

PROSPECTIVE EVALUATION OF CVD POLYPHARMACY PRESCRIPTIONS AMONG GERIATRIC PATIENTS

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ABSTRACT

Aim: The aim of this study was to determine adverse drug reactions and drug-drug interactions due to polypharmacy in elderly patients on cardiovascular drugs. **Method:** A prospective observational study was conducted among geriatric patients aged above 60. The study was conducted in the department of cardiology of a tertiary care centre. Prescriptions of 100 elderly patients were analysed for patient demographic details like age, gender, comorbidities, and drugs prescribed. Adverse drug reactions, and drug -drug interactions were assessed using Medscape. **Results:** In this study, polypharmacy was found in 92 (92%) prescriptions, 72 (72%) prescriptions had drug-drug interactions. 3 (3%) prescriptions had adverse drug reactions. There was an increase in the use of 5-8 medications between ages 60 and 89. Women experienced greater polypharmacy. **Conclusion:** The finding of present study reveals that there is a positive correlation between age and number of drugs prescribed and women experienced greater polypharmacy. It is found that polypharmacy increases the risk of adverse drug reaction and drug-drug interaction, which can be minimized by pharmacokinetic and pharmacodynamics modification of the drug regimen. Cautionary guidelines can be developed and implemented and also computer-based screening, patient education might help to prevent adverse drug reactions and drug-drug interactions due to polypharmacy.

Keywords: Adverse drug reaction, cautionary guidelines, drug-drug interactions, geriatric.

I. INTRODUCTION:

1. Polypharmacy

Polypharmacy is a common problem in the geriatric population, and a necessity. Geriatrics is prone to numerous comorbid conditions that pave the way for the need for more medicines. With an increased number of medicines for heart patients, there is a tendency to cause drug-related problems such as ADRs, drug-drug interactions (DDIs) etc. Polypharmacy refers to the usage of 5 or more than 5 medicines.^[1] The aim should be to minimize excessive polypharmacy (irrational prescription of too many medicinal products) and to ensure adequate usage of drugs (rational prescription of multiple medicinal products based on best available evidence and taking into account individual patient factors).

Polypharmacy can be categorized into appropriate and inappropriate polypharmacy. Appropriate polypharmacy is when medication therapy has been optimized to minimize the risk of adverse drug reactions (ADRs). Inappropriate polypharmacy occurs when one or more medicines are prescribed that are not or no longer needed, either because there is no evidence-based indication, the indication has expired or the dose is unnecessarily high.^[2]

2. Polypharmacy Consequences

The major consequence of polypharmacy observed is increased side effects- Adverse drug reactions and Drug interactions.^[3]

(a) Adverse Drug Reactions

Adverse drug reactions (ADRs) are considered top of the pyramid, containing all drug-related problems (DRPs) and are a major concern for public health. ADRs account for 3-7% of hospital admissions and 5-9% of hospital inpatient costs. More than half of the ADRs are deemed preventable.

Elderly ADRs are available in many different settings. The elderly are predisposed to ADRs by multiple drug use and changes in pharmacokinetics and pharmacodynamics.^[4] ADRs could have profound effects on the quality of life of patients and could also create an increased burden on the healthcare system. The term adverse drug reaction was defined as 'any noxious change suspected of occurring due to a drug, occurs at doses normally utilized in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'.^[5]

Risk factors

Risk factors that have been reported to be associated with ADRs in the elderly include aging disease, female gender, multiple co-morbidities, multiple drug treatment, and duration of hospital stay and use of medications that are unsafe for the elderly.^[4]

Types of ADRs: 1) Dose related 2) Idiosyncratic 3) Allergic

Classification of ADRs: Originally, adverse drug reactions were classified into 2 subtypes. Type A ADRs is dose-dependent and predictable; they are increases in the drug's known pharmacological effects, such as orthostatic hypotension with antihypertensive drugs. Type B ADRs are rare and unpredictable depending on the drug's known pharmacology; they are dose-independent and affect a small population, suggesting that individual host factors are important. Examples of type B ADRs are hypersensitivity (allergic) reactions. Type A reactions were later called augmented reactions, and bizarre type B reactions. Finally, two other types of reactions were added: chronic reactions, both dose- and time-related (type C) and delayed (type D). Subsequently, withdrawal became the fifth group (type E), and most recently, unexplained therapy failure became the sixth (type F).^[6]

