ORIGINAL RESEARCH PAPER

Pharmacy

KEY WORDS: Drug-Drug Interactions, Multi-specialty hospital, Prescriptions, Life threatening effects, improved therapeutic outcomes.

EXPLORATION OF PRESCRIPTIONS CONTAINING DRUG-DRUG INTERACTIONS IN MULTISPECIALITY HOSPITALS

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ABSTRACT

Objective: To determine the drug-drug interaction with the management of adverse drug interactions (ADIs) in elderly population.

Methods: The prospective observational study include all inpatients taking at least two medications who were admitted to General wards of a Multi specialty hospital and were followed until discharge. DDIs were identified using standard references.

Results: A total of 233 drug-drug interactions were detected from 109 patients over the six month study period. In 109 patients, 64 (58.71%) were male patients and 45 (41.28%) were female patients, that (41-60 years) age group had 46 patients which contributes (42.20%) followed by (61-80 years) age group had 28 patients which contributes (25.68%) in the total study population. Many interactions were observed in elder patients, In 902 drugs were prescribed to 109 patients. The average number per patient was 8.25. 72(66.04%) were using 6-10 medications followed by 20(18.34%) patients were using more than 10 medications and 17(15.59%) patients were using 3-5 medications has found. Severity shows that 107(45.92%) were moderate interactions followed by 104(44.63%) were major drug interactions and 22(9.44%) were minor drug interactions. In mechanism 108 (46.35%) were pharmacodynamic drug interaction followed by 94 (40.34%) were pharmacokinetic drug interaction and 31 (13.30%) were unknown mechanism in the total interactions. not specified onset of action were 121(51.93%) and the delayed onset of interactions was found to be 78(33.47%) on the rapid onset of interactions were 34(14.59%). Among 233 pDDIs, there are 47 adverse drug interactions were observed and recorded during the study period. The percentage of adverse drug interactions was found to be 20.17% Anti-hypertensive agents, Anti-coagulants and NSAIDS are most common drug which were present in observed drug interactions. Table 6.11 shows that based on clinical effects hypotension 6(12.76%) was most important effect followed by hyperkalemia 4(8.51%) and bleeding 4(8.51%). In the adverse drug interactions, 21(44.68%) interactions were PD and 17(30.17%) were pharmacokinetic interactions. From that adverse interactions, 31(65.95%) were moderate interactions followed by 10(21.27%) were major interactions and 6(12.76%) were minor interactions respectively. The monitoring for the adverse drug effects 168(72.10%) was the most popular intervention followed by dose adjustment 25(10.72%) and avoid concurrent use 16(6.86%) following potential drug-drug interactions. interventions to 233 drug interactions, in which the suggestion was accepted to 64 (27.46%) pDDIs and suggestion was not accept to 169(72.53%) pDDIs. In that 64 (27.46%) pDDIs has managed by dose adjustment, administration time change and drug alteration with in same pharmacological class.

Conclusion: Clinicians need to be aware of most common DDIs occurring in the clinical practice and should be cautious in using the medications especially inpatients as they are more susceptible to DDIs. Clinical pharmacist can play a vital role in the detection, prevention and management of DDIs which can result in improved therapeutic outcomes and decreased unnecessary healthcare expenditure.

INTRODUCTION:

A drug interaction is a circumstance in which one drug affects the activity of another drug, when both are administered simultaneously. The net effect of the interaction may be, Synergism or additive effect, Antagonism or substractive effect and Idiosyncratic effect. Typically, interactions between drugs are known as drug-drug interaction. However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (drug-plant interactions). Drug Interaction is an increasingly important cause of adverse drug reactions.[1]

There are many drug-drug interactions found now-a-days in various prescriptions by different hospitals or clinics. These interactions may alter the desired therapeutic effect and lead to many serious complications, overdoses, toxicity and which may sometimes also lead to death [2-4]. These drug - drug interactions are classified into major/severe, moderate/significant and minor [5].These can be predicted by knowing the standard dose and frequency, pharmacology, adverse effects, contraindications of all the drugs prescribed by the physician.[3]The incidence of drug-drug interactions increases with increase in number of drugs taken by the patient that is may be prescribed drugs or non-prescribed drugs [poly pharmacy] [6-7].

