Potential Drug-Drug Interactions and Their Severity Among the Patients Admitted to General Medicine in Tertiary Care Hospital

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ABSTRACT

BACKGROUND: Drugs are mainly intended to decrease disease symptoms. Drug interactions are major challenges to all health care professionals in order to provide safe and effective treatment to a patient health care professional should aware of general drug-drug interactions. The main objectives of this study are to identify general 1. drug-drug interactions and their severity, 2. To improve the patient quality of life by avoiding drug-drug interactions and polypharmacy.

METHODS: A prospective and observational study conducted to identify the general drug-drug interactions. All the required source of data collected from patient medical records, case sheets and by interviewing patient.

RESULTS: In this study a total of 202 patients were enrolled out of them 145 prescriptions have 290 potential DDIs and among the 290, 100(34.48%) interactions were pharmacokinetic and 190(65.52%) were pharmacodynamic. In pharmacokinetic 45(15.51%), 42(14.48%), 13(4.48%) were absorption, metabolism, excretion type of interactions was observed. In pharmacodynamic additive 101 (34.82%), synergism 54(18.62%), antagonism 35(12.09%) interactions was observed. In total of 290 interactions 35(12%) were major type of interactions and 222(76.55%) were moderate type of interactions and 33(11.3%) were minor type of interactions identified.

CONCLUSION: prolong use of drugs which are involving in interactions may cause serious problem to the patient. Close monitoring of patient medication is necessary. Clinical pharmacists and other health care professionals required to know the general drugs involving interactions and consequences of PDDIs.

KEY WORDS: Drug-drug interactions, pharmacokinetic interactions, pharmacodynamic interactions, severity of interactions.

INTRODUCTION

Drugs are mainly intended to produce therapeutic effect and to alleviate disease symptoms and improve the patient quality of life. however, many drugs were reported to cause unwanted effects ranging from mild rashes to severe adverse reactions [1]. Multiple drug therapy is preferred in present days due to many reasons. The treatment of certain diseases like hypertension, diabetes cardiovascular diseases, infectious diseases and cancer and patient who is suffering from two or more

diseases require multiple drug therapy. In such cases number prescribing drugs will be increases leading to increased drug combinations [2,5].

Drug interactions mainly occur when the pharmacological activity of one drug is altered by the concomitant use of another drug. The drug whose activity is affected by such interactions called object drug and agent which precipitates such interaction called precipitant [3]. Drug interactions (DIs) are one of the major therapeutic challenges to healthcare professionals for treatment of inpatients. The severity and frequency of Drug interactions are more common when the patients receiving multiple drugs. Around 11.0% of patients may be found vulnerable for at least one DDI, and the chances of DDI increase nearly 40.0% among patients taking 5 drugs and >80% in patients taking 7 or more medications [4]. The incidence of drug interactions increases with polypharmacy [8].

The severity of drug - drug interactions classified into three levels they include minor, moderate, and major. There is no medical intervention is needed for minor interaction, which is considered as tolerable in most cases. Moderate interaction needs medical interventions. Therapeutic failure, hospitalization, permanent injury, and sometimes death will be occurred due to major interaction. This type of interaction will cause irrecoverable side effects on the patient.

It has been estimated that 20%–30% of all drug side effects and adverse drug reactions are because of DDIs, and clinical attention is needed for 70%, raised by 80% in old people. Some interactions may cause irreversible side effects. a study in Norway revealed that approximately 18% of deaths were associated with drug interactions directly or indirectly. Within the short period of time some drugs get removed from the market due its unexpected drug toxicity and its severity. Example of such drugs include anti-histamines like terfenadine, astemizole, and drugs used to treat heartburn like cisapride, grepafloxacin increases the QT interval on the electrocardiogram [2,6,7]. Adverse drug reactions are mainly due to over dose, wrong drug prescribing, polypharmacy, over the counter medication and organ failure. Elderly persons, pregnant women, children, and neonates are the most vulnerable group for drug interactions [8].

