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Research Article

CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS AND THEIR ASSOCIATION WITH POLYPHARMACY IN ELDERLY PATIENTS

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ABSTRACT

To identify the potential drug drug interactions of clinical significance and assess its relation with polypharmacy, the prospective observational study was conducted to identify drug-drug interactions according to severity and to show the relation between number of prescribed medications and actual DDIs in elderly patients in a tertiary care teaching hospital. Micromedex Healthcare Series 2.0. was used to identify actual and potential DDIs. Drug therapy details by medication chart review and clinical review of 120 elderly inpatients (52% male and 48% female) was carried out and analyzed for incidence of any actual and potential drug-drug interactions. Polypharmacy was observed in almost all cases, wherein 45% were prescribed 11-15 drugs and 32% patients were with 6-10 drugs per prescription. 256 no. of DDIs were encountered in the study, comprising of 32 actual and 224 potential DDIs. As per severity, 34.37% were major and 65.62% were moderate. Multiple object drug and precipitant drugs were involved in actual and potential DDIs. Most common outcome of these actual DDIs was found to be increased blood pressure and blood sugar level, electrolyte and fluid imbalance, decreased diuretic effect of drugs. Elderly patients taking multiple medications concurrently because of their comorbid and multimorbid health conditions have lead to polypharmacy. The actual and potential DDIs increase as per number of drugs in prescription.The management of clinically relevant DDIs can be improved by clinical pharmacist interventions. Advice on withdrawal or substituting the precipitant drug would be beneficial.

Keywords: Elderly, Polypharmacy, Drug-drug interactions

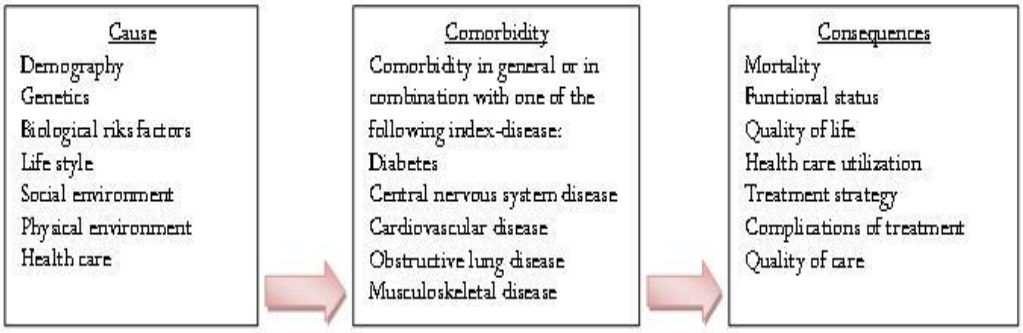
1. INTRODUCTION

The elderly population (aged 60 years or above) account for 7.4% of total population in 2001. For males it was marginally lower at 7.1%, while for females it was 7.8%. Both the share and size of elderly population is increasing over time. From 5.6% in 1961 it is projected to rise to 12.4% of population by the year 2026.The rapid growth of the elderly may lead to considerable social cost in long term care. The boundary of old age cannot be defined exactly because it does not have the same meaning in all societies. Government of India adopted 'National Policy on Older Persons' in January, 1999. The policy defines 'senior citizen' or 'elderly' as a person who is of age 60 years or above [1].

Older patients in medical or geriatric care represent a population with a particularly high prevalence of comorbidities and functional disabilities. A high prevalence of multiple disorders ultimately leading to more complications [2]. Treating elderly is complicated by many factors unique to this age group these include age-related physiologic and pharmacological changes, altered reported and presentation of depressive disorders, multiple conditions and unintentional noncompliance, and increased sensitivity to drug effects leading to a higher percentage of adverse drug reactions [3].

The term comorbidity refers to the co-occurrence of two disorders or syndromes (not symptoms) in the same patient. Defined as broadly as that, every pair of disorders or syndromes for which the diagnosis of one does not categorically exclude the diagnosis of the other are "comorbid. "Comorbidity" indicates some relationship between two disorders. It is possible that the comorbidity is not specific to a particular type of disorder but is general to all serious and disabling disorders [4]. Multimorbidity is the presence of multiple chronic diseases, is common in the elderly population (65–80%) further adding to the complexity of treating the elderly patient [5].

