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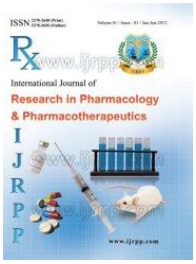

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Research article ***Open Access***

Prevalence and causality assessment of adverse drug reactions; clinical consequences of drug interactions and polypharmacy in patients presenting to a secondary care hospital

Nagireddy, Syeda Majeeda Sultana, Syeda Mariya Anjum, Umama Yezdani, Kashifa Ayman

Department of Clinical Pharmacy, MRM College of pharmacy, Hyderabad, Telangana.

***Corresponding author: Nagireddy**

Email: nagiredddy2404@gmail.com

ABSTRACT

Background

Drug use is frequently considered to be hazardous for an elderly, due to greater vulnerability of an elderly to drugs and multiple drug use. Poly-pharmacy is unavoidable in the elderly as they suffer from multiple co-morbidities. Adverse drug reaction (ADR) is the sixth leading cause of death. Drug-drug interaction due to polypharmacy and potentially inappropriate medication must be carefully assessed.

Material and methods

The study was conducted in both Inpatient and Outpatient in all departments of Thumbay Hospital New Life, Hyderabad for 6 months from October 2018 to March 2019.537 prescriptions was randomly collected and evaluated for adverse drug reactions and clinical consequences of drug interactions and polypharmacy in patients presenting to a secondary care Hospital.

Results

A total of 537 patients were observed of which 203 patients experienced ADR's which accounted for 21.5% of the incidence and 143 DDI's were observed. Most of the DDI's were Pharmacokinetic drug interactions (26.7%) followed by Pharmacodynamic drug interactions (12.70%). A severity assessment showed that the majority of DDI's were moderate 34.96% followed by minor 32.86%. Poly-pharmacy was more frequent in the elderly of age 56-65 (both males and females) and totally 321 ADEs were observed and the incidence of ADR's and DDI's increased non-significantly as the number of drugs used for long term period. Majority of ADRs were suspected due to antibiotics, anti-hypertensive responsible for causing GI complaints and rash. Neurological system (26%) was the most common organ system affected due to ADRs. In the cases of treating LRTI and urinary tract infections, there was an enormous risk of ADR's. The number of drugs increases as the age and the co-morbid conditions increases with an average of 20.

Conclusion

From the present study we can conclude that relatively high incidence of Adverse drug reactions has been recorded which shows that not only geriatric patients but also adults are also more susceptible to ADR's and poly-pharmacy leads to serious DDI's and hence to improve drug safety- appropriate prescribing, TDM is important.

Keywords: Adverse drug reactions, Drug interaction, Poly-pharmacy and potentially inappropriate medication.

INTRODUCTION

Drugs are the most common medical interventions primarily used to relieve sufferings. But it has been recognized long ago that they themselves can prove fatal as the saying rightly goes "Drugs are double-edged weapons." Adverse drug reactions monitoring and reporting are important in characteristic the adverse reaction trends in native population [1]. In its simple definition, an ADR is an undesirable effect of a drug beyond its anticipated therapeutic occurring during clinical use. The WHO defines an ADR "a response to a drug that is noxious Associate in Nursing unplanned, and which occurs at doses normally used in men for the prophylaxis, diagnosis, or medical aid of illness, or for the modification of physiological operate. "The world is on the point of a demographic milestone.

Adverse drug reactions (ADR) are known perils of drug therapy. An ADR may be simply defined as an undesirable effect of a drug besides its expected therapeutic action transpiring during clinical use [2].

Age-related, chronic diseases such as dyslipidemia; hypertension, diabetes, and depression usually require the use of multiple drugs, a state named polypharmacy. This refers to the use of many medications and/ or more medications than clinically indicated. It is estimated that more than 40% of adults aged 65 or older use 5 or more medications, and 12% use 10 or more different medications. However, the scope of the problem among older adults is still scarcely known in most countries [3]. Drug interactions talk over with modification of response to at least one drug by another once they square measure administered at the same time or in fast succession.

When a patient is prescribed more than one drug in the same prescription drug interactions arises which increases with the number of drugs although, the severity of this interaction in most of the cases is unpredictable [4]. The risks refer to side effects and interactions that may lead to hospitalization and to morbidity, resulting from inadequate or incorrect use and from non-compliance [5]. It remains unclear whether the adverse drug reactions found were due to interactions or to one of the drugs used. The problem is that the most studies looking into the risk of multiple drug regimen refer to the potential for interactions, not at actually occurring adverse effects, leaving the clinical relevance in general practice uncertain [6]. Adverse drug reaction is considered to be the sixth leading cause of death. The incidence rate estimates approximately 2% of hospital admission are due to ADR's. Drug attributed deaths are estimated to be 0.17% in all medical inpatient. About 0.40% of ADR's identified were directly linked to high costs [6].ADR monitoring is primarily essential for drugs with narrow therapeutic index [7]. Older adults with polypharmacy are predisposed to drug interactions. In a prospective cohort study of older hospitalized adults taking 5 or more medications, the prevalence of a potential hepatic cytochrome enzyme mediated, drug-drug interactions was 80%. The probability of drug-drug interactions increases with the number of medications. A patient taking 5-9 medications had a 50% probability whereas the risk increased to 100% when a patient was found to be taking 20 or more medications [8]. In the US 25% of ambulatory patients taking drug combinations were at risk for clinically important interactions. A European study of 1601 ambulatory elderly patients, taking an average of 7 different drugs, found that 46.0% were at risk for at least one clinically important potential drug-drug interactions [9].

Furthermore, attention should be paid to the fact that the body of the older adults presents changes in their physiological functions that may lead to a differentiated pharmacokinetic and greater sensitivity to both therapeutic and adverse drug effect [10]. Pharmacokinetic, pharmacodynamics and clinical outcomes are affected by a number of patient's specific factors including age, sex, genetics, polypharmacy, drug dose, and frequency, social

history, and many other factors. The above highlights that population aging is a global phenomenon and the practice of polypharmacy is dangerous for patients in particular for older adults because it favors the emergence of drug-drug interactions, ADR, side effects, longer hospital stays, and iatrogenic diseases and may also lead to complications that induce patient death. Thus the purpose of the present study was to conduct a broader integrative review aimed at identifying and summarizing studies examining both drug interactions and ADR in older adults.