Knowing about drug-drug interactions helps in detecting which drugs should not be given in combination, which drugs have narrow or broad spectrum of activity, or which drug dose or frequency are to be adjusted when many drugs are given or which drugs need intensive monitoring for their plasma concentrations.

Knowing about these is also important as it help to know about the medicines we take. If several different medications are prescribed by physicians or any health care provider [8], careful and keen follow up should be made so as to prevent the drug-drug interactions which lead to decreased desired therapeutic effect or further complications. This help us to avoid potential drug interactions.

Increased vigilance by clinicians at the time of changing or adding drugs to assess the correct diagnosis improves the chance of identifying unwanted drug interactions before they cause significant harm by causing drug-drug interactions [7-12].

ETHICAL CLEARANCE:

The ethical clearance for the study was obtained from the local institutional ethical committee.

MATERIALS AND METHODS:

All patients admitted to the general wards were screened on a daily basis to enroll in to the study. Patients receiving more than one drug and admitted for more than a day was the inclusion criteria to enroll subjects in to the study. Patients who satisfied the study criteria were enrolled and followed till the day of discharge.

Patient's demographic details, present and past medical history as well as current medications were collected from various sources and documented. The medications of all those patients who were enrolled into the study were subjected to analysis for potential DDIs. Potential DDIs were identified using the online version of computerized interaction detection system such as Lexicomp®, Micromedex®, Medscape® and Drugs® and Stockley's Drug Interaction textbook to promote greater sensitivity in the study. Only potential DDIs rated as contraindicated, major, moderate or minor by at least any two of the DDIs-checkers were included in the analysis.

Patients were monitored intensively for occurrence of ADRs. The reported ADR was categorized as adverse drug interaction (DDI) where the suspected drug is involved in the DDI. The DDIs which led to DDIs were classified as pharmacokinetic (absorption, distribution, metabolism or elimination) and pharmacodynamic (synergism / additive effect or antagonism) interactions and their percentage values were calculated. The onset of DDIs was classified into either rapid (the effect of interaction occurred within 24 hours of administration) or delayed (the effect occurred if the interacting combination is administered for more than 24 hours, that is, days to weeks).

RESULTS:

DDI is always a matter of concern in the effective management of patient illness. It may pose a significant health hazards to patients when risk benefits ratio of combining interacting drugs is not accurately estimated. Drug- drug interactions can result in anything from minor morbidities up to fatal consequences.

1.Patient Demographic Data:

The present study identified the pattern of pDDIs among patients admitted to the hospitals. The data of 260 patients admitted to inpatients during the period of Feb 2018- July 2018 were analyzed for assessment of pDDI. Out of 260 patients 109 patients prescription having pDDIs and 151 patients prescription didn't contains any pDDIs. Shows in Figure 6.1.

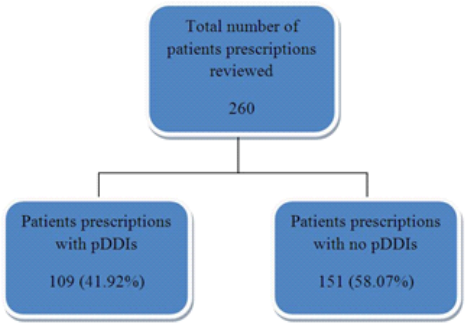

FIGURE 6.1: OCCURRENCE OF PDDIS IN STUDY POPULATION

1.Gender wise distribution:

Table 6.1: Gender wise distribution (N=109)

Gender	N	%
Male	64	58.71
Female	45	41.28
Total	**109**	**100%**

Table 6.1 showed that out of 109 patients, 64 (58.71%) were male patients and 45 (41.28%) were female patients. More interactions were seen in male patients when compare to female patients.

