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ASSESSMENT OF POLYPHARMACY AND ASSOCIATED PROBLEMS IN CARDIO VASCULAR DISEASED PATIENTS IN A SECONDARY CARE HOSPITAL

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ABSTRACT

Background: Polypharmacy is a major public health problem among the hospitalized patients. The prescription of multiple medications leads to polypharmacy, adverse drug reactions, drug-drug interactions and non-adherence to treatment. **Objective:** The present study was designed to analyze the polypharmacy in patients with cardiovascular disease and associated problems like drug-drug interactions, drug duplication and adverse drug reactions in patients prescribed with polypharmacy. **Methodology**: A prospective observational study was performed in secondary care hospital of cardiovascular department in Salem, Tamilnadu, India. Only patients prescribed with polypharmacy were included in our study. **Results:** A total of 140 cardiovascular patients were analyzed in which 65.72% of patients were male and 34.28% of patients were females. The major fraction 54% of the patients was in the age group of 61-80 years and 30% of the patients aged above 80 years. The prevalence of polypharmacy is more common in male 61.0% and 38.9% in females. In a study group 46.42% population has coronary artery disease and 13.57% had rheumatic heart disease. Polypharmacy was observed in almost all cases, wherein 14.29% were prescribed more than 16 drugs, 17.86% of patients were with 13-16 drugs, 35.71% of patients were with 9-12 drugs and 32.14% were with 5-8 drugs. Anti-coagulants are most commonly prescribed drugs 64.2% followed by 51.41% prescribed with anti-platelet drugs. Micromedix and Medscape drug interaction checker was used to analyze the drug interaction. A total of 32 potent drug interactions were found and 25 ADR were found during our study. **Conclusion:** Results of the study revealed that polypharmacy is a major cause for drug-drug interaction and adverse drug reactions in cardiovascular patients. The clinical pharmacist should address the valuable services to minimize drug-interactions and ADR due to polypharmacy.

KEYWORDS: polypharmacy, drug-drug interaction, adverse drug interaction, drug duplications.

INTRODUCTION

Cardiovascular diseases (CVDs) are group of disorders that mainly affects heart and blood vessels, one of the leading causes of death worldwide, more people die annually from CVDs than any other cause. CVD accounts for 7-10% in African people and in that heart failure constitutes about 3-7%.[1] It was estimated that by 2020, cardiac disease and stroke will become leading cause of both death and disability worldwide and number of fatalities projected to increase to over 20 million a year and by 2030 to over 24 million a year. Eighty percent of all global CVDs related to deaths in low and middle income countries. There are many types of cardiovascular diseases which are inter-linked with each other. For example high bad cholesterol causes atherosclerosis; hypertension is linked with stroke, myocardial infarction, heart failure and peripheral arterial disease. Non-cardiovascular diseases are also strongly inter-connected with the cardiac complication. Obesity, diabetes, periodontal infection and depression promote the development of cardiovascular risk factors.[2, 3] In result, cardiovascular drugs alone are not sufficient to cure the cardiac patients. Thereby multiple disease states create the demand for multiple drug therapy. Thus multiple drug therapy is widely used for the treatment of problems including hypertension, Ischemic Heart Disease (IHD) and heart failure together. Consequently, multiple drug therapy creates a concept of 'polypharmacy'.[2, 4] Polypharmacy is defined as prescribing four or more medications to the same patients.[5] The national service framework for old people shows that 5-17% hospitalized patients develops adverse drug reactions.[6] Being sometimes inevitable, polypharmacy is not always efficacious and safe.[7] The elderly people represents growing segment of population and their use of medication is increasing significantly. Several studies shows that polypharmacy is more common in elderly patients during the pharmacological therapy which leads to specific health related problems due to multiple diseases and chronic disease condition.[8-