These are valid and reliable indices [6].



Due to the number and severity of chronic comorbid medical conditions both frequency and number of medications given to elderly are more. Frail or malnourished patients, and those with renal or hepatic impairment or multiple pathologies are at greater risk of developing adverse drug interaction. Some drugs pose a greater risk due to their inherent toxicity,non-linear pharmacokinetics or potent enzymes inducing or inhibiting ability. e.g. phenytoin, rifampicin, carbamazepine, oral anticogulants,digoxin [7].

The term polypharmacy comes from two Greek words: poly, meaning many, and Pharmacia meaning medicines or drugs [8]. Polypharmacy has been defined in various ways. It is simply defined as the simultaneous use of multiple drugs. It also defined as the use of clinically non-indicated or inappropriate drugs, and yet others as the use of two or more drugs of the same chemical class. From a quantitative point of view, polypharmacy is associated with adverse drug reactions, drug–drug interactions, nonadherence and increased risk of hospitalization. Polypharmacy may be unavoidable in most chronic conditions which require multiple medications for proper treatment [9].

Usually a problem for older adults who may have co-morbidities, polypharmacy may cause problematic side effects. Also, it's possible that new symptoms will occur based on one drug, and be treated by taking another drug instead of exploring the root cause for the symptoms - the original drug. Over time patients may be prescribed many drugs that just compound problematic symptoms, masking the roots of their original medical problem [9].

A drug drug interaction may be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or co-administration of a second drug [10]. The interaction may lead to symptoms of drug toxicity or loss of therapeutic efficacy of one or both drugs. These interactions may shows effects that are unexpected based on the pharmacology of either drug [11].

There are different types of drug interactions responsible for alteration of clinical effect of drugs. Drug-drug interaction between prescribed drugs or between OTC drugs, interaction of drugs with food may change the absorption and transit rate of drugs. Interaction of drugs with environmental contaminants like industrial fumes, solvent vapors, pesticides may responsible for altered outcome of therapy. A number of variables likes age, gender, disease state and genetic constitution of individual influence the activity of drug and its ability to interact with other agents to produce effect of drug interaction.

The drug interactions are classified as pharmacokinetic or pharmacodynamic type, even the combination of these actions may be responsible for drug interaction. Pharmacokinetic drug interaction may arise either from alteration of absorption, distribution, biotransformation or excretion of one drug by the other. Pharmacodynamic interaction results from a combination of their actions and effects [12]

Prescribing of multiple medication and increased prevalence of comorbidity in elderly patients may results in DDIs with altered clinical outcomes therefore this study carried out to assess prescribed medications, comorbidity and DDIs which will be useful in minimizing DDIs.

2. METHOD OF STUDY

A prospective observational study over 6 months duration was undertaken from October 2011 to march 2012, in Bharati Hospital and Research Centre, a 850 bedded tertiary care teaching hospital, Pune, India. The study protocol was approved by Institutional Ethical Committee.120 patients of elderly age group (≥60yrs) were included in the study. Surgical reference and accidental cases were excluded from the study.

The names of patients and prescribing doctors were kept confidential throughout the study. Drug-Drug Interactions in administered drugs were checked by using Micromedex Healthcare Series 2.0. The results were classified into three levels (major, moderate and minor) based on their significance.

3. RESULT

120 elderly patients were included and evaluated for indications of drug therapy, incidence of polypharmacy and potential drug interactions associated with it. The average age

was 68.76 years. Age range of these patients was found to be 60-90 years, 48.33% were comprised of females and 51.66% were males patients. The reason for hospitalization was found to be cardiovascular diseases like IHD, Hypertension and cardiac mayopathy. Infectious diseases like pneumonia, urinary tract infection, pulmonary tuberculosis. diabetes mellitus, chronic kidney disease, anemia were also observed in large number of patients as multimorbidity. As many as 1500 drugs were prescribed in 120 patients with mean of 1-21 drugs per patient. Also 80 patients were found to be on 11 or more drugs. The distribution of number of drugs per prescription is shown in table 1.

Due to maximum prevalence of cardiovascular diseases in this study, more cardiovascular drugs (22.60%) were observed in prescribing pattern followed by antihypersecretory (21.50%), antibiotic (20.13%), antiemetic (14.24%), antihyperlipidemics (7.80%), antiplatelets (7.26%), antidiabetics(6.43%). The utilized drugs according to the therapeutic class is shown in fig. 1.