2.Age group distribution:

Table 6.2: Age group distribution (N=109)

Age	Male		Female		Total	
	N	%	N	%	N	%
Less than 5 years	0	0	1	0.91	1	0.91
5-20 years	6	5.50	3	2.75	9	8.25
21-40 years	7	6.42	7	6.42	14	12\.84
41-60 years	29	26.60	17	15.59	46	42.20
61-80 years	17	15.59	11	10.09	28	25.68
Above 80 years	5	4.58	6	5.50	11	10.09
Total	64	58.69%	45	41.26%	109	100%

Table 6.2 shows that (41-60 years) age group had 46 patients which contributes (42.20%) followed by (61-80 years) age group had 28 patients which contributes (25.68%) in the total study population. Many interactions were observed in elder patients.

3.Duration of Stay:

The relationship between the hospital stay and occurrence of drug interactions in patients are explained as follow's.

Table 6.3: Duration of Stay (N=109)

Days	Male	%	Female	%	Total	%
3-4	20	18.34	19	17.43	39	35.77
5-6	42	39.62	25	22.93	67	61.46
> 7	2	1.83	1	0.91	3	2.75
Subtotal	**64**	**59.79%**	**45**	**41.27%**	**109**	**100%**

Table 6.3 shows that the 5-6 days admitted patients showed higher interactions than others. The number of patient is 67 (61.46%), followed by 3-4 days admitted patients contributes 39(35.77%), and more than 7 days admitted patients were 3(2.75%).

4.Number of drugs used by study patients:

Table 6.4: Number of drugs used by study patients (N=109)

No. of drug prescribed	Male	%	Female	%	Total	%
3-5	11	10.09	6	5.50	17	15.59
6-10	43	39.44	29	26.60	72	66.04
> 10	10	9.17	10	9.17	20	18.34
Total	**64**	**58.72%**	**45**	**41.27%**	**109**	**100%**

In the study there are 902 drugs were prescribed to 109 patients. The average number per patient was 8.25. Table 6.4 shows that, 72(66.04%) were using 6-10 medications followed by 20(18.34%) patients were using more than 10 medications and 17(15.59%) patients were using 3-5 medications has found.

2.POTENTIAL DRUG-DRUG INTERACTION:

Out of 260 prescriptions analyzed, 109 prescriptions comprised of potential drug interactions, according to the web source (i.e Lexicomp and Medscape interaction software etc.,) which is used to find pDDIs, drug interaction mechanism's and onset of action we found that 233 drug interactions were present. Among 233 drug interaction different types of interaction combinations were it identified.

Severity Of Drug-drug Interaction:

Out of 233 pDDIs, has classified into three classes they are minor, moderate and major interactions based on its severity.

Table 6.5: Severity of drug-drug interaction (N=233)

Severity	Male	%	Female	%	Total	%
Minor	11	4.72	11	4.72	22	9.44
Moderate	73	31.33	34	14.59	107	45.92
Major	56	24.03	48	20.60	104	44.63
Total	**140**	**60.08%**	**93**	**39.91%**	**233**	**100%**

(Where N is a total number of DI)

Table 6.5 shows that 107(45.92%) were moderate interactions followed by 104(44.63%) were major drug interactions and 22(9.44%) were minor drug interactions.

5.MECHANISM OF DRUG-DRUG INTERACTIONS:

They are different types of mechanism of drug interactions namely pharmacokinetic, phamacodynamic or unknown drug interaction. In this study we found out the mechanism of drug interaction theoretically.