12] Recently polypharmacy is described as use of in-appropriate or more medications than indicated. The prevalence of inappropriate use of medication in elderly population ranges from 11.5 to 62.5%. The problems associated with polypharmacy or multiple drug therapy includes adverse drug reactions and drug to drug interactions, drug to disease interactions, medication errors, non-adherence to treatment, and increased risk of cognitive impairment, hospital admission, economic burden and increased risk of morbidity and mortality rates.[8, 3, 13-15] One of the greatest problems globally in 21st century is increasing the burden of chronic diseases, as a result multiple medications or polypharmacy become common.[16] Nowadays Polypharmacy is a preventable and it is a major contributor to morbidity and mortality, an evidence-based intervention is needed to address and to prevent downstream harm to the patients.[17] The following preventive measures should be taken to prevent polypharmacy. Obtain an accurate medication and medical history, each prescribed medication to a disease state. Identify medications that are treating side effects. Initiate interventions to ensure adherence, Reconcile medications upon any discharge from hospital or skilled nursing facility.[18-20]

METHODOLOGY

A prospective observational study was carried out in General Medicine Department of Teaching Hospital Salem, Tamilnadu, India. The data was collected between November 2013 to April 2014.

Sample size: 140 patients.

Patient Inclusion Criteria

The study includes patients of all age groups of both gender, mainly patients with cardiac disorders prescribed with >5 drugs.

Patient Exclusion Criteria

The study excludes patients who had hepatic insufficiency, pregnant women and lactating women and those prescribed with <5 drugs.

Data collection

A regular ward round participation with a health care team was taken, in order to collect the data of in-patients. A separate data collection form has been prepared by clinical pharmacist for the collection of patient details which includes demographic details, concomitant medical problems, laboratory investigations (CBC, blood parameters, renal function and lipid profile test), prescribing patterns, medication details, life style modifications (physical activity, smoking habits, alcohol consumption, dietary habits, changes in body weight), family history of disease, medication errors, adverse drug reaction and drug- drug interaction.

Data analysis

The data was collected from medicine department through designed proforma and thoroughly assessed. The assessments of drug-drug interaction and ADR were mainly done.

RESULTS

In our study, a total of 160 cases were collected from the general medicine ward of Cardiovascular Diseases, for period of 6 months from November 2013 to April 2014. From 160 cases 20 cases were excluded as they were prescribed with less than 5 drugs. A total of 140 cardiovascular patients were analyzed in which 92(65.72%) patients were male and 48(34.28%) patients were females. Among the study sample 54% of the patients aged -61-80 years and 30% of the study population aged above 80 years. In a study group 46.42% population has coronary artery disease which was the highest number followed by rheumatic heart disease 13.57%, presence of other cardiovascular disease was depicted in table no 1. Based on duration of hospitalization majority of patients 48.57 %(68) were admitted for 1-4 days, followed by 32.9 %(46) patients were admitted for 5-8 days.

Table no.1 Patients demographic details and presence of diseases

Patients characteristics	No of patients	percentage
Gender		
Male	92	65.72
Female	48	34.28
Age group		
20-40	6	4.29
41-60	17	12.14
61-80	75	53.50
80 above	42	30.00
Presence of disease		
Coronary artery disease (CAD)	65	46.42
Rheumatic heart disease (RHD)	19	13.57
Cardiac surgery patient	35	9.28
Congestive cardiac failure (CCF)	10	7.14
Unstable angina	6	4.28
Atrial septal defect closure (AST)	3	2.14
Atrial septal defect (ASD)	6	4.28

Coronary artery bypass surgery	4	2.85
Coronary heart disease (CHD)	3	2.14
Aortic valve replacement (AVR)	3	2.14
Myocardial infarction (MI)	4	1.42
Co-morbidities diseases		
Diabetes mellitus	45	32.14
Hyperlipidemia	27	19.28
Anemia	14	10.0
Bronchial asthma	12	8.57
Kidney diseases	7	5.0
Days of hospitalization		
1-4 days	68	48.57
5-8 days	46	32.86
9-12 days	15	10.71
Above 12 days	11	7.86