MATERIAL AND METHODOLOGY

Sample size

This study conducted in each inpatients and out-patients altogether the departments of Thumbay Hospital, New Life, Hyderabad.

Study style

Hospital based mostly prospective study.

Study amount

The study is dole out for a amount of half dozen months from Gregorian calendar month 2018 to March 2019.

Study population

The study sample collected from the in-patients elderly >18 years of all the departments within the hospital.

Study size

537 patients

CRITERIA OF THE STUDY

Inclusion criteria

- Patients of > 18 years of age
- ADR's occurring after hospital admission
- Patient admitted to hospital primarily due to ADR's
- Patient on polypharmacy.
- Care of medication error
- Patients with co-morbid conditions.
- Patients with chronic diseases.
- Patient requiring for long term therapy.
- Patient on polypharmacy.

Exclusion criteria

- Pregnant women
- Nursing mothers
- Pediatrics
- Patients with intentional and accidental poisoning
- Patient who does not want to give consent

Source of data

The data for this study is taken by interviewing patients, past medical history, past medication history, patient case notes, treatment chart, laboratory reports, and discharge cards.

Forms used in the study

The study procedure involved the use of some forms for data collection, documentation and analysis of data. Forms used in the study are patient profile forms, adverse drug reaction documenting form, drug interaction documenting form, intervention reporting form.

Methodology

This is a prospective, observational study which was conducted in Thumbay Hospital on prevalence and causality assessment of adverse drug reactions; clinical consequences of drug interaction and polypharmacy in patients presenting to secondary care teaching hospital. The study was to be conducted by reviewing and collecting the case sheets of patients who were diagnosed with a different type of diseases and admitted in the hospital. Patient demographic details such as name, age, sex were collected. Common and uncommon sign and symptoms observed in patients were noted. Past medical history of patients, as well as the family, was noted. Past medication history of patients was documented. Smoking, drinking, and other social habits of the patients were noted in patients profile form. Therapeutic data such as the name of drug, dose, frequency, and duration of therapy was collected from the treatment chart of patients. Drug Interactions in the treatment regimen of patients were assessed using drug database Micromedex 2.0 and the interactions found were documented in the drug-drug interaction form, any interventions made during the study time were documented using intervention reporting forms, follow up of all patients were done

until discharge from the hospital. The assessment of the patient data, treatment, and response from that treatment was analyzed as per the guidelines of the Naranjo Algorithm Scale. The in-patient and out-patient data were collected and created separately in a computer-based format, stored and retrieved whenever required in MS Office access format.

RESULTS

Among 537 patients which included 286 In – patients (IP) and 251 Out-patients (OP) for 6 months after enrollment, we identified 321 ADEs and 143 drug interactions. The overall occurrence of ADRs due to polypharmacy was under the age group of 56-65 i.e. 24.9%.The more number of medications were prescribed under the age group of 56-65 in which males 398 and females 385 and an average number of medications were prescribed was 22 to each patient.

Table 1: Age gender distribution

AGE	No of Patients (IP)		No of Patients (OP)	
	Males	**Females**	**Males**	**Females**
15 – 25	23	23	10	26
26 – 35	15	12	10	19
36 – 45	14	24	11	32
46 – 55	27	24	17	26
56 – 65	**36**	**30**	16	34
66 above	30	28	21	29
TOTAL	**145**	**141**	**85**	**166**

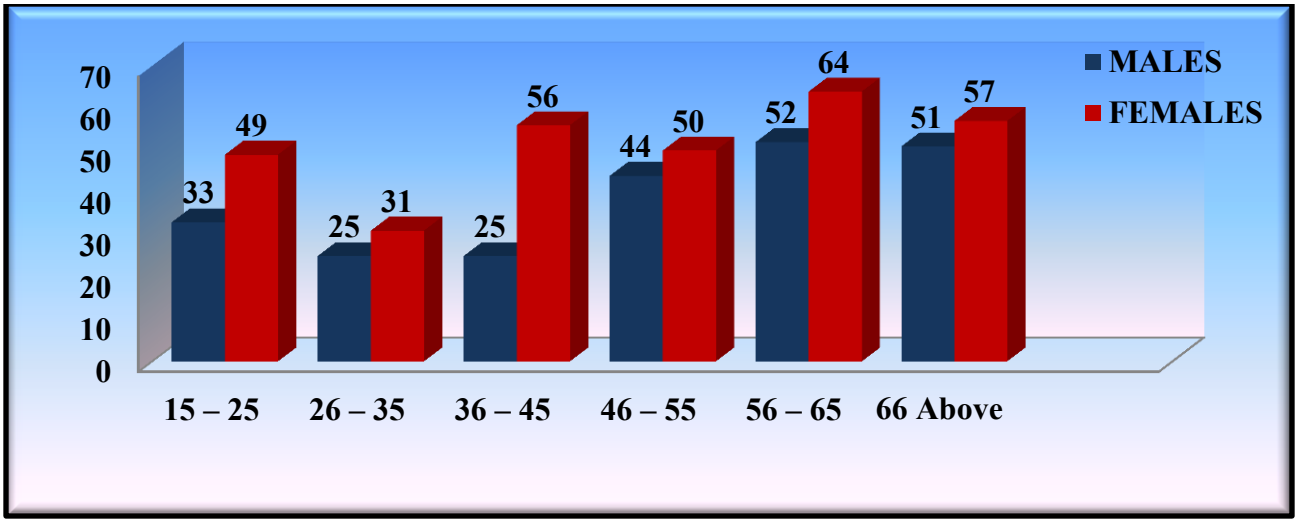

Figure 1

Table 2 Distribution of ADRs based on age gender

	Male	Female		Male	Female	
15-25	9	26	13.2%	**4**	**8**	**21.4%**
26-35	14	16	11.3%	0	7	12.5%
36-45	14	17	11.6%	2	6	14.2%
46-55	16	25	15.4%	2	9	19.6%
56-65	29	28	21.5%	0	9	16.0%
66 Above	**33**	**38**	**26.7%**	2	7	16.0%
TOTAL	**115**	**150**	**99.7%**	**10**	**46**	**99.7%**
	265			**56**		