Many medical conditions are treated with combination drugs and the components of drugs are compliment to each other actions example; antibiotics are used along with the analgesics to treat painful infective condition. Adrenaline is used with the lidocaine for local anesthesia action [5]. Some organisms produce enzyme that will destroy the drugs e.g. amoxicillin is destroyed by β lactamase enzyme. Organism may develop bacterial resistance against the amoxicillin. So, amoxicillin is always given with β lactamase inhibitor such as potassium clavulanate. (amoxicillin + potassium clavulanate). Combination of imipenem and cilastatin is prescribed for UTI. Several drug interactions are desirable e.g. diuretics + ACE inhibitors used to treat the hypertension. Cotrimoxazole is mixture of sulfamethoxazole +trimethoprim used to treat the bacterial infections [2,5]. Estrogen and progesterone combination for oral contraceptives. Decreased adverse effects by the levodopa and carbidopa combination [14].

St John's wort is an herbal extract used for treatment of depression. It causes adverse effects by enzyme induction. Drug interactions with food and drink are also known to occur, exemplified by the well-known interaction between monoamine

oxidase inhibitor antidepressants (MAOIs) and tyramine-containing foodstuffs. Grapefruit juice is a potent inhibitor of cytochrome P450 and CYP 3A4 and cause clinically chronic interactions with a number of drugs including simvastatin and atorvastatin, thereby increases risk of statin-induced adverse reactions such as myopathy and myositis [6].

Regular medications involving in drug interactions include; antidiabetics, antihypertensives, anti-anginal, anti-arthritic drugs, anti-epileptic drugs, anti-parkinsonism drugs, oral contraceptives, anti-coagulant's, anti-asthmatic drugs, psychopharmacological drugs, anti-peptic drugs, corticosteroids, anti-tubercular drugs, anti-retroviral drugs. The physician may take care and pay attention to the possibility of drug interactions when patient receiving more than one medication or patient may having two or more diseases [5]. In order to recognize the harmful drug interactions physician or clinical pharmacist should aware of general drug interactions and drugs pharmacological activity [6].

Types of drugs most likely to be involving in the significant drug interactions

Drugs with narrow therapeutic index e.g., Digoxin, Insulin, Lithium, Antidepressants, Phenytoin, Warfarin, Aminoglycosides.

Drugs which are closely related to the body functions e.g. antihypertensives, antidiabetics, anticoagulants

Highly plasma protein bind drugs e.g., NSAIDS, Sulphonamides and Anticoagulants

Drugs which are metabolized by the saturation kinetics e.g., Phenytoin, Theophylline [5].

MATERIALS AND METHOD

STYDY DESIGN

This is a prospective and observational study conducted to identify the potential drug-drug interactions and their severity in patients admitted to department of general medicine at Mamatha general hospital Khammam. This study conducted between Nov-20/April-21. This study was approved Institutional Ethics Committee [IEC] of Anurag Pharmacy college.

INCLUSION CRITERIA

Patients above 15 years old, patients who are prescribed with multiple drugs. Patients having more than one disease, polypharmacy (a greater number of drugs for individual prescription. Almost all diseased patients in general department.

EXCLUSION CRITERIA

Infants were not included in this study and patients who were not willing to participate in this study.

DATA COLLECTION

All the required source of data collected from patient medical record and patient previous medication history and by interviewing patients.

DATA ANALYSIS

Drug-drug interactions were classified on the basis of its pharmacological activities and type of interactions occurred pharmacokinetic or pharmacodynamic and severity like major, moderate, minor by using Drugs.com an interaction checker online data source.

STATISTICAL ANALYSIS

Descriptive statistics were used (mean-SD) describe the frequency and percentage of values. We used chi square test to analyze the DDIs and used SPSS statistics for Microsoft version 20.

RESULTS

1. GENDER WISE CATOGORISATION OF PATIENTS WITH DDIs

In this study a total of 202 patients were enrolled out of them 145 prescriptions have potential DDIs and among 145 patients, 103 (71%) were male and 42(28.9%) were female. Among the 145 patients, male patients71% were more prone to drug-drug interactions than the female 28.9%. This is mainly due to individual life style of males like smoking, alcohol consumption, lack of physical activities and lack of proper diet main reasons for multiple diseases like HTN, DIABETIC this led to necessary use of multiple prescribed drugs and their concomitant administration cause drug-drug interactions.

