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Research Article

Prevalence and Risk Factors of Potential Drug-Drug Interactions in the In-Patient Medical Wards: A Hospital-Based Cross-Sectional Study

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Abstract: Evidence shows that half of the Adverse Drug Reactions (ADRs) resulting from Drug-Drug Interactions (DDI) are predictable and preventable. Hospitalized patients are more expected to develop DDI. The current study aims to assess the prevalence, risk factors, and severity of PDDIs among hospitalized patients. This is a cross-sectional study that was conducted in medical wards of a NGO charity hospital located in Bathalapalli, Anantapur district. Patients aged 18 years or more, and admitted to the in-patient medical wards taking more than one medication have been selected for the study. A total of 310 subjects who met the study criteria were enrolled in the study after taking oral and written informed consent. Patient demographics, a list of medications, and clinical characteristics were collected from admission to discharge by the review of medical records and patient interviews. The collected data were subjected to identify and grade the severity of PDDI by using IBM Micromedex® Drug Interaction Checker. Among 310 in-patients, 82 cases had 127 PDDI with a prevalence of 26.45%. The majority of the PDDI are moderate (57; 44.9%) in severity level. Factors like the advanced age group of more than 40 years, more than one comorbidity, staying in the hospital for more than four days, and more than five drugs per prescription were positively associated with having PDDI with a P value less than 0.05. Clinical pharmacists need to work with the healthcare team to provide interventions to reduce clinically significant interactions and improve clinical outcomes.

Keywords: Drug interaction, DDI, Predictors, Prevalence and Severity

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1. INTRODUCTION

The drug-related problems like adverse drug reactions, drug-drug interactions, and medication non-adherence remain a major challenges in the clinical practice to enhance better clinical outcomes.[1] A drug-drug interaction (DDI) is an event that occurs when the effect of one drug is modified by another drug that has been taken concomitantly.[2] The effect of a concomitant drug is altered by either pharmacokinetic or pharmacodynamic interaction.[3] The DDI may result in a change in the drug's efficacy, treatment failure, or anything that may range from minor illness to fatal outcome.[2] However, not all potential drug-drug interactions (PDDI) develop a clinically significant adverse outcome. Sometimes, DDI brings particular beneficial or desired outcomes by enhancing the effect of the concomitant drug and reducing the risk of an adverse effect.[3] A DDI's undesired outcomes will increase the treatment's morbidity, mortality, and cost[4]. The Boston Collaborative Drug Surveillance Program revealed that among 10,000 patients who were getting exposed to 83,200 drugs, 3600 developed ADRs. Of this 6.5% resulted from DDI. [5] The Harvard medical practice study also shows that 20% of adverse events in the hospital are due to drugs, in these 8% were due to DDI.[6] According to a report published by the Institute of Medicine, annually, 98000 deaths occur due to drug-related errors in hospitals[7]. In India, the prevalence of PDDI ranges from 8.3% to 63%.[8–10] Globally, the prevalence of PDDI ranges from 2.8% to 63.0%, depending on the population under investigation and study settings.[11] Becker et al found that 0.54% of emergency visits, 0.57% of hospital admissions, 0.12% of patients readmitted to the hospital due to possible DDIs, and 4.8% of the elderly admissions to the hospital were due to drug interactions[12]. The DDIs impart a 20-30% incidence of ADRs, which may increase hospital admission or prolong the length of hospital stay.[13] A study conducted in Ethiopia reported that the rate of PDDI in five and seven or more drugs prescription was 40.0% and 80.0%, respectively.[14] One more study conducted in Pakistan revealed that 164 (75.9%) patients taking seven or more medications have at least one PDDI. Advanced aged or elderly people are at high risk for developing DDI, because this population is under multiple medication therapies to manage chronic conditions.[17] Evidence from various Indian studies revealed that clinically significant DDI is attributed to a rise in the morbidity of patients admitted to tertiary care hospitals. Interestingly, half of the ADRs resulting from DDI are predictable and preventable.[15] Hospitalized patients are expected to develop PDDI, because of comorbidities, risk factors, polypharmacy, modification of drug therapy, and changing physicians for single therapy.[16] It is necessary to synthesize evidence on prevalence of DDI and associated risk factors targeted towards rural hospital settings. With this background, this study was conducted to assess the prevalence, risk factors, and severity of PDDIs among hospitalized patients in an NGO charity hospital in the Anantapur district.