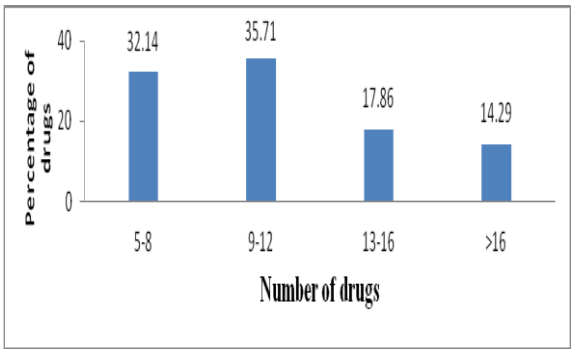

Figure No. 1 Number of drugs on admission for cardiovascular patients (n=140).

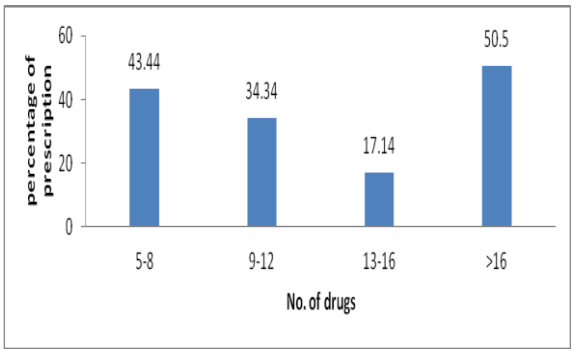

Figure No. 2 Number of drugs on discharge of cardiovascular cases in our hospital (n=140)

A total number of drugs prescribed for each patients during the admission were analyzed in that, 14.29% (n=20) patients were taking more than 16 drugs and 17.86% (n=25) were taking 13-16 drugs, 35.71% (n=50) were taking 9-12 drugs and 32.14% (n=45) were taking 5-8 drugs. Which is represented in figure no 1.

A total of, 43.44% (n=43) patients were discharged with 5-8 drugs, 34.34% (n=34) patients were discharged with 9-13 drugs, 17.14% (17) patients were discharged with >16 drugs, 50.50% (n=5) patients were discharged with more than 10 drugs on their prescription and remaining 41 cases were discharged with less than 4 drugs which is excluded from our study which is represented in figure 2.

Table No. 2 the most frequently prescribed drug classes for cardiovascular cases.

Drug Class	No. of prescriptions	Percentage
Anticoagulants	90	64.28
Antiplatelates	72	51.41
HMG CoA reductase inhibitors	71	50.71
H_2 blockers	54	38.57
Diuretics	63	45.00
ACE inhibitors	36	25.71
Calcium channel blockers	26	18.57
Beta 2 adrenergic blockers	23	16.42
Cardiac glycosides	19	13.57
Nitro glycerides	15	10.71

During our study period the most frequently prescribed drugs were analyzed in which, 64.28% (n=90) were prescribed with anticoagulants which was the highest number followed by 51.41% (n=72) were prescribed with antiplatelets and 50.71% (n=71) were prescribed with HMG-CoA reductase inhibitors which is represented in table 3. Among the 140 cases 51.42% (n=72) were prescribed with clopidogrel on admission which was highest, followed by Atorvastatin 47.14% (n=66), Furosemide with 45% (n=63).

Table no. 3. Relationship between Polypharmacy and age (n=140)

	Taking ≥10 medications on admission			
	YES		NO	
Age	Number	Percentage	Number	Percentage
0-20	3	3.90	3	4.76
20-40	9	11.69	8	12.70
40-60	41	53.25	34	53.97
60 above	24	31.16	18	28.57
Total	77	100	63	100

From the data collected we calculate the relationship between polypharmacy and age in it 53.25% (n=41) patients of age group 40-60 were taking more than 10 drug which is highest and followed by 31.16% (n=24) patient of age group above 60 were taking more than 10 drugs which is represented in table no. 3.