Table 1

GENDER	NUMBER OF PATIENTS	PERCENTAGE
MALE	103	71%
FEMALE	42	28.9%
TOTAL	145	100%

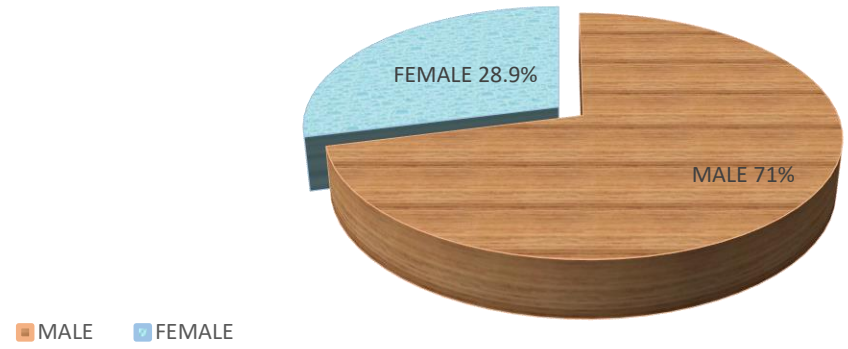


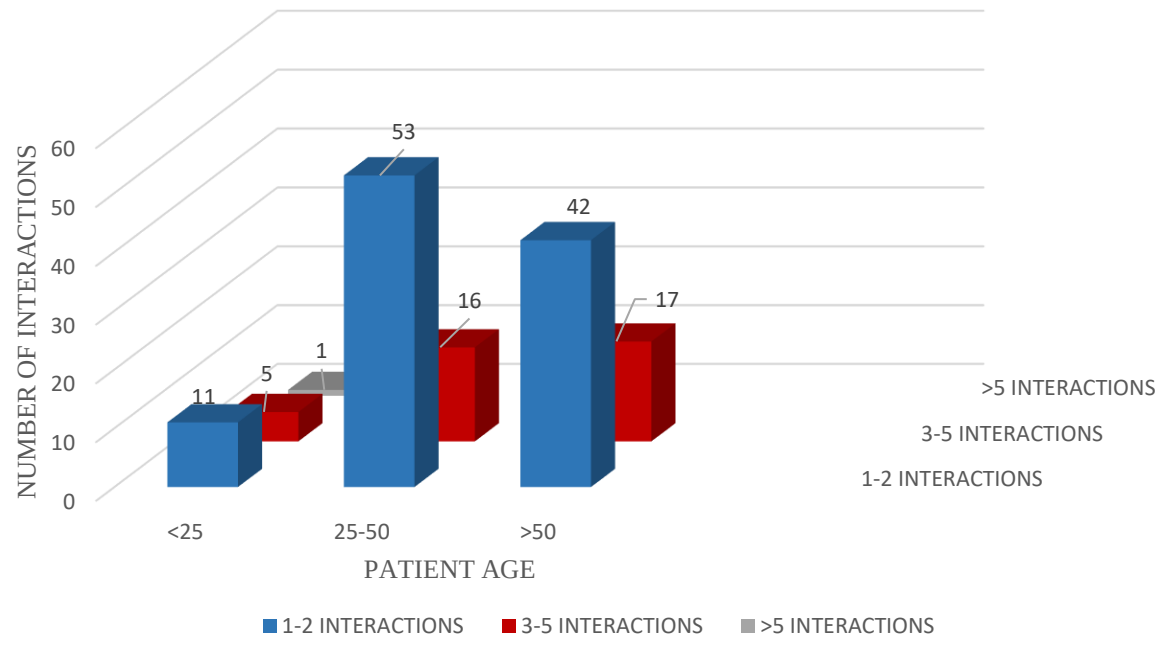
figure-1: Gender wise catogorisation of DDIs