2. MATERIALS AND METHODS

2.1 Study Design and Settings

This is a cross-sectional analytical study conducted in the in-patient general medicine department of a secondary care referral hospital located in a small village in Bathalapalli, Anantapur district, Andhra Pradesh, India. This study was carried out for a period of six months from March 2019 to August 2019. The study was initiated after getting due permission from the hospital administrative department and clearance from the RIPER Institutional Review Board.

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

- ✓ Patients irrespective of gender, aged 18 years or more, and admitted to the in-patient medical wards
- ✓ Patients taking more than one medication are eligible for the study.

2.2.2 Exclusion Criteria

- ✓ Patients under treatment on an ambulatory, outpatient, and Intensive Care Unit (ICU) basis
- ✓ Also, patients who were unwilling to give consent relapsed of disease during the study period and were discharged before collecting data.

2.3 Ethical Considerations

The study was approved by the RIPER Institutional Review Board (Reg. No: RIPER-IRB-PP-2018-043). All the participants were explained about study objectives, outcomes, and anticipated benefits before taking oral and written informed consent. The data regarding subjects were kept confidential and anonymity was maintained before, during, and after the completion of the trial.

2.4 Sample Size and Sampling Technique

To estimate the prevalence of the PDDI, a single proportional population formula was used to calculate the required sample size for the current study. By considering a prevalence of PDDI as 19.3% reported in the study conducted in a South Indian hospital, 95% confidence interval, 5% of margin of error, design effect 1%, and 80% power, which was calculated as 239.[9] To adjust withdrawal and missing data 10% was added for the required sample and the final sample size was estimated as 263. The eligible participants were selected for the study by using a non-probable convenient sampling technique.

2.5 Study Procedure

Pre-designed data collection forms were used to collect the data from the case sheets of all in-patients admitted in male and female medical wards of a secondary care NGO charity hospital, Bathalapalli, Anantapur during the study period. A total of 310 subjects who met the study criteria were enrolled in the study after taking oral and written informed consent. Patient's demographics (age, and gender), and clinical (working/established diagnosis, comorbidities, length of hospital stay, the average number of drugs, and list of medications administered concomitantly) were collected from admission to discharge by the review of medical records and patient interview/caregiver interview. The collected data were subjected to identify and grade the level of severity, onset, and scientific evidence of PDDI by using IBM Micromedex® Drug Interaction Checking – electronic version (IBM Watson Health, Greenwood Village, Colorado, USA).[17]

Level of severity

- *Contraindicated*: The drugs are contraindicated for concomitant administration.

- *Major:* The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects
- *Moderate:* The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy
- *Minor:* The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in the therapy
- *Unknown:* Unknown
- Level of onset
- *Rapid:* The effect of interaction appears within 24 hours of administration of the drug combination
- *Delayed:* The interaction effect appears beyond the 24 hours of administration of the combination drugs.
- Level of scientific evidence (documentation)
- *Excellent:* The interaction has been very clearly demonstrated in well-controlled trials
- *Good:* Studies strongly support that interaction exists; however, evidence of well-controlled trials lacking
- *Fair*: Available evidence is poor, but clinicians suspect the interaction based on the pharmacological mechanism or, evidence is good for an interaction of pharmacologically similar drug or category
- *Poor:* Theoretically, the interaction may occur, but reports are very limited, such as few case reports are present in the literature
- *Unlikely:* Data are very poor and lack a pharmacological basis.

