4 (0.2 to 0.6)	<0.01	0.5 (0.3 to 0.8)
Neoplasm	67	18	<0.01	0.4 (0.2 to 0.7)	0.08	0.5 (0.2 to 1.0)
Poisoning	30	4	<0.01	0.1 (0.06 to 0.4)	0.03	0.28 (0.09 to 0.8)
Others	24	5	0.01	0.2 (0.1 to 0.8)	0.09	0.35 (0.1 to 1.1)

checking software, it is important for clinicians to have a sound knowledge of patients' comorbid conditions to predict the DDIs. An electronic drug interaction checker is important to minimise DDIs and prevent DDI-related ADRs.¹³ Most of the DDIs can be prevented by dose adjustment which can be done by evaluating the clinical effects of drugs on a regular basis and making changes in the drug regimen.¹¹

The results of this study suggest that severe pDDIs are of concern; these may alter the patients' disease condition and therapeutic outcome. These research findings give signals to clinicians for closer monitoring of patients aged >59 years, prescribed with >6 drugs and with multiple comorbid conditions to prevent DDI-related ADEs.

Limitations of study

ADEs were not monitored during both the hospital stay and after discharge from the ward. Actual drug interactions were not recorded because therapeutic drug level monitoring and therapeutic outcome estimation were beyond the scope of this study.

CONCLUSION

This study found 433 prescriptions (46%) with one or more pDDIs in internal medicine wards of a tertiary care hospital. Moderate severity interactions were recorded in the highest number followed by interactions of major severity. Increasing age of patients and a higher number of prescribed drugs are the major predictors for occurrence of pDDIs. Patients admitted due to cardiovascular disease were more prone to exposure to pDDIs. It is recommended that patients with multiple comorbidities, polypharmacy (>6 drugs) and those aged >59 years should be closely monitored for adverse consequences due to drug interactions.

Key messages

What is already known on this subject

- Drug–drug interactions cause 6–30% of all adverse drug reactions
- The prevalence of potential drug interactions has been evaluated in various study populations including cardiovascular and ambulatory patients
- In our study setting the prevalence and predictors of potential drug interactions has not been evaluated, so this study was undertaken

What this study adds

- 433 prescriptions (46%) had at least one interacting drug pair, which shows that nearly half of the patients were prescribed with interacting drug combinations
- It is necessary to closely monitor patients aged >59 years prescribed >6 drugs and those with cardiovascular disease for any adverse drug interaction.

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