2.AGEWISE CATEGORISATION OF DDIs PER PRESCRITPION

AGE IN GROUP	1-2 INTERACTIONS		3-5 INTERACTIONS		>5 INTERACTIONS		TOTAL
	NO OF PATIENTS	%	NO OF PATIENTS	%	NO OF PATIENTS	%	
<25	11	7.5%	5	3.4%	1	0.6%	17
25-50	53	36.55%	16	11%	0	0	69
>50	42	28.9%	17	11.7%	0	0	59
TOTAL	106	72.95%	38	26.1%	1	0.6%	145

Table 2

figure 2: Age wise categorisation DDIs per prescription



Chi square test value 1.56. table value 9.49 [9.49>1.56 accept the Null hypothesis]. There is no greater difference between observed and expected value.

Total 11 patients with age <25 and 53 patients with age 25-50 and 42 patients with more than 50 years of age effected to 1-2 interactions per prescription.5 patients with <25 years and 16

patients with 25-50 years and 17 patients with more than 50 years of age effected to 3-5 interactions per prescription. One patient with <25 years of age effected to > 5 interactions per prescription.

3.NUMBER OF DRUG-DRUG INTERACTIONS PER PRESCRIPTION

Total 145 patients with 290 interactions were observed among 103 patients (71.03%) with 1-2 interactions,41 patients (28.27%) with 3-5 interactions and 1 patient (0.68) with >5 interactions were observed. Most of the patients were prone to 1-2 drug-drug interactions. The maximum number of drugs per a prescription is 14 and minimum number of drugs per a prescription is 3.

NUMBER OF INTERACTIONS	NO OF PATIENTS	PERCENTAGE
1-2	106	72.95%
3-5	38	26.17%
>5	1	0.6%
TOTAL	145	99.72%

Table 3

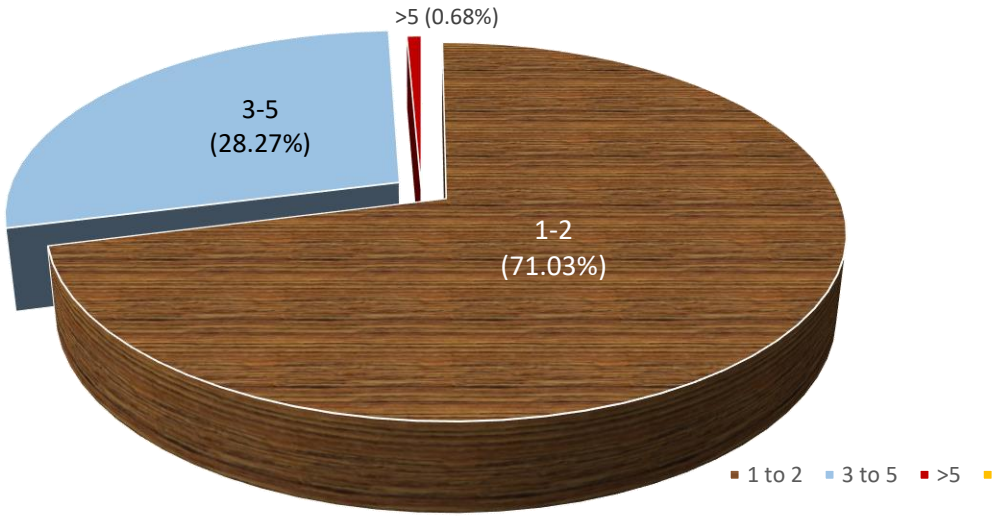


figure 3: NUMBER OF INTERACTIONS PER PRESCRIPTION

4. DISTRIBUTION OF DRUG-DRUG INTERACTIONS ACCORDING TO THE TYPE AND MECHANISM OF INTERACTIONS

Among the 145 cases, a total of 290 interactions were found in that 100 were pharmacokinetic interactions (PK) and 190 were pharmacodynamic (PD) interactions. In pharmacokinetic 45(15.51%), 42(14.48%), 13(4.48%) were absorption, metabolism, excretion type of interactions was observed. In pharmacodynamic additive 101 (34.82%), synergism 54(18.62%), antagonism 35(12.09%) interactions was observed. Comparing all type of interactions additive type of interactions were found to be more common because drugs with similar pharmacological activity and similar class can show the additive type of interactions. In synergism type of interactions one drug will increases the pharmacological actions of another drug. Patients with severe condition were treated with a greater number of drugs concomitantly that may lead to DDIs.