Table 6.6: Mechanism of drug-drug interactions N=233

Mechanism of DDI	Total	%
Pharmacokinetic drug interactions	94	40.34%
Pharmacodynamic drug interactions	108	46.35%
Unknown	31	13.30%
Total	**233**	**100%**

Table 6.6 shows that 108 (46.35%) were pharmacodynamic drug interaction followed by 94 (40.34%) were pharmacokinetic drug interaction and 31 (13.30)% were unknown mechanism in the total interactions. From this, pharmacodynamic interactions are higher than others.

6.PHARMACOKINETIC DRUG INTERACTION:

The pharmacokinetic drug interaction divided into four types that is absorption, distribution, metabolism and elimination. Among 233 drug interactions pharmacokinetic drug interactions are 94 which contributes 40.34% can be found out theoretically by DI software's, from that 94 interactions 17 interactions were clinically observed. The types of pharmacokinetic drug interactions details are listed below.

Table 6.7: Pharmacokinetic drug interaction (N=94)

Mechanism		Male		Female		Total	
		N	%	N	%	N	%
Pharmacokinetics	Absorption	9	9.57	6	6.38	15	15.95
	Distribution	2	2.12	0	0	2	2.12
	Metabolism	35	37.23	24	25.53	59	62.76
	Elimination	11	11.70	7	7.44	18	19.14
Subtotal		**57**	**60.62%**	**37**	**39.35%**	**94**	**100%**

(Where N is total number of PK DI)

Table 6.7 showed that out of 94 pharmacokinetic drug interactions, 59(62.76%) were metabolic drug interactions followed by elimination 18(19.14%), absorption 15(15.95%) and distribution 2 (2.12%). In which metabolism of DDI having more interactions than others.

7.PHARMACODYNAMIC DRUG INTERACTION:

The pharmacodynamic drug interaction divides into two types that is synergism and antagonism. Among 233 drug interactions pharmacodynamic drug interactions are 108 which contributes 46.35% can be found out theoretically by DI software's, from that 108 interactions 21 interactions were clinically observed. The types of pharmacodynamic drug interactions details are listed below.

Table 6.8: Pharmacodynamic drug interaction (N=108)

Mechanism		Male		Female		Total	
		N	%	N	%	N	%
Pharmacodynamic	Synergism	38	35.18	27	25	65	60.18
	Antagonism	25	23.14	18	16.66	43	39.81
Subtotal		**63**	**58.32%**	**45**	**41.66%**	**108**	**100%**

(Where N is total number of PD DI)

Table 6.8 shows that out of 108 PD interactions 65(60.18%) interactions were synergism and 43(39.81%) were antagonism.

8.UNKNOWN MECHANISM OF DRUG INTERACTION:

Out of 233 drug interactions 31(13.30%) drug interactions mechanism were not clearly understand.

Table 6.9: Unknown mechanism of drug interaction (N=31)

Mechanism	Male		Female		Total	
	N	%	N	%	N	%
Unknown	20	64.51	11	35.48	31	100

(Where N is total number of Unknown DI)

Table 6.9 shows that 31 drug interactions are unknown mechanism from that 20(64.51%) were male patients and 11(35.48%) were female patients.

IX.ONSET OF ACTION IN DRUG INTERACTION:

Table 6.10: Onset of action in drug interaction (N=233)

Onset of action	Male	%	Female	%	Total	%
Rapid	21	9.01	13	5.57	34	14.59
Delayed	50	21.45	28	12.01	78	33.47
Not specified	69	29.61	52	22.31	121	51.93
Total	**140**	**60.07%**	**93**	**39.89%**	**233**	**100%**

(Where N is a total number of DI)

Table 6.10 shows not specified onset of action were 121(51.93%) and the delayed onset of interactions was found to be 78(33.47%) on the rapid onset of interactions were 34(14.59%)

X.CLINICAL OBSERVED POTENTIAL DRUG-DRUG INTERACTIONS:

Out of 233 drug interactions 47 DDIs were found out by clinical observation.