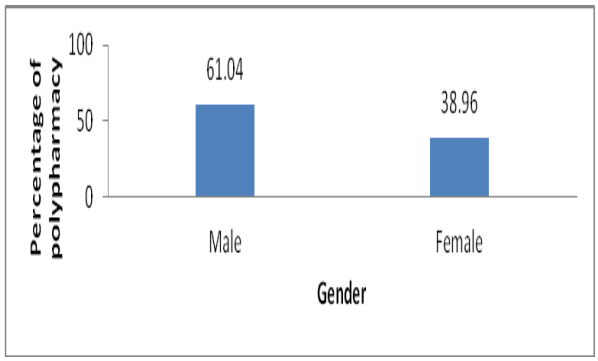

Figure no.3 Relationship between polypharmacy and gender (n=140).

During the study period the relationship between polypharmacy and gender were compared in which 61.04% (n=47) male patients were taking more than 10 drug and 38.96% (n=30) female patients were taking more than 10 drugs which is represented in figure no 3.

Table No. 5. Possible significant potential drug interactions.

Digoxin + Atorvastatin	Inc. steady state digoxin level	Monitoring
Clopilet + Tramadol	Inc. risk of stomach and intestinal bleeding	Monitoring
Furosemide + Metformin	Antagonize the hypoglycemic effects	D/W
Furosemide + Aminoglycosides	Risk of ototoxicity	D/W
Furosemide + Cephalosporin's	Risk of nephrotoxicity	D/W
Furosemide + Hydrocortisone	Antagonize by hydrocortisone	Monitoring
Furosemide + Enalapril	Severe hypotension	D/W
Furosemide + NSAIDs	Inhi. diuretic and anti- hypertensive effects	Monitoring
Furosemide + Digoxin	Incidence of premature beats	Monitoring
Cardivelol + Digoxin	Increase the serum level of digoxin	Monitoring
Ceftriaxone + Amikacin	Nephrotoxicity	D/w
Diltiazem + Amiodarone	Inc. depression of cardiac conduction	D/W
Diltiazem + Digoxin	Inc. depression of cardiac conduction	Monitoring
Pantoprazole + Digoxin	Inc. digoxin concentration	Monitoring
Tramadol + Ondansetrone	Dec. the analgesic efficacy	Monitoring
Levofloxacin + Sucralfate	Dec. the absorption of levofloxacin	D/W
Levofloxacin +Tramadol	Risk of CNS stimulation and seizures	Monitoring
Telmisartan + Heparin	Inc. the risk of hyperkalaemia	Monitoring
Ofloxacin + Hydrocortisone	Inc. the risk of tendon rupture	D/W
Ofloxacin + Tramadol	Seizures	D/W
Calcium + Furosemide	Milk alkali syndrome and hyperkalaemia	Monitoring
Calcium + Digoxin	Precipitate digitalis intoxication	D/W
Losartan + Furosemide	Hyperkalaemia	Monitoring
Verapamil + Amiodarone	Inc. the cardiac depressant effects	D/W
Verapamil + Digoxin	Inc. the risk of Bradycardia	Monitoring
Amiodarone + Digoxin	Inc. the plasma concentration of digoxin	Monitoring
Glyceryl trinitrate + Aspirin	Dec. the efficacy	Monitoring
Prazosin + Nifidepine	Risk of hypotension	Monitoring

D/W: Drug Withdrawal, Inc: Increased, Dec: Decreased, Inhi: Inhibited.

A total of 28 drug interactions were found during our study period and which of those were frequently repeated in many prescriptions this is represented in table no.4. Based upon the mechanism of interaction, 65.62% (n=21) of interaction produced were pharmacodynamic, 28.12% (n=9) interaction were pharmacokinetic and 6.25% (n=2) were of unknown mechanism.