(b) Drug Interactions

Drugs are a tool of medical practice and are a major advance in pharmaceutical sciences. Nevertheless, the occurrence of drug-drug interactions (DDIs) that can be detected when the pharmacological or clinical reaction to the administration of a combination of two drugs is different than intended based on the known effects of both drugs when individually administered. The concept of "Potential Drug-Drug Interaction" (potential DDI) refers to the possibility that a drug may have to alter another's effects when both are administered simultaneously.

Drug interaction is characterized as the situation where the effect of one drug is changed or altered by the presence of another medication that is administered to the same patient simultaneously or concurrently. Understanding the possible drug interaction is crucial, as these can cause serious adverse reactions or lead to failure of therapy.^[7]

Interactions between drugs include: Pharmacodynamics and Pharmacokinetics.

In pharmacodynamics interactions, by having the same (agonistic) or antagonistic (blocking) effect, one drug changes tissue sensitivity or responsiveness to another drug. These effects typically occur at receptor level but can occur intracellularly. Pharmacological synergism: synergism occurs when two drugs are administered together to produce an additive effect with a similar pharmacological or side effect. Example: in combination with potassium-sparing diuretics or specific aldosterone antagonists such as spironolactone and eplerenone, the aldosterone-antagonistic effect of ACE inhibitors induces dangerous hyperkalemia or renal failure. Pharmacological antagonism: It occurs when one drug's activity precludes another's pharmacological impact. Example: Reduction by NSAID in the diuretic activity of a thiazide diuretic.

Pharmacokinetic interactions are those in which a drug alters absorption, distribution, protein binding, metabolism or excretion of another drug. These types of interactions when occurs changes amount and availability of another drug at receptor site thus changing magnitude and duration of drug effect and not type of effect. These can be monitored vide knowledge of each drug administered/prescribed or estimating concentration of drug in patient's serum.^[8]

Drug interactions may be classified into three groups:

1. Drug interactions with other drugs/ Drug-drug interactions (narcotics interactions)
2. Alimented drugs / drug-food interactions
3. Drug with condition of a disease / Drug-disease interactions.

Drug-drug interactions: The interactions between drugs result when two or more drugs react with each other. Such medicines may be from a combination of prescription and/or over-the-counter (OTC) medicines. Drugs with a limited therapeutic range (small gap between the therapeutic and lethal dose) are more likely to face severe drug

exposure events. For example, taking digoxin with antibiotics such as erythromycin or clarithromycin will increase digoxin toxicity because antibiotics affect liver enzymes, resulting in a slower metabolism (inactivation) of digoxin.

Drug-food interactions: These interactions are caused when drugs react with food or dietary supplements or beverages (including alcohol). Some drugs may interfere with nutrient absorption capacity in the body. Likewise, other herbs and foods may minimize or increase a drug's effects. Smoking and drinking habits can have a negative impact on drugs.

Examples:

1. Alcohol increases the hypoglycemic effect of anti-diabetic medications, and the hypotensive effect of many medicines for blood pressure.

2. Persons on warfarin must avoid eating large quantities of green leafy vegetables such as broccoli, spinach and watercress because the high vitamin K content of these foods counters warfarin's influence.

3. Chili inhibits substance P and the incidence of coughing in patients on ACE inhibitors is reportedly increased.^[9]

Drug-disease interactions: Drug-condition interactions can be seen when an existing medical condition worsens or exacerbates due to a drug. For example, a pseudoephedrine-containing nasal decongestant increases blood pressure and therefore people who are hypertensive (having high blood pressure) have to avoid that.^[8]

3. Prevalence of Cardiovascular Diseases in Geriatrics

An estimated 856 million American adults (> 1 in 3) suffers from one or more types of CVD. Of these, an estimated 43.7 million are approximately 60 years of age. For the age group of 60–79, the following are the percentages of CVDs: 69.1% of men; 67.9% of women. For the 80 + age group, CVDs are as follows: 84.7% of men; 85.9% of women. Approximately two thirds of CVD deaths occur in people of 75 years of age and older.^[10]

4. Cardiovascular Diseases

The leading causes of death according to the American Heart Association (AHA) are cardiovascular diseases (CVDs).