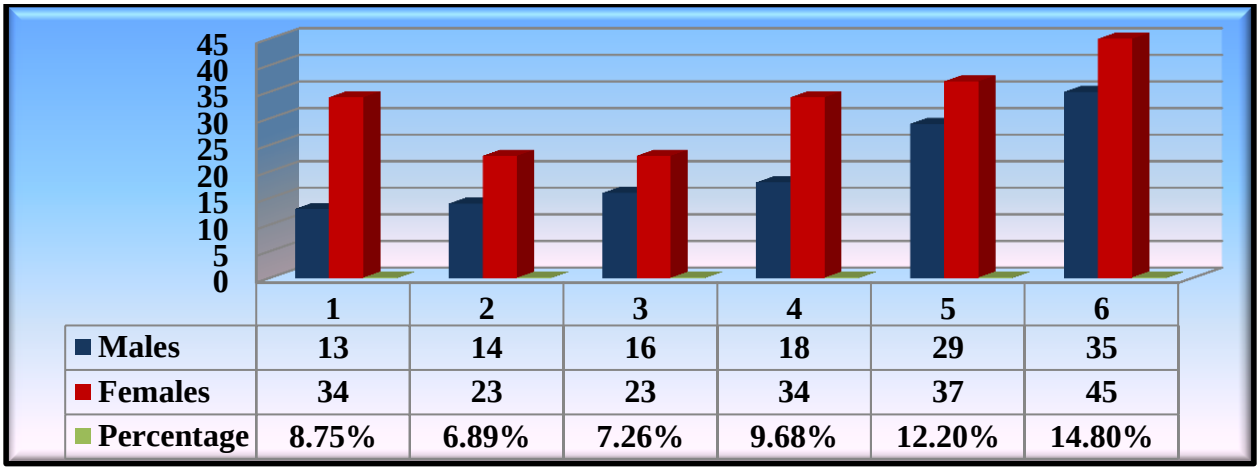

Figure 2

Table 3: Distribution of ADR in a different system of the body

	Frequency	Percentage	Frequency	Percentage
GASTROINTESTINAL	49	12.6%	13	16.0%
RESPIRATORY	22	5.69%	4	4.93%
NEUROLOGICAL	**110**	**28.4%**	**20**	**24.6%**
CARDIOVASCULAR	26	6.73%	3	3.70%
ENDOCRINOLOGICAL	15	3.88%	0	0%
NEPHROLOGICAL	10	2.59%	1	1.23%
HEPATOLOGICAL	11	2.84%	0	0%
HAEMATOLOGICAL	15	3.88%	1	1.23%
DERMATOLOGICAL	35	9.06%	16	19.7%
OTHERS	93	24.0%	23	28.3%
TOTAL	**386**		**81**	

Table 4: Severity of ADR based on Naranjo algorithm

Severity	ADRs [IP]	%[IP]	ADRs[OP]	%[OP]
HIGHLY PROBABLE (≥9)	2	0.75%	2	3.57%
PROBABLE (5-8)	111	41.8%	23	41.0%
POSSIBLE (1-4)	**129**	**48.67%**	**24**	**42.8%**
DOUBTFUL (0)	23	8.67%	7	12.5%

Table 5 Classification of Rawlin and Thompson

1	TYPE A	147	45.79%
2	TYPE B	96	29.9%
3	TYPE C	78	24.29%

Table 6 Management of reported ADRs

Drug withdrawal	48	14.95%
Symptomatic treatment	48	14.95%
No change	0	3.11%
Dose altered	0	0%
Specific treatment	56	17.44%
Drug withdrawal + specific treatment	34	10.59%
Drug withdrawal + symptomatic treatment	82	25.54%
Dose alteration + symptomatic treatment	43	13.39%

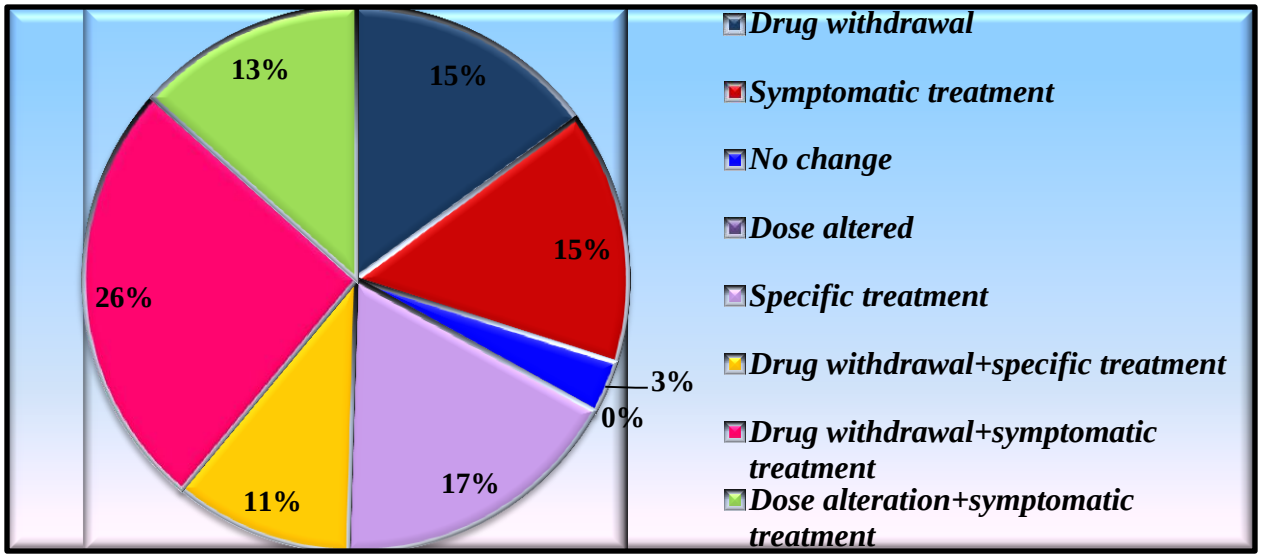

Figure 3

Table 7: Causes of ADRs

S.NO	CAUSE	FREQUENCY	PERCENTAGE
1	Drug Drug interaction	37	11.5%
2	Self-medication	87	27.10%
3	Wrong dosing	47	14.64%
4	Lack of knowledge	82	25.54%
5	Non compliance	68	21.18%