Table 6.11: Clinical observed potential drug-drug interactions (N=47)
(Where N is clinically observed pDDIs)

Drugs	Clinical effects	Severity			Mechanism			Total	%
		Mild	Moderate	Major	PK	PD	Uknown		
Levothroxine + Pantoprazole, Omeprazole + Levothyroxine	Increased TSH level	2	1	0	0	0	3	3	6.38
Aspirin + Hydrocortisone, Aspirin + Meloxicam	GI Ulcer	2	1	0	3	0	0	3	6.38
Ranitidine + Theophylline	Theophylline toxicity	2	0	0	2	0	0	2	4.25
Amlodipine + Aspirin, Heparin + Clopidogrel, Aspirin + Fondaparinux	Bleeding	0	3	1	0	4	0	4	8.51
Digoxin + Furosemide, Digoxin + Atorvastatin, Digoxin + Torsemide	Arrhythmias	0	3	0	0	3	0	3	6.38
Amlodipine + Metoprolol, Ramipril + Torsemide, Rxamipril + Metalozone	Hypotension	0	6	0	0	6	0	6	12.76
Asprin + Spironolactone, Potassium chloride + Spironolactone	Hyperkalemia	0	4	0	0	4	0	4	8.51
Phenytoin + Clopidogrel, Omeprazole + Alprazolam	Ataxia and Tremor	0	2	0	2	0	0	2	4.25
Aspirin + Insulin	Hypoglycemia	0	1	0	0	0	1	1	2.12

Torsemide + Clopidogrel	Muscular cramps	0	2	0	2	0		2	4.25
Moxifloxacin + Hydrocortisone	Tendonitis	0	2	0	0	0	2	2	4.25
Acetaminophen + Phenytoin, Acetaminophen + Carbamazepine	Hepatotoxicity	0	3	0	3	0	0	3	6.38
Atorvastatin + Ranolazine, Verapamil + Atorvastatin	Myopathy	0	2	1	3	0	0	3	6.38
Levofloxacin + Diclofenac	Seizure	0	1	0	0	1	0	1	2.12
Haloperidol + Ondansetron, Domperidone + Atorvastatin	QT interval prolongation	0	0	2	1	1	0	2	4.25
Verapmil + Carvedilol	Bradycardia	0	0	1	1	0	0	1	2.12
Metolazone + Torsemide	Electrolytic imbalance	0	0	1	0	0	1	1	2.12
Prometazine + Tramadol, Pentazocin + Tramadol	Serotonic syndrome	0	0	2	0	1	1	2	4.25
Nabumetone + Methotrexate	Thrombocytopenia	0	0	1	1	0	0	1	2.12
Clobazam + Mirtazapine	CNS depression	0	0	1	0`	1	0	1	2.12
Total		**6**	**31**	**10**	**17**	**21**	**9**	**47**	
%		**12.76%**	**65.95%**	**21.27%**	**36.17%**	**44.68%**	**19.14%**	**100%**	

Among 233 pDDIs, there are 47 adverse drug interactions were observed and recorded during the study period. The percentage of adverse drug interactions was found to be 20.17% Anti-hypertensive agents, Anti-coagulants and NSAIDS are most common drug which were present in observed drug interactions. Table 6.11 shows that based on clinical effects hypotension 6(12.76%) was most important effect followed by hyperkalemia 4(8.51%) and bleeding 4(8.51%). In the adverse drug interactions, 21(44.68%) interactions were PD and 17(30.17%) were pharmacokinetic interactions. From that adverse interactions, 31(65.95%) were moderate interactions followed by 10(21.27%) were major interactions and 6(12.76%) were minor interactions respectively.

XII. MANAGEMENT OF POTENTIAL DRUG-DRUG INTERACTIONS:

The available management options for all the drug interactions were obtained by different web sources (Medscape and Lexicomp drug interaction software etc.,).