Table No.5 Irrational prescription of drug combinations in our hospital and the reasons for irrationality

Irrational drug combinations	Reasons for irrationality
Clopilet + Tramadol	Increase risk of stomach and intestinal bleeding
Furosemide + Amikacin	Risk of ototoxicity
Furosemide + Ceftriaxone	Risk of nephrotoxicity
Carvidilol + Digoxin	Increase the serum level of digoxin
Ceftriaxone + Amikacin	Nephrotoxicity
Furosemide + Enalapril	severe hypotension
Diltiazem + Amiodarone	Increases depression of cardiac conduction
Diltiazem + Digoxin	Increases depression of cardiac conduction
Metaprolol + Digoxin	Negative effects on SA/AV node conduction
Levofloxacin + Tramadol	Increases the risk of CNS stimulation and seizures
Calcium + Furosemide	Milk alkali syndrome and hyperkalaemia
Digoxin + Calcium	Increases the cardiac effects
Amiodarone + verapamil	Increases the cardiac depressant effects
Digoxin + verapamil	Risk of bradycardia, conduction disturbances
Losartan+Furosemide	Hyperkalaemia
Lasilactone+Amikacin	Ototoxicity

From the data collected irrational prescription of drug combinations and the reasons for irrationality were noted, which is depleted in table no. 5.

Table No. 6 Drug Duplication used in the prescription in our hospital

Drugs combination	Number of cases	Percentage of cases
Ramipril + Carvidilol	13	35.13
MVT + BCT	10	27.02
Acetaminophen + Tramadol	09	24.32
Neb. Duolin + Budecort	04	10.81
Asthalin + Budecort	01	2.70

MVT: Multi Vitamin Tablet, BCT: B complex, Neb: Nebulization.

The drug duplication were analyzed during our study Ramipril + Carvidilol drug combination was found in 35.13% (n=13) of cases which is highest and followed by other drugs combination which is represented in table no.6.

Table No.7 Drugs which caused adverse drug reactions in our hospital.

Drug	Adverse drug Reaction	No. of patients	Percentage
Digoxin	Diarrhea(5),dizziness(3)	8	32.00
Amlodipine	Peripheral oedema(3),fatigue(2)	5	20.00
Clopidrogrel	Pruritis(4),rashes(3)	7	28.00
Enalapril	Dry cough(3)	3	12.00
Aspirin	Epigastric pain(2)	2	8.00

A total of 25 ADR were found during our study, 32% (n=8) were caused by Digoxin, which is highest and followed by amlodipine, clopidrogel, enalapril and aspirin (8%) respectively. This is represented in table no 7. During the study period 48% (n=65) of ADRs occurred in coronary artery disease patients which is highest and followed by rheumatic heart disease. These are represented in figure no. 5.

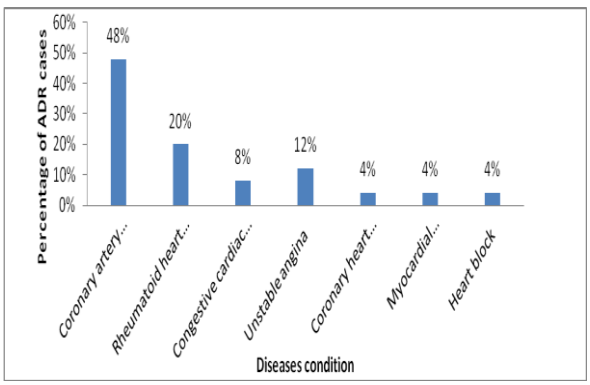

Figure no. 5 Relationship between ADRs and Different disease condition

Table No.8 Type of adverse drug reaction according to wills and Brown classification

Type of reaction	No of ADRs
Type A Augmented reactions	12(48.00%)
Type B Bizzare reactions	-
Type C Chemical reactions	-
Type D Delivery reactions	-
Type E Exit reactions	-
Type F Familial reaction	-
Type G Genotoxicity reactions	-
Type H Hypersensitivity reactions	13(52.0%)
Type U Unclassified reactions	-

Classification of ADRs was done according to Wills &Brown method. Type A Augmented reaction occurred in 48% (n=12) of patients and Type H Hypersensitivity reaction occurred in 52% (n=13) of patients which is the maximum in number compare to other reaction. These details are given in above table no 8.