2.6 Data Processing and Analysis

The collected data were analyzed by using SPSS software v16 (SPSS Inc., Chicago, IL, USA). Demographics, PDDI, and severity level of PDDI was presented in descriptive statistics like frequency, proportion, mean, and SD. Whereas the association between patient demographics (Gender, age, comorbidities, hospital stay, and an average number of drugs) and the development of PDDI was analyzed by Binary Logistic regression analysis by considering $P < 0.05$ as statistically significant.

3. RESULTS

Among 310 in-patients, 82 cases had 127 PDDI with a prevalence of 26.45%. Majority of the patients were males (188; 60.6%), aged between 18-40 years (129; 49.6%), suffering with infectious diseases (78; 25.2%), and no comorbidities (177; 57.1%). The average length of hospital stays and number of drugs prescribed during hospital stay were 4.68±2.34 and 6.43±3.56 respectively. Distribution of the patient demographics and clinical characteristics was represented in Table 1.

Table 1: Demographic and clinical characteristics of the study participants (n=310)

Variable	Frequency (%)
Gender	
Male	188 (60.6)
Female	122 (39.3)
Age in years (Mean ± SD)	49.64±8.3
18-40	129 (41.6)
41-60	97 (31.3)
>60	84 (27.1)
Diagnosis	
Infectious diseases	78 (25.2)
Diabetes mellitus	27 (8.7)
Cardiovascular disorder	48 (15.5)
Joint disorders	34 (10.9)
Gastrointestinal problems	18 (5.8)
Liver disease	12 (3.9)
Haematological disorders	21 (6.8)
Respiratory problems	15 (4.8)
Thyroid disorders	18 (5.8)
Renal disorders	12 (3.9)
Neurological problems	5 (1.6)
Stroke	8 (2.6)
Others	22 (7.1)
Comorbidities	
None	177 (57.1)
One	80 (25.8)
Two	38 (12.2)
More than or equal to three	15 (4.8}
Hospital stays (Days)	4.68±2.34
≤ 4 days	214 (69.0)
> 4 days	96 (30.9)
Average no. of drugs/day	6.43±3.56
<5	194 (62.6)

≥5	116 (37.4)
Last 12 months, hospital admissions	
Yes	174 (56.1)
No	136 (43.8)

SD=Standard Deviation

A total of 127 PDDI were identified among the inpatients of the medical wards. Majority of the PDDI are moderate (57; 44.9%) in the severity level. The distribution of the severity level of PDDI and observed DDI and their outcomes were represented in Figure1 and Table 2 respectively. All observed PDDI were communicated to the respective consultant or physician to make changes in the clinically significant DDI.