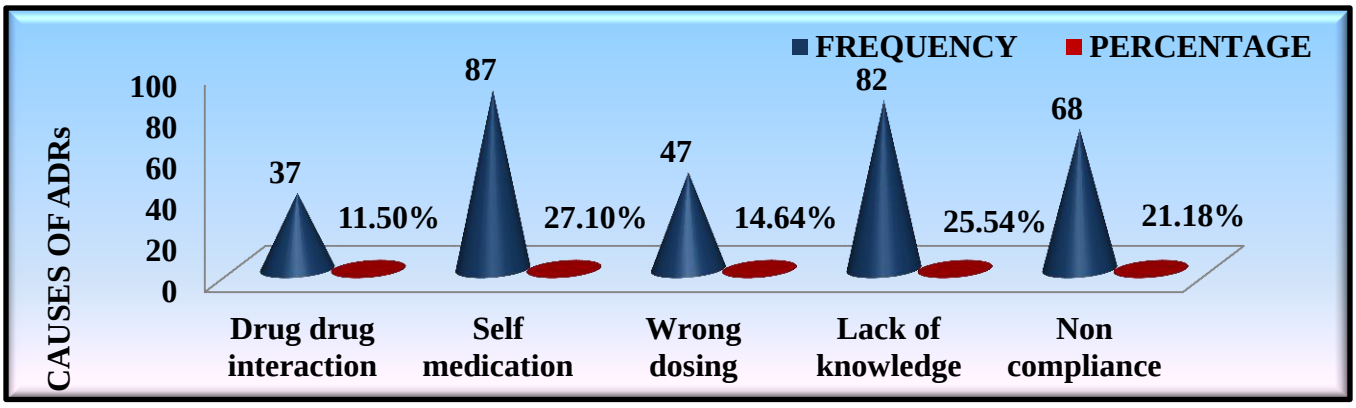

Figure 4

- **ADR Observed Prednisone causing puffiness of face in ‘‘Nephrotic syndrome’’ patient.**
- **Ceftriaxone induced rashes.**

Figure 5

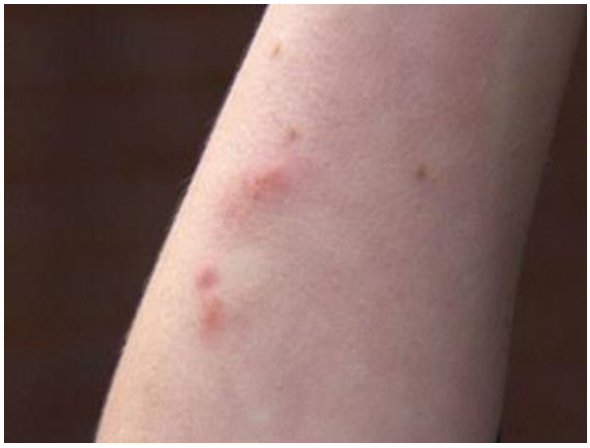

Figure 6

Table 8: Patients on Polypharmacy

Age	No of patients with polypharmacy in (IP)		Percentage (IP)	No of patients with polypharmacy in (OP)		Percentage (OP)
	Males	**Females**		**Males**	**Females**	
15-25	**6**	**4**	**3.49%**	1	3	1.59%
26-35	1	1	0.69%	0	3	1.19%
36-45	1	6	2.44%	2	0	0.79%
46-55	1	5	2.09%	**2**	**6**	**3.18%**
56-65	4	1	1.74%	0	1	0.39%
66 above	2	1	1.04%	1	1	0.79%
TOTAL	**15**	**18**	**11.49%**	**6**	**14**	**7.93%**
	33			**20**		

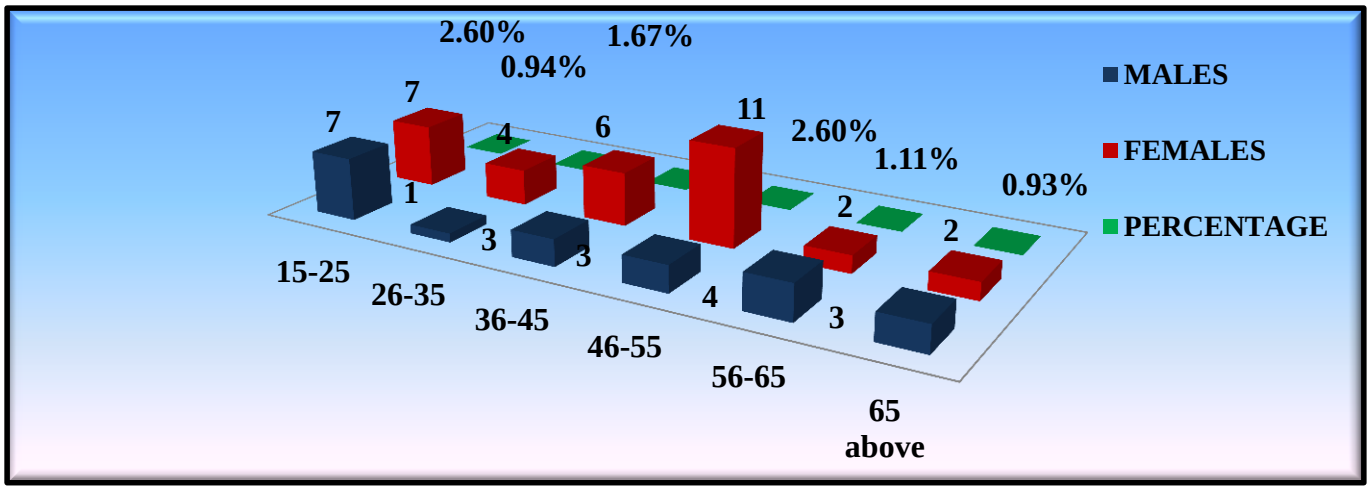

Figure 7

Table 9: Patients on Co-morbid Conditions

Age group	No of co-morbid in MALES			No of co-morbid in FEMALES			TOTAL		No of drugs Prescribed	
	2	**3**	**≥4**	**2**	**3**	**≥4**	**Male**	**Female**	**Male**	**Female**
15-25	2	0	0	4	1	0	2	5	199	241
26-35	5	2	0	0	0	0	7	0	145	134
36-45	7	0	1	10	8	6	8	24	189	281
46-55	14	8	3	11	7	2	25	20	284	258
56-65	**13**	**6**	**3**	**13**	**6**	**4**	**22**	**23**	**398**	**385**
66-75	4	3	5	8	7	2	12	17	308	266
76-85	6	4	1	9	4	2	11	15	157	209
≥86	1	0	3	0	0	0	4	0	62	0
TOTAL	**52**	**23**	**16**	**55**	**33**	**16**	**91**	**104**	**1,742**	**1,774**