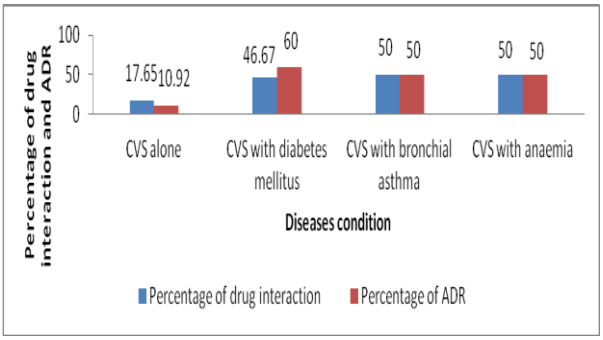

Figure No- 6. Number of drug interactions and ADR according to diseases conditions

Table no. 9 Relationship of polypharmacy with Drug Interactions and ADRs

Number of drugs	Number of drug interaction	Number of ADR
5-8	5	4
9-12	7	5
13-16	8	7
>16	12	9
Total	32	25

From the data collected it was found that both drug interaction and ADR were increasing as the numbers of drugs in prescriptions were increased. Drug interactions and ADRs were more in patients prescribed with >16 drugs, which is represented in table no 9.

DISCUSSION

Polypharmacy is a most important problem in the healthcare system. Patients admitted in the cardiology ward were mostly on polypharmacy due to the presence of co-morbid diseases, which demands number of medications. Cardiovascular drugs are one of the most important classes of drugs associated with medication errors, ADRs and drug-interaction, which need to monitor from time to time. Present study aimed in investigating the problems associated with polypharmacy and an evaluation of this status gives us some basic information for working towards improving the current situation. The literature review shows that there is interlink between the elderly patients and polypharmacy, in elderly patients the physiological changes that occurs with aging leads to number of chronic conditions leading to multiple conditions.[21, 22] During our study period 83% of the patients were elderly. These results were compared with the various studies.[23, 24]

Diabetes mellitus and hyperlipidemia are most common co-morbidity disease conditions during the study period 32.14%, 27.28% respectively, which may be the most common contributor for polypharmacy. However previous studies reported that diabetes mellitus, hypertension and dyslipidemia are contributors for polypharmacy, confirming that increasing number of medication in patients with cardiovascular disorders.[8] The prevalence of polypharmacy is 74% in a study conducted by Edisa Trumic et al., the number of interactions increase with the number of drugs.[25, 14] The use of cardiovascular drugs like beta-blockers, angiotensin II converting enzyme inhibitors, calcium channel blockers and anti-arrhythmic agents increases the risk of polypharmacy.[8]

During our study period, out of 140 patients 46.42% patients had coronary artery disease and 13.57% patients had Rheumatic heart disease. The hypertension (73%), hypercholesterolemia (54%), arthritis (6.2%) and MI (48%) is more common in a study conducted by Catherine I Wong.[10] study conducted by Mohamed N. Al-Arif et al., showed that the inappropriate prescribing is mainly due to drug interaction which is (55.7%) and hypertension is 91%, followed by dyslipidemia 74.9%, ischemic heart disease IHD (53.3%) and MI (12%).[8]