Table 1: Number of drugs per prescription

No. of Drugs	1-5 Drugs	6-10 Drugs	11-15 Drugs	16-20 Drugs	Above 21
Frequency	2	38	54	23	3
%	1.66	31.66	45	19.16	2.5

Fig 1:Prescribing Frequency

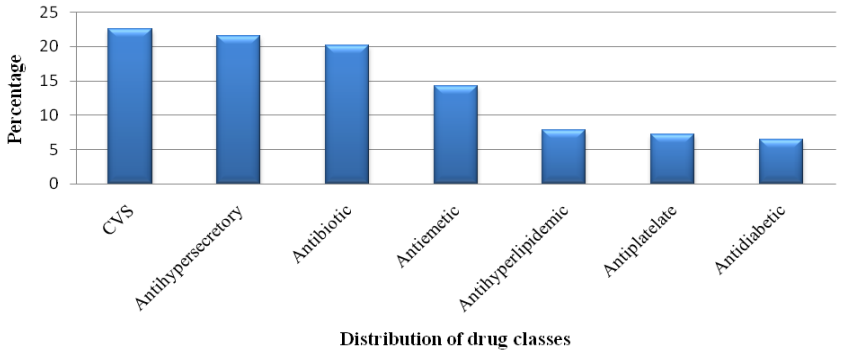


Table 2: Overall prevalence and prevalence without comorbidity

Disease	With comorbidity		Without comorbidity	
HTN	19	(15.83%)	13	(10.83%)
IHD	15	(12.50%)	01	(00.83%)
Anemia	14	(11.66%)	03	(02.50%)
DM	13	(10.83%)	09	(07.50%)
UTI	07	(05.83%)	01	(00.83%)
Spondolysis	06	(05.00%)	01	(00.83%)
COPD	03	(02.50%)	03	(02.50%)
Parkinsons disease	03	(02.50%)	--	--
Chronic renal failure	06	(05.00%)	04	(03.33%)

Growing proportion of elderly have multiple concurrent medical conditions and multiple drug prescribing. Multimorbidity is defined as any co-occurance of two or more chronic or acute diseases and medical condition in person. Multimorbidity is associated with higher mortality, decline functional status and lower quality of life [13]. In this study hypertension, IHD, anemia and diabetes mellitus were most common diseases associated with multimordity like respiratory tract infections, gastritis, malaria, hepatitis, asthma, DVT etc. Prevalence of comorbidity and disease is shown in table 2.

Table 3 shows DDIs found in the prescription with multiple drugs prescribed to 120 elderly patients. In this study it was observed that prevalence of actual DDIs increased as number of drugs increased in therapy. Prescription with 6 to 10 drugs shows 10.52% DDIs, 11 to 15 drugs shows 29.63%, 16 to 20 drugs shows 39.13% and 100% interaction observed in prescription with more than 21 drugs. In this study 32 actual DDI were observed with significant clinical effects, according to the severity analysis 21(65.62%) interactions were found to be moderate and 11(34.37%) were major. Major interactions are those which require medical intervention to minimize or prevent serious adverse effects and moderate interactions may exacerbate patient's condition and/or require an alteration in therapy. Table 4 shows occurrence of DDIs in this study. 224 potential DDIs were found; out of them 29.46% were major followed by 57.14% moderate and 13.39% minor. Drug-drug interactions are possible whenever two or more medications are administered to patients concurrently. For assessment purpose term object drug is use to signify the affected drugs. Therapeutic effect of object drug reduced by precipitant drug with different pharmacokinetic mechanism. Actual drug-drug interactions about 27% in 120 prescriptions were found with following objective and precipitant drug that is shown in Table no 5.

Table 3: Relation between medication prescribed and actual DDI

Sr. No.	No. of Drugs/ Rx	No. of Cases	Minor	Moderate	Major	Total	%
1.	1-5	02	-	-	-	**-**	**-**
2.	6-10	38	-	03	01	**04**	**10.52**
3	11-15	54	-	11	05	**16**	**29.63**
4.	16-20	23	-	07	02	**09**	**39.13**
5.	Above 21	03	-	-	03	**03**	**100**

Table 4: Severity of Drug-Drug Interactions.