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, a group of heart and blood vessel disorders. It is a major cause of impairment of function and loss of independence, and the most common disease among older people in the United States. Cardiovascular diseases (heart diseases) are the range of diseases which affect heart and blood vessel structure or function. These include - diseases of the blood vessels, arrhythmias, heart defects, heart valve disease and heart muscle disease (cardiomyopathy).^[11]

Most common types of medications used in the treatment of cardiovascular diseases include anticoagulants, antiplatelet, thrombolytic agents, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, vasodilators, digoxin, statins, anti-arrhythmic agents, beta blockers, ARB's.^[12]

II. METHODOLOGY

Study design

A prospective observational study was conducted to study and evaluate the effects of polypharmacy in geriatric cardiovascular disease patients.

Study site

The study was conducted in the in-patient setup of cardiology unit at a tertiary hospital, Hyderabad, India.

Sample size

The study was conducted on 100 patients who visited cardiology unit.

Study duration

The data of patients were collected during 6 months of study period.

Study criteria

Inclusion criteria

- Geriatric
- Patients suffering from cardiovascular disorders.
- Patients of both genders.
- Patients with or without comorbid conditions.

Exclusion criteria

Paediatric patients and adult patients.

Sources and Data

Patient case sheets.

Study procedure

The following data was collected based on study requirements:

1. Patient demographic details like gender, age.
2. Patient's diagnosis and lab data.
3. Patient's past medical and medication history.
4. Social history.
5. Medications used including name of drug, frequency, duration, indication.
6. Type of drug related problems, interactions.

Method of Study

The patient prescriptions of total 100 were collected from in-patient cardiology department. These were noted in the data collection form and the prospective study was done by evaluating the number of geriatric male and female affected with cardiovascular diseases, drug interactions, adverse reaction followed by co-morbid condition occurring with cardiovascular diseases.

Adverse drug reactions related to cardiovascular disease medications were listed out using Medscape and other related articles and journals. The suspected adverse drug reactions were reported in the CDSCO form.

The drug- drug interactions related to cardiovascular diseases regimen were evaluated and noted in the data collection form, a table was drawn to represent the interacting drugs and their respective effect and the severity of interactions. The drug- drug interactions were found in the patient using Medscape.

Statistical analysis:

The results were obtained using SPSS software.

Chi square test, t- test and Pearson's correlation were used to calculate the data.

III. RESULTS:

Polypharmacy is mostly seen in cardiovascular diseases. In this study, out of 100, 72 % patients were diagnosed with HTN, 52 % with DM, 28% with MI, 58 %with CAD along with other cardiovascular diseases. From 72% of HTN diagnosed patients, 94.44% of people were seen with polypharmacy in their therapy. Similarly, 98.08% of DM patients, 89.09% of MI patients and 93.10 % of CAD patients were victims of polypharmacy. This was expressed graphically in **figure I**.

Hypertension is the major risk factor for developing cardiovascular diseases. The highest comorbidity was found to be hypertension 73(46.20%), followed by diabetes mellitus 53(33.54%) and CAD 19(12.02%). It was expressed graphically in **figure II**.

Considering gender as a parameter to measure polypharmacy in individuals, with P- value of 0.0206 following independent t-test, given results are- Out of 38 % of female patients included in this study, 94.74% were seen with polypharmacy with mean 8.47 ± 2.68 number of drugs. Meanwhile, there were 62 % of males included in the study, out of which 90.3 % were present with polypharmacy with mean 7.29 ± 2.33 number of drugs, which was expressed in **table- I and figure- III**.

Age is major parameter relating to disease state of individuals as many physiological changes take place with age in human body hence contributing in number of medicines used. Pearson correlation is used to determine the

correlation between age and number of drugs prescribed, giving $r = 0.208$, which indicates that a positive correlation was found between age and number of drugs prescribed. It was expressed graphically in **figure -IV**.