During our study period anticoagulants 64.76%, anti-platelet drugs 51.41% and HMG co A reductase inhibitors 50.71% are most commonly prescribed drugs. The similar results were found in another study, the most commonly prescribed drugs are ACE inhibiters (77.2%), beta-blockers (74.9%), lipid lowering 76% and analgesic class of drugs Aspirin 68.3% [6], and these classes of drugs are most responsible for polypharmacy.[8] The study conducted by shalini et al., showed in her study the commonly prescribed medication in chronic basis in elderly patients were anti-hypertensive drugs 81%, NSAIDs 61% and antiplatelets 53%.[9] In a similar study cardiovascular drugs antihypertensive, anti-rheumatic

and analgesics were most frequently prescribed drugs.[25] During our study period 14.29% (n=20) patients were taking more than 16 drugs and 17.86% (n=25) were taking 13-16 drugs, 35.71% (n=50) were taking 9-12 drugs and 32.14% (n=45) were taking 5-8 drugs. Which is represented in figure no 1. The similar results were found in the study conducted by pawar et al., showed 45% of the patients received more than 11 drugs, 31.66% patients received more than 6 drugs, 19.16% patients received 16 drugs and 2.5% patients received more than 21 drugs.[22] The study results also compared with another study, 89% study patients received more than 5 drugs and 43% patients received more than 10 drugs.[26]

A drug interaction is a major health related problem in day to day practice. The drug interactions increased with increasing the number of drugs in prescription. Twenty eight drug interactions were observed during the study period. About 58.46% prescriptions had drug-drug interaction in our study, the results were compared with study conducted by kumarswamy et al., and in his study 54.46% prescriptions had drug-drug interactions.[27] The study results were similar to that of study conducted by shahabudin et al., in which of 66%.[28] The study results were compared with other studies in which patients prescribed with 6- 10 drugs shows 10.52% DDI, 11-15 drugs shows 29.563%, 16-20 drugs showed 39.13% and 100% DDI were seen the prescription with more than 21 drugs.[21] The use of prescription and non-prescription medications is more common in elderly patients in the US, which is continues to rise according to the center for diseases control and prevention.[23] The top 5 common drug interactions in a study conducted by shababudin et al., were ciprofloxacin+ insulin and digoxin+ spiranoactone which are most common responsible for drug-drug interactions.[28] But in our study we found that the major interaction were between furosemide, digoxin, quinolines (oflaxacin, levofloxacin) which are the top most drugs responsible for drug interaction. Another study reported that oflaxacin+ondansatran and metformin+ofloxacin are a major cause of drug interactions.[27]

Drug duplication is another problem analyzed during the study period 26.42% drug duplication occurred which is highest when compared to the previous studies. The drug duplication is 19.7% in the study conducted by fita et al. and unnecessary therapeutic drug duplication occurred 94.6% in another study.[29, 8] Many studies show that ADRs are more common in elderly patients. The incidence of ADRs increased with increasing the number of medication in an exponential rather than a linear manner.[24] In our study 17.85% of the patients reported with ADRs, in which most common ADRs due to digoxin in 8 patients followed by clopidogrel and amlodipine 7, 5 patients respectively. The results were compared with study conducted by Ayesha Romana et al., in which insulin produces ADRs in 5 patients, followed by Sulbutamol in 3 patients, amlodipine 2 patients and digoxin in 2 patients.[25] The similar results were found in study conducted by Rupawala et al., shows that anti-diabetics, anti-coagulants lead to majority of ADRs in elderly patients and the similar results found in study done by Yvonne Koh et al., shows that 8 ADRs identified during admission and 33 ADRs identified during hospital stay.[21, 24] Because of unnecessary new therapy the patients is risk of new adverse drug reactions.[30]

CONCLUSION

Polypharmacy is a major public health problem and the prevalence is increasing among the hospitalized patients. Results of the study revealed that polypharmacy is a major source for drug-drug interaction and adverse drug reactions in cardiovascular patients. As the number of drugs increased in the prescription the occurrence of drug interaction and adverse drug reaction gradually increases with it. The clinical pharmacist should address the valuable services to minimize drug-interactions and ADR due to polypharmacy. Educational programmes and interventions should be conducted to optimize the medication use and to improve the prescribing habits. Drug information services should also be started in the every hospital to provide the information about adverse drug reaction and drug-drug interaction to the physicians.

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