TYPE OF INTERACTION	NO. OF PATIENTS	PERCENTAGE
PHARMACOKINETIC	100	34.48%
PHARMACODYNAMIC	190	65.52%
TOTAL INTERACTIONS	290	100%

Table 4

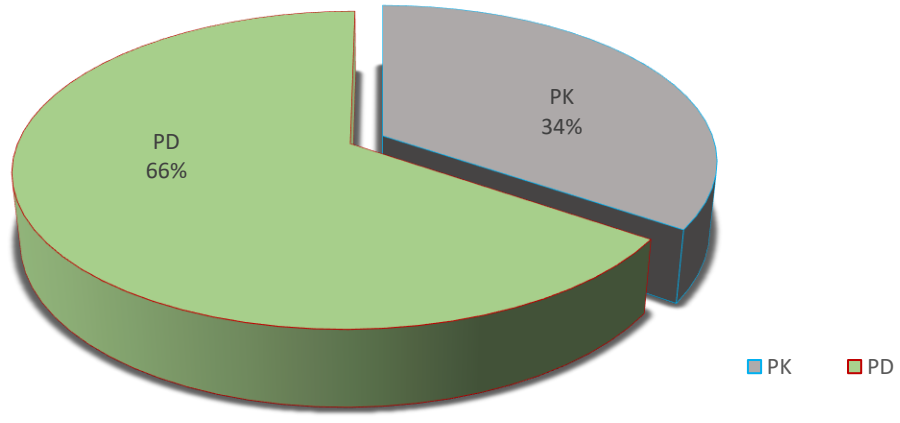
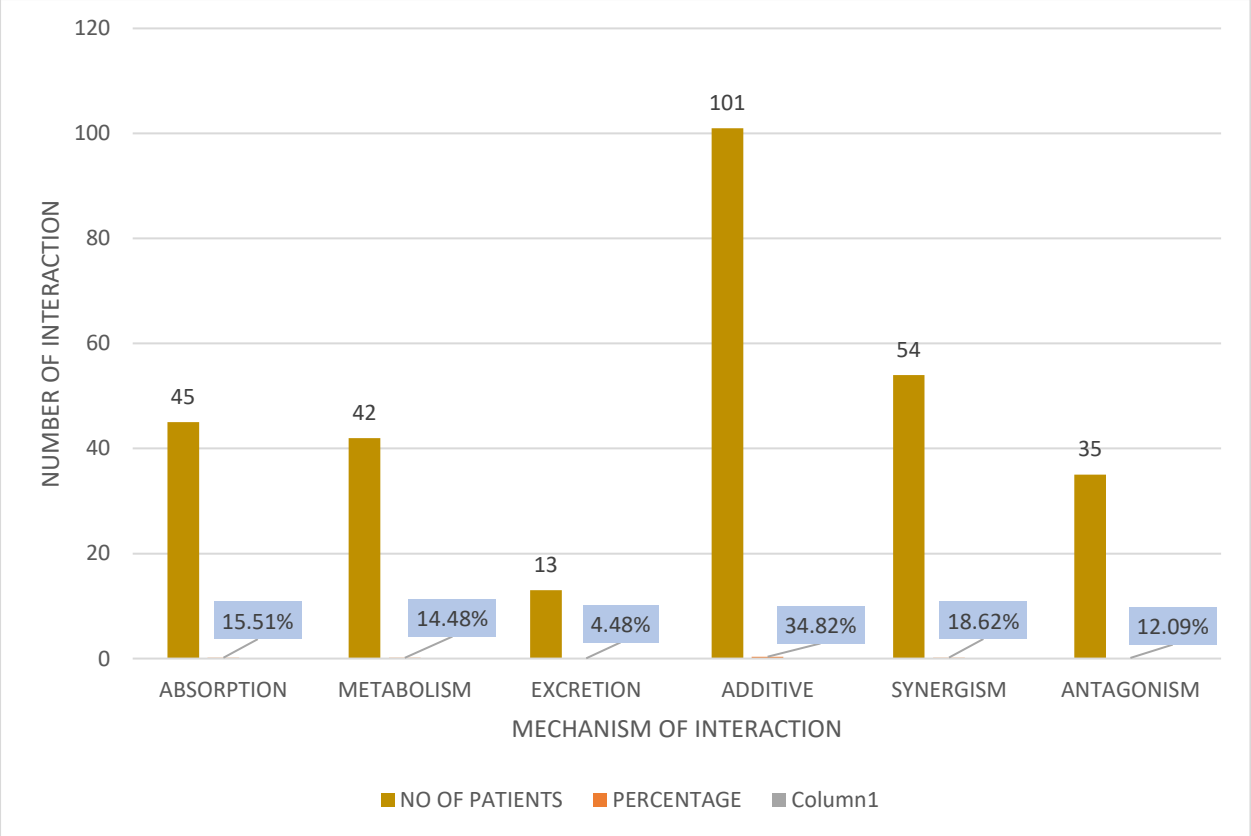