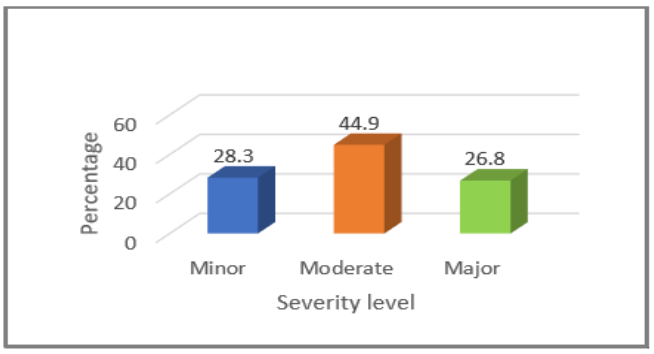

Fig 1: Distribution of the severity of drug-drug interactions

Table 2: Distribution of the drug-drug interactions and potential outcomes

Perpetrator drug	Object drug	Frequency(%)	Potential outcomes
		Minor Interactions	
Cyanocobalamin	Ascorbic acid	6 (4.7)	Reduce the effectiveness of cyanocobalamin
Diazepam	Omeprazole	8 (6.3)	Prolonged diazepam effects
Gentamycin	Penicillin	3 (2.4)	Decrease efficacy of Gentamycin
Amoxycillin	Gentamycin	11 (13.5)	Decrease efficacy of Gentamycin
Terbutaline	Theophylline	1 (0.8)	Decreases Theophylline concentration
Furosemide	Phenytoin	1 (0.8)	Reduce furosemide effect
Ranitidine	Aspirin	6 (4.7)	Reduce the antiplatelet effect of aspirin
		Moderate Interactions	
Iron	Pantoprazole	8 (6.3)	decreases iron bioavailability
Acetaminophen	Phenytoin	1 (0.8)	Decrease Acetaminophen concentration
Furosemide	Hydrocortisone	4 (3.1)	Hypokalaemia
Dexamethasone	Phenobarbital	3 (2.4)	Decreases the effect of steroid
Rifampin	Tinidazole	1 (0.8)	Reduce the concentration of tinidazole
Furosemide	Albuterol	5 (3.9)	Hypokalaemia
Omeprazole	IFA	4 (3.1)	Reduce iron bioavailability
Haloperidol	Olanzapine	1 (0.8)	Increased risk of parkinsonism
Aminophylline	Azithromycin	1 (0.8)	Increase serum theophylline concentrations.
Methylprednisolone	Phenytoin	2 (1.6)	Reduce the methylprednisolone effectiveness.
Digoxin	Furosemide	2 (1.6)	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias).
Ferrous sulphate	Levothyroxine	7 (5.5)	Resulting in hypothyroidism.
Diclofenac	Telmisartan	2 (1.6)	Renal dysfunction / Increased BP
Doxycycline	Rifampin	2 (1.6)	Loss of doxycycline efficacy
Ascorbic acid	pantoprazole	6 (4.7)	Decreased Bioavailability
Aspirin	Metoprolol	2 (1.6)	Increased blood pressure.
Aspirin	Captopril	4 (3.1)	Increased blood pressure.
Ceftriaxone	Aminophylline	1 (0.8)	Increased plasma drug concentration aminophylline
Atorvastatin	Azithromycin	1 (0.8)	Increased risk of rhabdomyolysis
		Major	
Ranitidine	Tramadol	2 (1.6)	Respiratory suppression
Prednisolone	Diclofenac	2 (1.6)	GI Bleeding
Prednisolone	Amlodipine	1 (0.8)	Elevated blood pressure
Ibuprofen	Prednisolone	2 (1.6)	Increased risk of bleeding
Diclofenac	Hydrocortisone	2 (1.6)	Increased risk of bleeding
Aspirin	clopidogrel	1 (0.8)	Increased risk of bleeding

Aspirin	Heparin	1 (0.8)	Increased risk of bleeding
Clopidogrel	Heparin	1 (0.8)	Increased risk of bleeding
Azithromycin	Digoxin	1 (0.8)	Digoxin toxicity
Metronidazole	Ciprofloxacin	1 (0.8)	Tachycardia
Metronidazole	Levalbuterol	1 (0.8)	Tachycardia
Piperacillin-tazobactam	Vancomycin	1 (0.8)	Nephrotoxicity
Ciprofloxacin	Metronidazole	1 (0.8)	QT Prolongation
Ciprofloxacin	Tramadol	1 (0.8)	Risk of seizure
Fluconazole	Metronidazole	1 (0.8)	QT Prolongation
Formoterol	Azithromycin	1 (0.8)	QT Prolongation
Azithromycin	Metronidazole	1 (0.8)	QT Prolongation
Salbutamol	Azithromycin	1 (0.8)	QT Prolongation
Azithromycin	Ondansetron	1 (0.8)	QT Prolongation
Formoterol	Ondansetron	1 (0.8)	QT Prolongation
Metronidazole	Ondansetron	1 (0.8)	QT Prolongation
Ondansetron	HCQ	1 (0.8)	QT Prolongation
Ondansetron	Tramadol	1 (0.8)	Serotonin syndrome
Ondansetron	Dextromethorphan	1 (0.8)	Serotonin syndrome
CPM	Ondansetron	1 (0.8)	Serotonin syndrome
Cetirizine	Clobazam	1 (0.8)	Increased risk of sedation
Clobazam	Lorazepam	1 (0.8)	Increased risk of sedation
Cetirizine	Tramadol	1 (0.8)	Increased risk of sedation
Diclofenac	Amlodipine	1 (0.8)	Elevated blood pressure
Diclofenac	Enoxaparin	1 (0.8)	Increased risk of bleeding