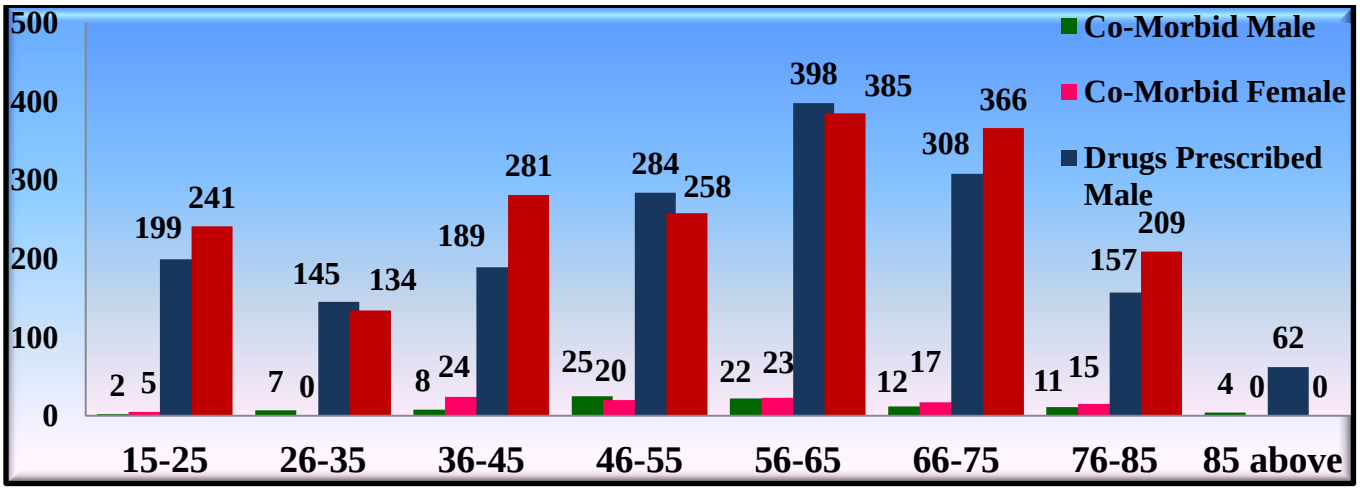

Figure 8

Table 10: Frequency of drugs prescribed based on classes.

CLASSES	FREQUENCY	PERECENTAGE
ANTIBIOTICS	**300**	**8.53%**
PROTON PUMP INHIBITOR (PPI)	228	6.48%
ANALGESICS	133	3.78%
VITAMINS	133	3.78%
ANTI-PLATELETS	129	3.66%
STEROIDS	122	3.46%
HYPOGLYCEMICS	118	3.35%
LAXATIVES	96	2.73%
DIURETICS	89	2.53%
ANTI- EMETICS	82	2.33%
CALCIUM CHANNEL BLOCKERS	69	1.96%
HYPER LIPIDEMIC	65	1.84%
BENZO DIAZEPINES	57	1.62%
ANGIOTENSIN RECEPTOR BLOCKER	54	1.53%
ANTI CONVULSANTS	42	1.19%
TOTAL	**1,717**	**48.77%**

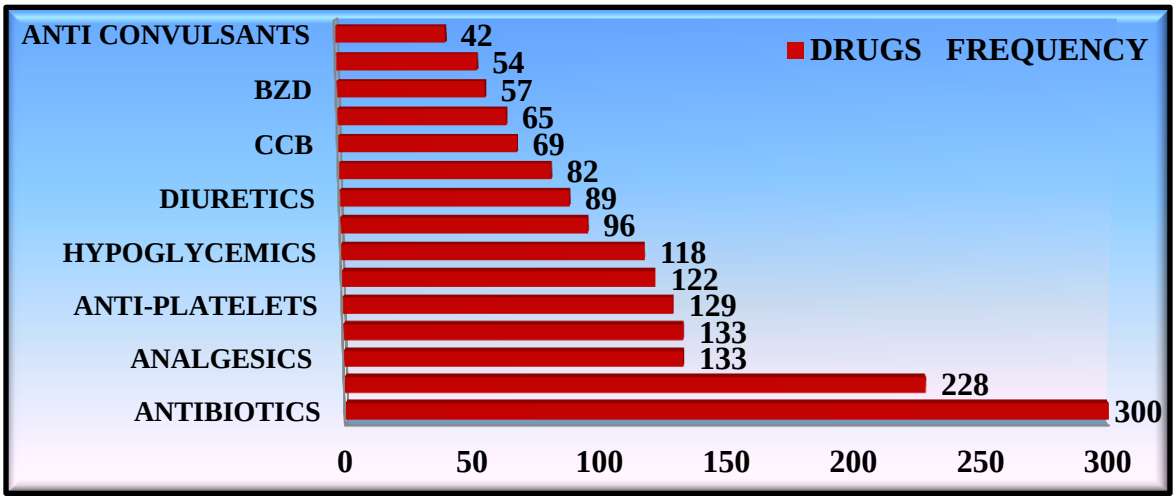

Figure 9

Table 11: Distribution of Drug Interactions based on mechanism.

MECHANISM	FREQUENCY	PERCENTAGE
Pharmacokinetic drug interactions	**97**	**18.0%**
Absorption	27	27.8%
Distribution	0	0%
Metabolism	**70**	**72%**
Excretion	0	0%
Pharmacodynamic drug interactions	46	8.56%
TOTAL	**143**	

Table 12: Categorizations of drug drug interactions based on severity.