Table 6.12: Management of potential drug-druginteractions (N=233)

Management	Male		Female		Total	
	N	%	N	%	N	%
Avoid concurrent use	7	3.00	9	3.86	16	6.86
Use of alternative drug	8	3.43	2	0.85	10	4.29
Discontinuation of drug	2	0.85	5	2.14	7	3.00
Dose adjustment	17	7.29	8	3.43	25	10.72
Continue with monitoring	101	43.34	67	28.75	168	72.10
Time alteration	5	2.14	2	0.85	7	3.00
Subtotal	**140**	**60.05%**	**93**	**39.88%**	**233**	**100%**

Table 6.12 shows that monitoring for the adverse drug effects 168(72.10%) was the most popular intervention followed by dose adjustment 25(10.72%) and avoid concurrent use 16(6.86%) following potential drug-drug interactions.

RESULT OF PHARMACIST INTERVENTION:

We proposed a interventions to 233 drug interactions, in which the suggestion was accepted to 64 (27.46%) pDDIs and suggestion was not accept to 169(72.53%) pDDIs. In that 64 (27.46%) pDDIs has managed by dose adjustment, administration time change and drug alteration with in same pharmacological class.

Table 6.13: Result of pharmacist intervention (N=233)

Recommendation	Male		Female		Total	
	N	%	N	%	N	%
Suggestion accepted	40	17.16	24	10.30	64	27.46
Suggestion not accepted	100	42.91	69	29.61	169	72.53
Subtotal	**140**	**60.07%**	**93**	**39.91%**	**233**	**100%**

Table 6.13 showed that out of 233 interventions proposed, 64(27.46%) interventions were suggestion accepted and 169(72.53%) were suggestion not accepted.

DISCUSSION:

Although many studies were conducted regarding the incidence, characteristics and predictors of potential DDIs, very few studies have been performed with respect to DDIs which led to ADRs.

The study conducted by (Venkateswarlu K et al., 2015) [13] reports that 60.97% of DDIs were found in males and 39.03% were found in female patients, which would similar to our study.

The study conducted by (M Ashok Kumar et al., 2011) [14] showed that 16 patients (11.26 %) belonged to the age group 21 - 40 years, 79 (55.63 %) to the age group 41 -60 years, 41 (28.87%) to the age group 61 – 80 years and 4 (2.81%) to the age group 81 – 100 years. While comparing both studies it look's similar. In generally elder patients were at high risk of drug interactions because they are likely to have multiple disease and polypharmacy, duration of disease and altered physiological conditions.

The study conducted by the (Venkateswarlu et al., 2015) [13] showed that moderate severity interactions were higher, i.e. 178 (54%) while 84 (26%) were major and followed by 66 (20%) minor while comparing those studies we found that reports were to be same like each other.

The study conducted by the (Nasrin Zaredar et al., 2017) [15] reported that in which 234 interactions, they found, 57.26% were pharmacodynamic, 36.75% were pharmacokinetic and 5.98% were unknown. Among pharmacokinetics 23.98% were metabolism interaction. Those results were similar to our study.

According to onset of action, this study showed majority of interactions has notspecified followed by delayed and then rapid. These results are in line with other studies which also showed that majority of drug interactions on onset were not specified (Shareef et al., 2017) [16]. These indicate that the interactions will not be evident immediately on administration of drug, but when this drugs are continued, it would result in adverse drug interactions.

CONCLUSION:

Out of 260 patients prescription 109 patient prescription containing 233 pDDIs. According to the severity of pDDIs 56 drug interactions were major and 73 DI were moderate. On the intervention for 233 DI, only 64 interventions were accepted and others are not accepted. We concluded that drug interactions are also one of the reason for therapeutic failure and worsen the patient health conditions. The pDDIs assessment on the inpatients prescriptions can help to avoid life threading DDI and drug injuries. Ensure the clinician about the possible DI before prescribing the medication to the patients, here clinical pharmacists having vital role on assessment, identification and minimization of DDI's. Medication review programs should be focused this enhances the better patients care.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: There are no conflict of interest for this study.

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