A total of 127 potential drug-drug interactions were observed in 82 patients with an average of 1.54. Most of the PDDI are moderate (57; 44.9%) in the severity level, pharmacodynamic mechanism (), and continue monitoring as the proposed intervention. Distribution of the prevalence of the PDDI among patients admitted in the medical wards were represented in Table 3.

Table 3: Prevalence of potential drug-drug interactions among patients admitted in medical wards

Variables	Frequency (%)
Total number of PDDI (average per prescription)	127 (1.54)
Severity level	
Minor	36 (28.3)
Moderate	57 (44.9)
Major	34 (26.7)
Prevalence according to mechanism	
Pharmacokinetic	38 (29.9)
Pharmacodynamic	63 (49.6)
Unknown	26 (20.4)
Proposed intervention for management of PDDI	
Dosage adjustment	21 (16.5)
Alternative drug	8 (6.3)
Continue with monitoring	40 (31.4)
No intervention	32 (25.1)
Multiple	26 (20.4)

Factors like advanced age group of more than 40 years, more than one comorbidity, staying in the hospital for more than four days, and more than five drugs per prescription were positively associated to have PDDI with a P value less than 0.05. The proportion of the PDDI distribution, odds ratio, and P value for each variable was represented in Table 4.

Table 4: Logistic regression analysis of factors associated with potential drug-drug interactions

Variable	Total (%)	Presence of PDDI (%)	Odds ratio (95% CI)	*P-value*
Gender				
Male	188 (60.6)	51 (27.1)	Ref	Ref
Female	122 (39.3)	30 (23.4)	0.82 (0.48-1.38)	0.544
Age in years (Mean ± SD)				
18-40	129 (41.6)	18 (13.9)	Ref	Ref
41-60	97 (31.3)	29 (29.9)	2.63 (1.36-5.09)	0.005
>60	84 (27.1)	34 (40.5)	4.19 (2.16-8.13)	<0.001
Comorbidities				
None	177 (57.1)	34 (19.2)	Ref	Ref

One	80 (25.8)	21 (26.2)	1.49 (0.80-2.79)	0.267
Two	38 (12.2)	17 (44.7)	3.40 (1.62-7.14)	0.001
More than or equal to three	15 (4.8)	9 (60.0)	6.31 (2.10-18.93)	<0.001
Hospital stays (Days)				
≤ 4 days	214 (69.0)	45 (21.0)	Ref	Ref
> 4 days	96 (30.9)	36 (37.5)	2.25 (1.33-3.82)	0.003
Average no. of drugs/day	6.43±3.56			
<5	194 (62.6)	41 (21.1)	Ref	Ref
≥5	116 (37.4)	40 (34.5)	1.96 (1.17-3.29)	0.014