SEVERITY	NO OF DDI's	PERCENTAGE
MAJOR	46	32.16%
MODERATE	50	34.96%
MINOR	47	32.86%
TOTAL	**143**	**99.98%**

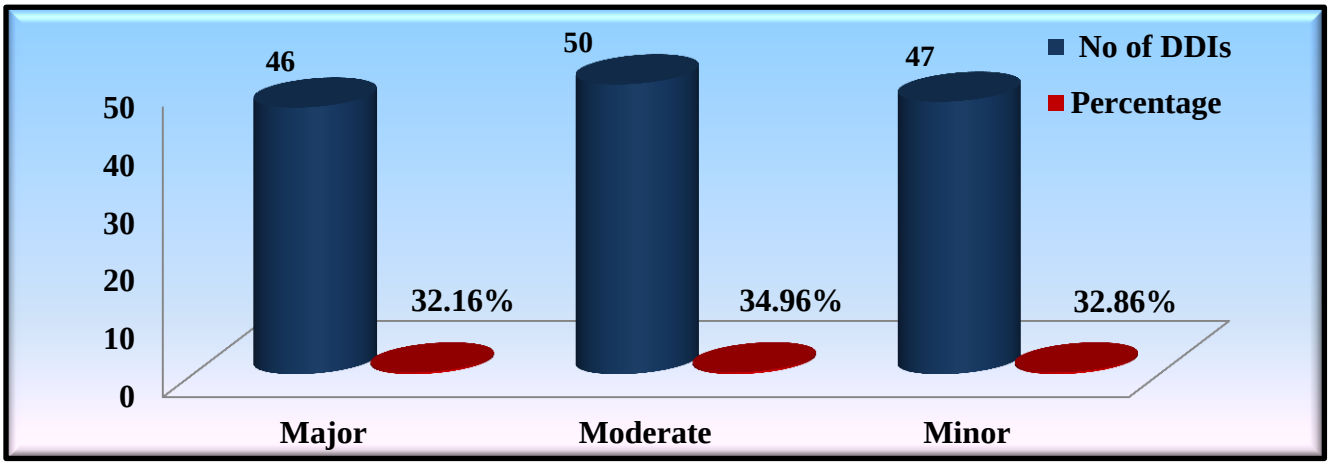

Figure 10

Table 13: Pharmacokinetics - Absorption

Interacting drugs	Effect	Frequency	Percentage
Pan + vitamin B12	Inhibition of GI absorption.	**11**	9.79%
Calcium carbonate + Rosuvastatin		1	
Lorazepam + vitamin B12		1	
Ciprofloxacin + Sucralfate		1	
		Total:-14	
Pan + Budesonide	↑se level of gastric Ph	5	7.69%
Pan + Ferricarboxymaltose		2	
Pan + Ferrous sulphate		2	
Pan + Digoxin		2	
		Total:-11	
Ampicillin +Pan	↓se level of gastric pH.	1	0.69%
Thiamine + Metronidazole	Altered intestinal flora	1	0.69%
TOTAL		**27**	18.8%

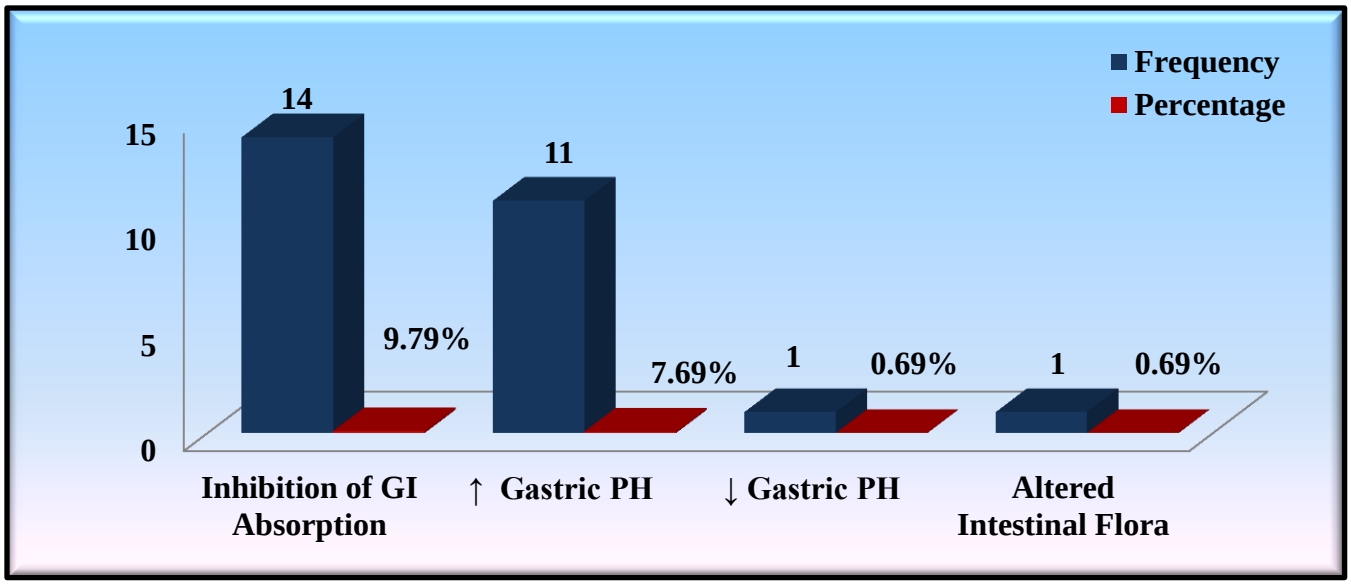

Figure 11

Table 14: Pharmacokinetics drug interactions based on metabolism.