figure 4: DISTRIBUTION ACCORDING TO THE TYPE OF INTERACTION

MECHANISM INTERACTION	NO. OF INTERACTIONS	PERCENTAGE
ABSORPTION	45	15.51%
METABOLISM	42	14.48%
EXCRETION	13	4.48%
ADDITIVE	101	34.82%
SYNERGISM	54	18.62%
ANTAGONISM	35	12.09%
TOTAL	290	100%



5.DISTRIBUTION OF DRUG-DRUG INTERACTIONS ACCORDING TO SEVERITY

In total of 290 interactions 35(12%) were major type of interactions and 222(76.55%) were moderate type of interactions and 33(11.3%) were minor type of interactions identified in this study. Moderate type of interactions was more when compared to the major and minor and this need medical interventions like change in dose, change in frequency or change in time of dos administration.

Table 6:

SEVERITY	NO. OF INTERACTIONS	PERCENTAGE
MAJOR	35	12%
MODERATE	222	76.55%
MINOR	33	11.37%
TOTAL	290	99.92%

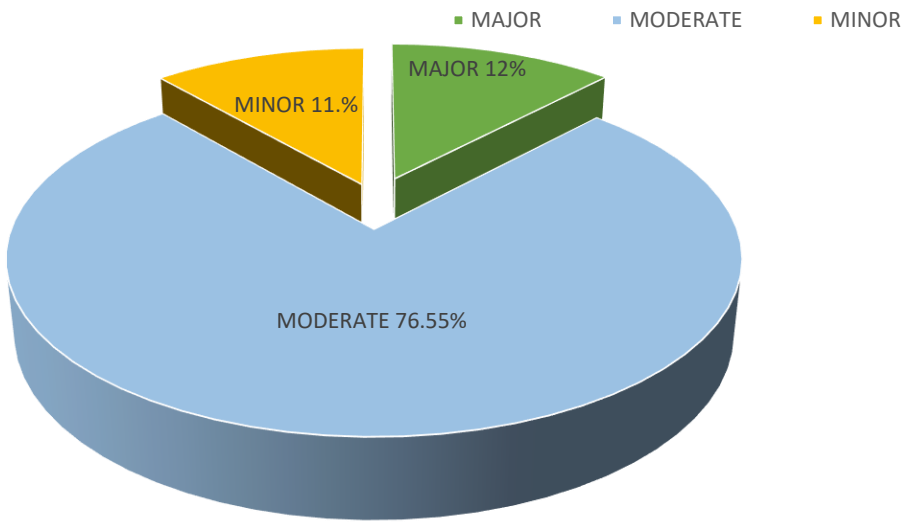


figure 5: DISTRIBUTION OF DRUG INTERACTIONS BASED ON SEVERITY

SEVERITY AND MECHANISM OF ACTION OF SOME DRUG-DRUG INTERACTIONS

SEVERITY	DRUG INTERACTION	MECHANISM OF INTERACTION	ANTICIPATED EFFECTS
MAJOR	HYDROCORTISONE+INFLIXIMAB	Corticosteroids along with immunosuppressants increase risk of infection	Risk of increasing infection
	CIPROFLOXACIN+HYDROXYCHLOROQUINE	Both will cause additive type of interaction	Prolong QT interval, electrolyte imbalance
	PREDNISOLONE+CIPROFLOXACIN	Prednisolone increases risk of tendon rupture when used along with quinolones	Tendon rupture when prolong used
	ATORVASTATIN+CLOPIDOGREL	Atorvastatin inhibit the metabolic activation of clopidogrel by inhibiting CYP450 3A4	Failure of antiplatelet activity leads to stroke
	HALOPERIDOL+PROMETHAZINE	Both will cause additive effects	QT interval prolongation
	CIPROFLOXACIN+THEOPHYLLINE	Ciprofloxacin inhibit the metabolism of theophylline by inhibiting CYP4501A2	Nausea, vomiting