4. DISCUSSION

Drug-drug interaction is the most common drug-related problem among hospitalized patients that can cause adverse reactions and change therapeutic efficacy. The current study provides the prevalence, severity of PDDI in hospitalized patients. This study also explores the various factors associated with the development of DDI in hospitalized patients. The prevalence of the potential DDI was found to be 26.45%. This estimate was little high compared to the prevalence (19.3%) of the study conducted in a tertiary care hospital located in southern part of India.[9] Whereas, one more prospective study conducted in the Bangalore showed a higher prevalence (52.17%) compared to our study.[18] Few of the studies conducted in Ethiopia (78.2%), Romania (78.03%), and Thailand (27.9%) also showed high prevalence compared to our study. A wide variation was observed in the prevalence of PDDI among intra and international studies. This is due to changes in the software used, practice guidelines, settings, availability of alternative drugs, and clinical pharmacists in the hospital. Involvement of clinical pharmacists in the review of medications charts will significantly reduce the prevalence of PDDI. Pharmacists can intervene with clinically significant DDI to improve the outcomes of hospitalized patients. Among 127 PDDI, major (26.8%) are less in relation with minor (44.9%) and moderate (26.8%) severity level. Whereas, the rate major PDDI was contrast in the studies conducted at Ethiopia (13.1%), India (53.3%), and Pakistan (7.0%) compared with our study.[1,2,9] The change in the rate of major PDDI among the studies was mainly due to change in prescribing practice, targeted population, study time and settings, and availability of the clinical pharmacist. Even if there will be a major PDDI in the prescription, it is very important to consider available documented evidence and the clinically significant interaction to make the decision in modification of the regimen. Antibiotics are involved in the development of major DDI. The frequency of the major, moderate, and minor depended on the frequency of the prescribing of that combination. The current study revealed that, there was no statistically significant difference between male or female in the development of DDIs. As the development of DDI is purely dependent on the prescribing pattern than the patient's individual factor called age. These findings also supported by a study conducted in a tertiary care hospital, Ethiopia[2]. The study shows that middle (41-60 Years) and advanced age (> 60 Years) categories are significantly associated to develop DRPs. This may be because,as age increases, the number of drugs required to treat multiple disease conditions also increases. Polypharmacy is the major risk factor for the occurrence of DRPs. Similar findings were also observed in the study conducted in Puducherry, India[15]. Other factors like, suffering with more than one co-morbid condition, hospital stay of more than four days, and average number of drugs of more than four are significantly associated with developing DRPs. Similar findings are also observed in the studies conducted in Ethiopia, India, and Pakistan.[1,2,18] If the person suffers with more comorbidities, we need to recommend multiple medications to improve the clinical outcomes. [19]The multiple medications administration is associated with high risk of developing DDI. [20] So, it is necessary to closely monitor the patients suffering with comorbidities, long length hospital stay, and polypharmacy for the occurrence of PDDI and treat clinically significant interactions with appropriate intervention. [21-23]

5. STRENGTHS AND LIMITATIONS

The current study provides evidence on the prevalence and predictors towards PDDI. This helps in formulating an appropriate intervention to reduce the burden of DDI in the secondary care referral hospital. As the study is a cross-sectional survey, it identifies associations, not an exact cause-effect relationship between predictors and the development of PDDI. Furthermore, the study was conducted in a rural secondary care referral hospital. So, the findings of this study may not generalize to primary and tertiary care hospitals.

6. CONCLUSION

The study concludes that the prevalence of PDDIs in hospitalized medical ward patients was 26.45%. Majority of the PDDI are moderate (57; 44.9%) in severity level. Factors like the advanced age group of more than 40 years, more than one comorbidity, staying in the hospital for more than four days, and more than five drugs per prescription were positively associated to have PDDI with a P value less than 0.05. Developing drug policy guidelines focused on factors related to PDDIs may reduce the burden of DRPs and improve patient outcomes. Clinical pharmacists need to work with the healthcare team in providing interventions to improve clinical outcomes.

7. ACKNOWLEDGEMENT

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8. AUTHORS CONTRIBUTION STATEMENT

This work was carried out in collaboration among all authors. Author Y Samhitha Reddy designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author K Somashekar Reddy helped in hypothesis framing, literature review, design, data collection, data entry, and managed the analyses of the study. All authors read and approved the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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