Interacting drugs	Effect	Frequency	Percentage
Acetaminophen + Levetiracetam	↑Metabolism	2	4.19%
Torsemide + Clopidogrel		2	
Phenytoin + Levofloxacin		1	
Acetaminophen + Lorazepam		1	
		Total: 6	
Metoprolol + Ciprofloxacin	↓Metabolism	1	0.69%
		Total: 7	**4.89%**

Table 15: Pharmacokinetic drug interactions based on CYP(P450) enzyme

Interacting drugs	CYP	Frequency	Percentage
Pan + Clopidogrel	Inhibit	**9**	10.48%
Fluconazole + Pantoprazole	2C19	3	
Rifampicine + Pantoprazole		1	
Fluconazole + Clopidogrel		1	
Modafinil + Clopidogrel		1	
Metronidazole + Acetaminophen	2E1A	5	5.59%
Doxycycline + Thiamine		1	
Furosemide + Pantoprazole		1	
Pantoprazole + Acetaminophen		1	
Metronidazole + Diclofenac	2C9/10	2	2.09%
Fluconazole + Sulfamethoxazole		1	
Atrovastatin + Telmisartan	↑ toxicity of drug by	2	2.79%
Atorvastatin + Clarithromycin	OATP1B1	2	
Modafinil + Ondansetron	1A2	1	0.69%
		TOTAL :31	**21.67%**

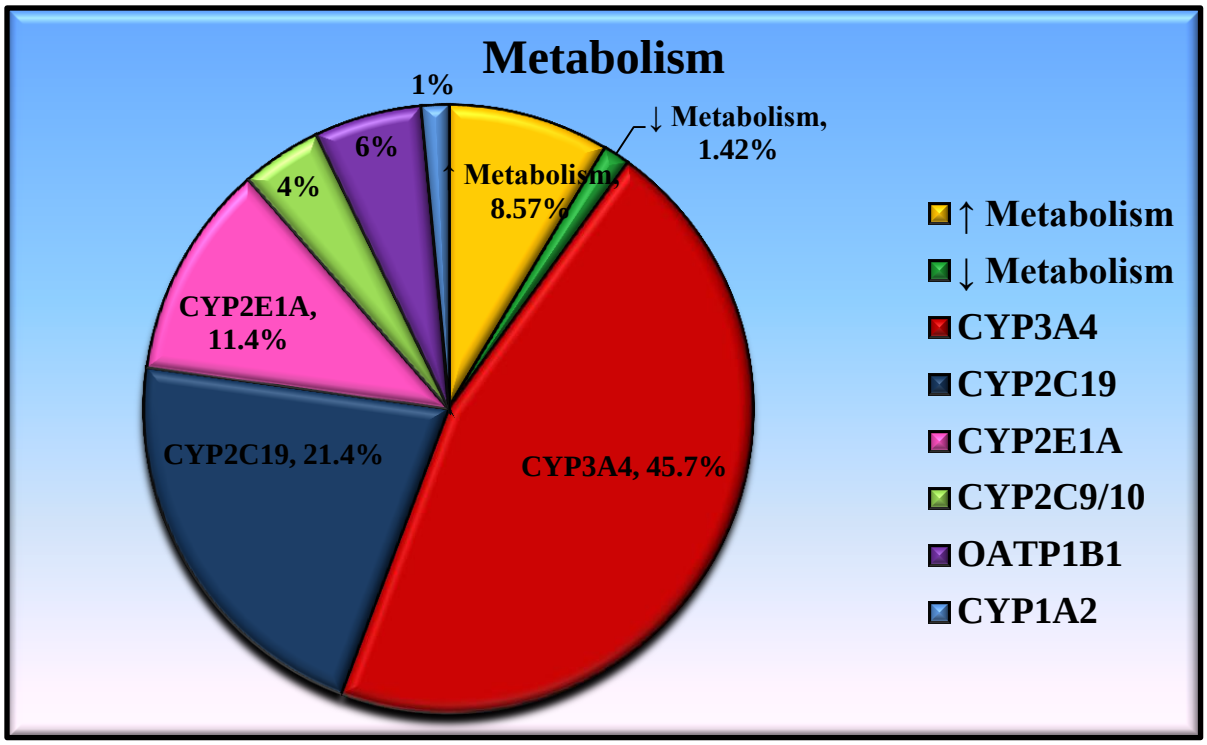

Figure 12

Table 16: Pharmacodynamic Drug interactions.

Interacting drugs	Effect	Frequency	Percentage
Anti-Hypertensive + Diuretic	Hypokalemia	4	17.3%
Anti-Hypertensive + Steroid		4	
Anti-Psychotic + Benzodiazepine	Sedation	3	19.56%
Hypnotics + Benzodiazepines		**6**	
Anti-Hypertensive + Antibiotic	Nephrotoxicity	3	10.8%
Anti-Hypertensive + Vitamin		2	
Anti-Coagulant + Anti-Hypertensive	Hyperkalemia	2	8.69%
Bronchodilator + Insulin		2	
Anti-Fungal +Anti-Emetic	↑QTC Interval	3	13.04%
Benzodiazepine+ Anti-Psychotic		3	
Anti-Depressant + NSAID	Hemorrhage	3	8.69%
Anti-Coagulant + Anti-Platelet		1	
Haemopoietic growth factor + Statin	Myopathy	2	4.34%
Other interactions	Alteration in body fluids	8	15.2%
Total :		**46**	**97.62%**