The major reasons for polypharmacy is irrational use of drugs leading to ADRs and DIs, for which additional burden of drugs is given to geriatrics to counteract ADRs or DIs caused. 3% of total cases studied evidently showed ADR'S and 60% cases were present with drug interactions. The common ADR of bleeding/ bleeding gums due to anti-coagulants Aspirin (ECOSPRIN) was observed in 1% of total cases. Metolazone (ZYTANIX) causes common ADR of severe diarrhoea which was observed in 1% of total cases. Also, in 1% of cases, there was seen hyperkalaemia as ADR due to spironolactone/furosemide (LASILACTONE), which is shown in **table- II and figure-V**.

Polypharmacy is the major cause of drug-drug interactions. Chi-square test was employed to determine severity of drug interactions with gender. p-value was found to be 0.453 ,which shows there is no statistical significant difference in severity of drug interactions between genders. This is shown in the **table- 111 and figure-VI**. The drug interactions were divided into minor, moderate, serious as per their severity, drawn in the **table-IV**.

IV. DISCUSSION:

Polypharmacy is mostly seen in cardiovascular diseases. The major reasons for polypharmacy is irrational use of drugs leading to ADRs and DIs, for which additional burden of drugs is given to geriatrics to counteract ADRs or DIs caused. Considering gender as a parameter to measure polypharmacy in individuals, with P- value of 0.0206 following independent t-test, it was observed that statistically significant difference was found between the genders .Age is major parameter relating to disease state of individuals as many physiological changes take place with age in human body hence contributing in number of medicines used. Pearson correlation is used to determine the correlation between age and number of drugs prescribed, giving $r = 0.208$, which indicates that a positive correlation was found between age and number of drugs prescribed. Polypharmacy is the major cause of drug-drug interactions. Chi-square test was employed to determine severity of drug interactions with gender. p-value was found to be 0.453, which shows there is statistical significant difference in severity of drug interactions between genders.

V. CONCLUSION

The finding of present study reveals that there is a positive correlation between age and number of drugs prescribed and women experienced greater polypharmacy. It is found that polypharmacy increases the risk of adverse drug reactions (ADRs) and drug-drug (DDI). These interactions and ADRs can be minimized by pharmacokinetic and pharmacodynamics modification of the drug regimen. Cautionary guidelines can be developed and implemented and also computer-based screening, patient education might help to prevent ADRs and DDI, due to polypharmacy.

ACKNOWLEDGMENT:

We would like to express our gratitude to Sultan ul uloom college of pharmacy and Aster prime hospital for providing this opportunity to carry out this project.

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LIST OF TABLES:

Table I: Polypharmacy between the Genders

Gender	Minimum	Maximum	Mean ± SD	P value
Male	3	14	7.27±2.33	0.0206
Female	4	14	8.47±2.68	

Table II: Proportion of ADR

ADR	N	%
Bleeding Gums	1	1
Severe Diarrhea	1	1
Hyperkalemia	1	1

Table III: Severity of drug interactions

Severity of drug-drug interaction	Gender		Total		P value
	Male	Female	N	%	
Mild	3	5	8	8	0.453
Moderate	41	28	69	69	
Serious	13	10	23	23	

Table IV: Drug interactions

S.NO	Precipitant drug	Object drug	Likely interaction	Severity of Interaction
1	Torsemide	Folic acid	Torsemide decreases levels of folic acid by increasing renal clearance	Minor
2	Metformin	Furosemide	Metformin decreases levels of furosemide	Minor
3	Aspirin	Diclofenac	Aspirin will increase the level or effect by acidic drug competition for renal tubular clearance	Minor
4	Metoprolol	Aspirin	Both increase serum potassium (hyperkalaemia)	Moderate
5	Spironolactone	Torsemide	Spironolactone increases and torsemide decreases serum potassium	Moderate
6	Telmisartan	Atorvastatin	Telmisartan increases toxicity of atorvastatin by other and increase risk of myopathy	Moderate
7	Aspirin	Clopidogrel	Either increases toxicity of the other	Moderate
8	Aspirin	Heparin	Either increases toxicity of the other by anticoagulation	Moderate
9	Ticagrelor	Heparin	Either increases toxicity of the other by anticoagulation and increase risk of bleeding	Moderate
10	Sacubitril/Valsartan	Torsemide	Sacubitril/valsartan increases and torsemide decreases serum potassium	Moderate
11	Bisoprolol	Aspirin	Both increase serum potassium	Moderate
12	Atenolol	Amlodipine	Both drugs lower blood pressure	Moderate
13	Carvedilol	Spironolactone	Both increases serum potassium	Moderate
14	Enalapril	Spironolactone	Risk of hyperkalaemia	Moderate
15	Diltiazem	Rivaroxaban	Diltiazem increases levels of rivaroxaban by affecting hepatic/intestinal enzyme	Moderate
16			Maintenance dose of aspirin above 100mg decreases	