	PREDNISOLONE+METFORMIN	Prednisolone increases glucose levels	Alteration of hypoglycaemic action of metformin
	PRAZOCIN+AMLODIPINE	Prazosin cause vasodilation both will show additive actions	Increase anti HTN activity
	VALPROIC ACID+PROMETHAZINE	Pharmacodynamic synergistic action	Increase sedation and dizziness
MODERATE	ASPIRIN+CLOPIDOGREL	Clopidogrel potentiate the anti-platelet activity of aspirin	Increase risk of bleeding
	TRAMADOL+LACTULOSE	Bowel cleansing medication can cause loss of K, Mg, electrolytes	Irregular heart rhythms

	FUROSEMIDE+CEFOPERAZONE	Furosemide reduce the clearance of cephalosporins	Nephrotoxicity
	ONDANSETRON+TRAMADOL	5HT3 receptor antagonist along with analgesic may potentiate the risk of serotonin syndrome	Confusion, hallucinations
	FUROSEMIDE+DIGOXIN	Both will cause hypokalaemia and hypomagnesemia	Irregular heart rhythms
	OFLAXACIN+BISACODYL	Quinolones potentiate irregular heart rhythms when taken along with laxatives	Irregular HR

	LORAZEPAM+CHLORDIAZEPOXIDE	Both have synergistic actions	CNS depression, drowsiness
	METRONIDAZOLE+LOPERAMIDE	Both can cause hypomagnesemia or hypokalaemia	QT interval prolongation
MINOR			
	METOPROLOL+DIAZEPAM	Pharmacological activity of diazepam increased by metoprolol by inhibiting its metabolism	Excessive fall in Blood pressure
	CIPROFLOXACIN+METRONIDAZOLE	Pharmacodynamic additive actions	QT interval prolongation
	AZITHROMYCIN+ONDANSETRON	Both can increase the irregular heart rhythms	QT interval prolongation
	METRONIDAZOLE+TRAMADOL	Irregular heart rhythms	QT interval prolongation
	NITROFURANTOIN+FLAVOXATE	Anticholinergics reduce gastric motility and it increases the nitrofurantoin bioavailability	Nitrofurantoin toxicity
	HYDROCORTISONE+SODIUM BICARBONATE	Antacids reduces the absorptions of corticosteroids	Failure of corticosteroids activity
	OXAZEPAM+ACETAMINOPHEN	Oxazepam inhibit the metabolism acetaminophen	Acetaminophen toxicity