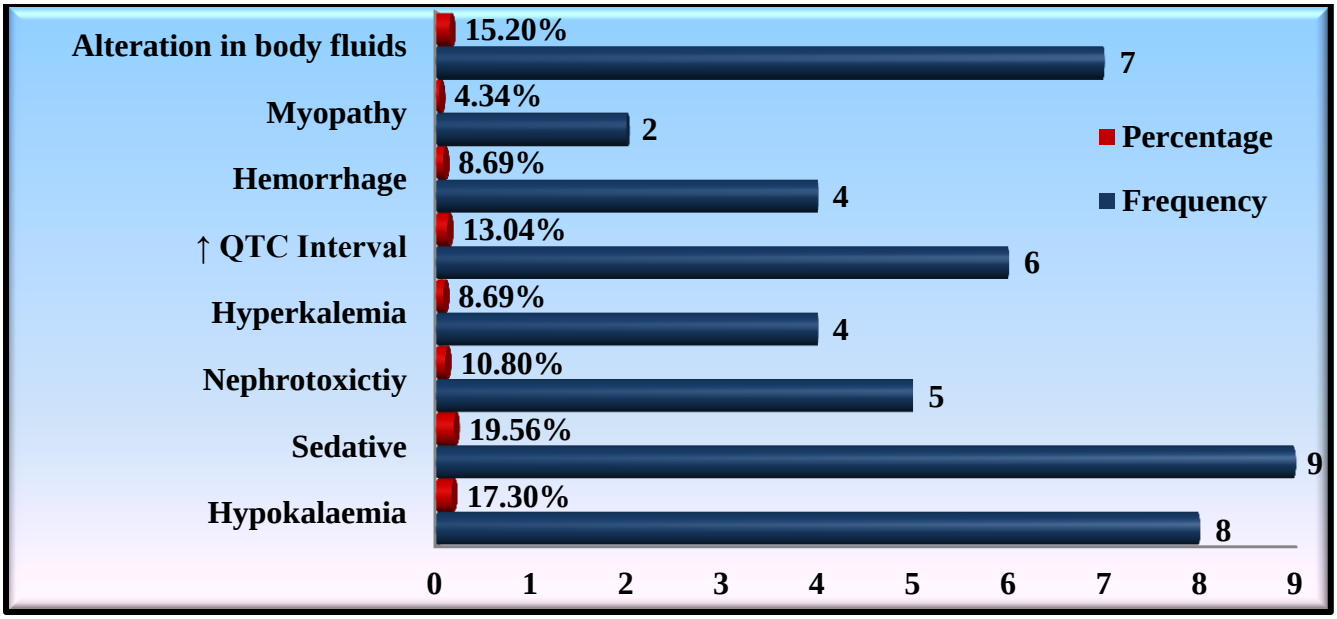

Figure 13

DISCUSSION

In our study we define polypharmacy as the simultaneous use of two or more medications for a longer period of time; the study provides data to assess the prevalence of polypharmacy ADRs, Drug-Drug interactions and inappropriate use of medications from the age group of 15 to ≥65. Polypharmacy is unavoidable as the chronic conditions of the patient's increases which demand the use of multiple drugs. DDI and ADR are frequently the end results of polypharmacy and are associated with other factors eg: age, gender, diagnosis of disease, social history, multiple co-morbidities, OTC medications. Nowadays, non-adherence to the treatment is a common problem in older adults and teenagers.

The total numbers of 537 patients were observed, which included 286 in patients and 251 outpatients, the patient age of 15≥65 years were included in the study of which the female's participants were 307 and males were 230 respectively. The highest no of patients was admitted under General Medicine in both IP and OP department with 35.1% followed by Neurology, Pulmonology, and Cardiology departments were 13.0%, 10.4%, and 10.0% respectively. A total number of 321[59.7%] ADR's were observed, among 321 ADRs the Incidence of adverse drug reactions was high in the age group 66 above with 26.7% in which females adult experience highest of 45 ADRs with least in male adults of 35 ADRs. The Incidence of adverse drug reactions was high in the age group 15 - 25 which was 21.4% in which females with the highest number experienced 7ADRs and male with at least 4 ADRs. Neurological System was the most common organ system affected due to adverse drug reactions with 24.2% followed by Dermatological (9.49%) and gastrointestinal system (11.5%) respectively. Naranjo Algorithm was used to assess the causality which revealed that 28.4% ADRs as Possible, 24.9% as probable and 0.7% as highly probable which is shown in [Table 6]. An outcome of Patients indicates 33.8% ADRs were recovering and 25.8% ADRs were continuing in IP and OP. The high Prevalence of ADRs could be attributed to multiple drugs intakes which were evident in the study as drugs prescribed to patients irrespective of Age, Gender, and Disease. Drugs contributing majority to ADRs with highest Prevalence rate with Telmisartan (0.65%), followed by ceftriaxone (0.42%), Meropenem and Atorvastatin with (0.34%). The more number of patients on polypharmacy were observed in IP under the age of 15-25i.e; 3.49% and OP 46-55 i.e.; 3.8% according to the study. the patients on single OTC medications are on higher ratio i.e.; 7.07% in which the number of males patients exceed the females. The more number of medications were prescribed under the age group of 56-65 in which males 398 and females 385 an average number of medications were prescribed was 22. The patient's on co-morbid conditions were more

under the age group of 56-65 in which males 22 females 23. The patients on two co-morbid conditions are more as compare to triple co-morbid. According to the study, the number of drugs prescribed was 3,516 in 537 patients in which the higher ratio of antibiotics with 300 frequency, PPI-228 and analgesics 133.we find that among all the given conditions most frequent co-morbid conditions were HTN+DM likewise triple co-morbid conditions more patient was with HTN+DM+CVA in which females were on the higher ratio. The total number of 143 drug interactions was reported in which 15.8% pharmacokinetic interactions observed and 7.50% pharmacodynamics interactions, it was found that major type of drug-drug interactions was 32.16% moderate with 34.96% and minor with 32.8%. Assessment of drug interactions was made based on severity and found that the most repetitive categories found to occur between steroids and antacid with its frequency 11. In pharmacokinetics drug interactions the number of absorption was 4.4% the most common effect was inhibition of GI absorption with the frequency of 51.8%. Among pharmacodynamics drug interactions the total numbers of drugs increasing the metabolism activity were 8.57% and drugs decreasing the metabolism activity were1.42%. Based on CYP3A4 the most commonly found interaction was between steroids and antacid among the other CYP450 enzymes the highest a=enzyme e that was found to be affected is CYP2C19 with 21.4%followed by CYP2E1A with 11.4%. Therefore the research shows that they are different types and frequencies of ADR and DDI which occur due to drug-related problems associated with different categories of drugs.

CONCLUSION

The use of medicines in disease is necessary, but unnecessary use of drugs by the patient increases the safety problems. Our study helped us in understanding the most susceptible age group common mechanism and disease conditions that can cause unnecessary effects in patients. It shows that polypharmacy is common in older adults due to the need to treat a various disease that develops as the patient ages and in younger population due to drug abuse and unnecessary use of OTC medications. Unfortunately, with this increase in the use of multiple medications comes with an increased risk for ADR's, DDI's, medication non-adherence, decreased functional status. High incidence of adverse drug reactions was observed i.e.; [42.7%] and has been recorded which shows that not only elderly but other age groups are suspected to adverse drug reaction. Many drug interactions are the result of alteration in CYP450 metabolism. It was observed that the prevalence of CYP- mediated drug interactions were found in adults and pharmacodynamics interactions were mostly observed in elderly patients. To improve drugs safety in high-risk population appropriate prescription is more important than reducing the number of prescribed drugs. Thus the potential risk of DDI and ADR can be managed by careful therapeutic drug monitoring and dose individualization by the professionals with proper prescriptions monitoring and patient education.

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