	Aspirin	Ticagrelor	effectiveness of ticagrelor	Moderate
17	Telmisartan	Nebivolol	Both increase serum potassium	Moderate
18	Aspirin	Perindopril	Decreases renal function	Serious
19	Aspirin	Ramipril	Decreases renal function	Serious
20	Digoxin	Atenolol	Risk of bradycardia	Serious
21	Telmisartan	Ramipril	Increases risk of hypotension, hyperkalaemia and renal impairment	Serious
22	Digoxin	Metoprolol	Digoxin increases toxicity of metoprolol and increase risk of bradycardia	Serious
23	Diltiazem	Amlodipine	Diltiazem increase the level or effect of amlodipine by affecting hepatic/intestinal enzyme CYP3A4 metabolism and causes bradycardia, sinus arrest ,decrease cardiac out put	Serious
24	Fenofibrate	Atorvastatin	Decreases TG and increase HDL'S. Fenofibrate increase risk of rhabdomyolysis	Serious
25	Spirolactone	Potassium chloride	Both increase serum potassium (hyperkalaemia)	Serious

LIST OF FIGURES:

Figure I: Diagnosis

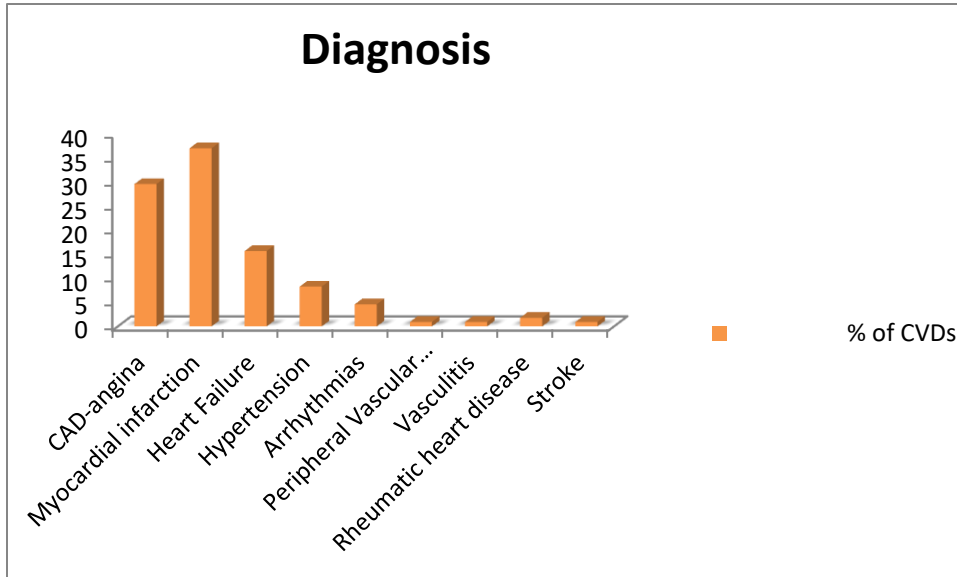


Figure II: Co morbidities

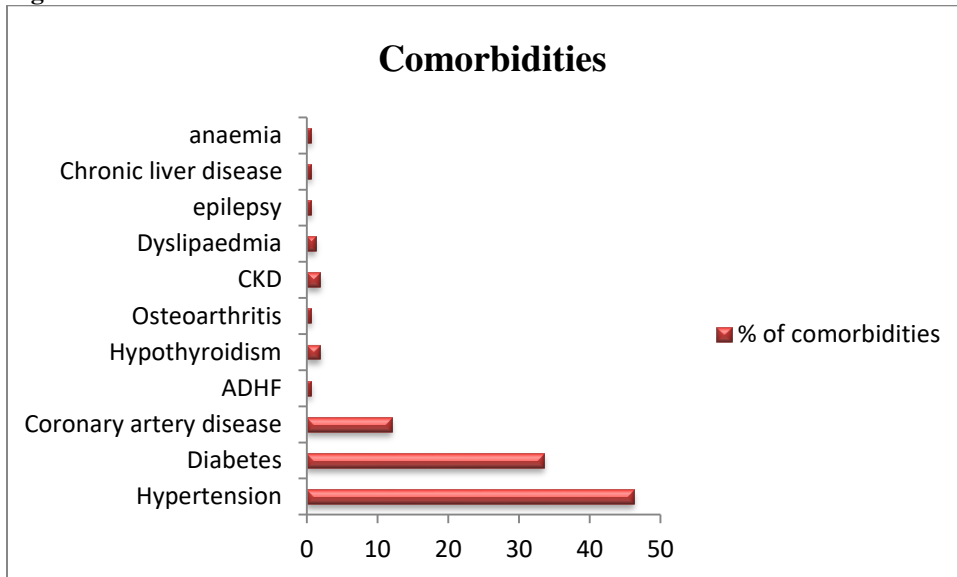


Figure III: Polypharmacy between genders

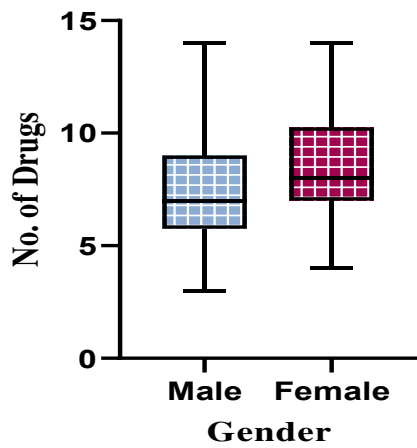


Figure IV: Correlation between age and number of drugs prescribed

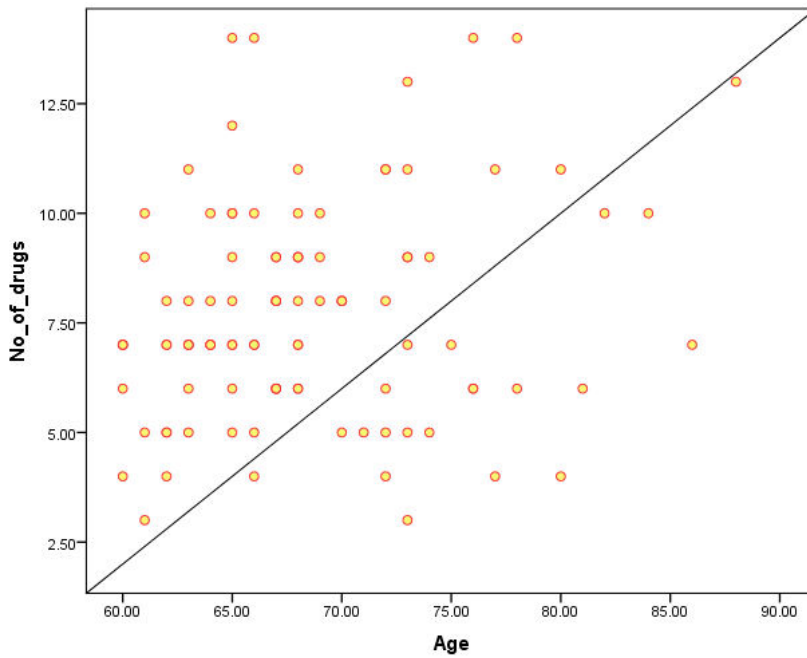





Figure V: Proportion of ADR

-  BleedingGums
-  Hyperkalemia
-  SevereDiarrhea

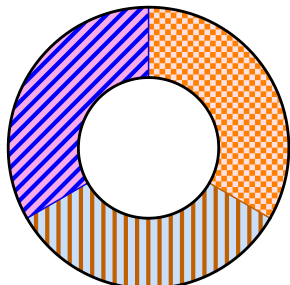


Figure VI: Severity of drug interactions