6.MOST PREVALENT DRUG-DRUG INTERACTIONS

S. NO.	DRUG INTERACTION	FREQUENCY	TYPE OF INTERACTION	SEVERITY	CONSEQUENCES OF INTERACTION
1	ASPIRIN+CLOPIDOGREL	7	Pharmacodynamic	Moderate	QT interval prolongation
2	LACTULOSE+TRAMADOL	2	pharmacodynamic	moderate	Irregular heart rhythms
3	FUROSEMIDE+CEFOPERAZONE	2	pharmacokinetic	moderate	Increases nephrotoxicity
4	ATORVASTATIN+CLOPIDOGREL	4	pharmacokinetic	moderate	failure of antiplatelet action of clopidogrel
5	FUROSEMIDE+PANTOPRAZOLE	3	pharmacodynamic	moderate	Can cause hypomagnesemia
6	ONDANSETRON+TRAMADOL	9	pharmacodynamic	major	QT interval prolongation/seroton in syndrome
7	OFLAXACIN+BISACODYL	1	pharmacodynamic	moderate	Cause tachycardia
8	METOPROLOL+DIGOXIN	1	pharmacodynamic	moderate	Cause bradycardia
9	FUROSEMIDE+DIGOXIN	1	pharmacodynamic	moderate	Hypokalemia/hypomagnesemia
10	AZITHROMYCIN+ONDANSETRON	3	pharmacodynamic	moderate	QT interval prolongation
11	METRONIDAZOLE+OFLAXACIN	1	pharmacodynamic	minor	QT interval prolongation
12	CIPROFLOXACIN+PREDNISOLONE	1	pharmacodynamic	moderate	Tendon rupture due to over usage
13	AZITHROMYCIN+METRONIDAZOLE	1	pharmacodynamic	minor	QT interval prolongation
14	PREDNISOLONE+INFLIXIMAB	1	pharmacodynamic	major	Increase allergic condition on over use

DISCUSSION

As the number of drugs per prescription or to a patient increases the complexity of therapy also increases. This drug interactions leads to adverse drug reactions or any drug related problems.

Maximum number of drugs for per prescriptions is 14 and minimum number of drugs for a prescription is 3. A total of 202 patients were enrolled in this study among them 145 patients have 290 interactions. In this study male (71%) were more effected to drug-drug interactions than the female (28.9%) which was similar to study conducted by Bajacharya et. al 2018 in their study males 59% were affected to drug interactions than female 41%. In our study 25-50 years of age group people were more effected to drug interactions. Among the 145 patients most of patients contains 1-2 interactions. Among the 290 interactions 106 (72.95%) patients were with 1-2 drug interactions and 38 patients with 3-5 interactions and 1 patient effected to more than 5 drug-drug interactions. Drug interactions were analyzed in this study by using Drugs.com online source which is similar to study of Nermeen Nabel et.al 2018.

Among the total 290 interactions, 100(34.48%) were pharmacokinetic and 190(65.52%) were pharmacodynamic this study is similar to the bajacharya et.al 2018 study. Moderate type of interactions was more common comparing to the major and minor. Moderate 222 (76.55%), minor 33(11.37%), major 35(12%) which is similar to the study conducted by Bjacharya et.al 2018 their study concludes that among the 657 DDI 6 were contraindicated, 240(36.5%) were major, 374(59.9%) were moderate, 33(5.6%) were minor type of interactions. Severity of drug-drug interactions in our study include QT interval prolongation, electrolyte imbalance, frequent fall in blood pressure. Decreased therapeutic actions of a drug due to enzyme induction, increased toxicity of a drug due to enzyme inhibition or decrease clearance. Decreased clearance of a drug leads to nephrotoxicity, over activity of immunosuppressants leads to increase infections which is similar to the study of Nermeen Nabel et.al 2017.

CONCLUSION

Our study concludes that majority of patients receive polypharmacy. Age, polypharmacy, and multiple diseases are main responsible for incidence of drug-drug interactions. Hence it is important to develop a systemic approach to reduce the drug-drug interactions. Clinical pharmacist plays a vital role in detection of newer drug-drug interactions and they are responsible for safe and effective therapy to patients and to reduce the risk of patients. General awareness on most common drug-drug interactions is important for every health care provider. This helps the practioners to prescribe drugs with low risk to DDIs thereby prevent the concomitant use harmful drug combinations.

LIMITATIONS

Non prescribed medications/ OTC medications or herbal products or herbal drugs were excluded. Patients should encourage to show their previous and present medications to the pharmacist or physician this will avoid the drug-drug interactions.

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