Level of severity	Frequency	
	Potential DDIs n=224	**Actual DDIs n=32**
Major	66(29.46)	11(34.37)
Moderate	128(57.14)	21(65.62)
Minor	30(13.39)	--

Table 5: Actual DDIs with object drug, precipitant drug and clinical effects.

Sr. no.	Object Drug	Precipitant Drug	Clinical Effects
1.	Furosemide	Metolazone	Electrolyte & fluid imbalance
2.	Digoxin	Clarithromycin	Digoxin toxicity
3.	Clopidogrel	Esomeprazole	Thrombosis
4.	Digoxin	Cal. Carbonate	Arrthymia & CVS collaps
5.	Furosemide	Etodolac	Decreased diuretic & Anti-HTN efficacy
6.	Propanolol	Furosemide	Hypotension & bradycardia
7.	Amlodipin	Aspirin	Hypertension
8.	Glimepride	Metoprolol	Hyperglycemia
9.	Furosemide	Aspirin	Decreased diuretic effect
10.	Metformin	Hydrochlorothiazide	Hyperglycemia

Following object drug and precipitant drug involved in potential DDIs with their outcomes.

Table 6: Potential DDIs with object drug, precipitant drug and clinical effects

Sr. no.	Object drug	Precipitant drug	Clinical effects
1.	Propanolol	Ipratopium bromide	Hypertension
2.	Doxepine	Clarithromycin	Cardiotoxicity(cardiac arrest)
3.	Linezolide	Tramadol	Serotonin syndrome
4.	Alprazolam	Chlorzoxazone	Repiratory depression
5.	Furesomide	Metolazone	Electrolyte & fluid imbalance
6.	Digoxin	Clarithromycin	Digoxin toxicity.
7.	Ceftriaxone	Cal.gluconate	Formation of ceftriaxone-cal.precipitant
8.	Aspirin	Fluoxetin	Bleeding
9.	Glimpride	Ciprofloxacin	Hypoglycemia or hyperglycemia
10.	Chloroquine phosphate	Ondansetron	QT interval prolongation

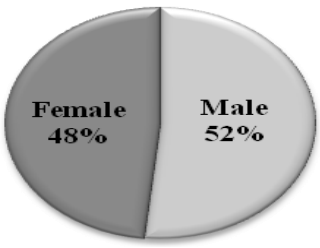
Majority of DDIs shows pharmacodynamic mechanism in this study. It was responsible for altered therapeutic outcome in 25% patients. Age related pharmacokinetic changes in geriatric patients were important triggering factor for DDIs in this study. Outcomes of this study significantly show the prevalence, severity and effects of DDIs in elderly patients which show the necessity of monitoring the patients and help to avoid potentially adverse consequences.

Age distribution:

Table 7 : Distribution of Age

Class	Male	Female	Total
60-70	38	42	**80**
71-80	32	20	**12**
81-90	05	03	**08**

Gender:



4. DISCUSSION

With the progressive aging of the population, the long-term nursing care and drug safety for the elderly are gradually gaining attention**.** The aim of this study was to assess the prescribed medications, the occurrence of DDIs and the association between the number of drugs and DDIs with a view to reinforce drug safety for the elderly [14].

120 patients above 60years of age were included during the study period, 62(51.66%) were males and 58(48.33%) were female. Age related changes in pharmacokinetics and pharmacodynamics lead to a reduction in physiologic functions/reserves. The physiological changes that come with aging are often compounded by an increasing number of chronic conditions necessitating multiple medications [15].

Sickness is as natural as the process of ageing. Drug therapy is necessary to treat acute illness, maintain current health and prevent further decline. But drug therapy for older patients is challenging because people over the age of 60 years have a higher prevalence of chronic illnesses, disabilities and dependency than those <60 years [16].

However, some western studies carried out the ratio of male and female is slightly high Robert J. Michocki et al [17] showing more than 80 % patients were over 60 years and the ratio of male female were 56% and 44 % but is approximate similar to the other Indian studies carried out by HG Zaveri et al [18] showing that male female ratio were 53.07% and 46.93% of Hospitalized patients.

In the elderly, concomitant use of several drugs (polypharmacy) is very common because of chronic health problems and illness. Polypharmacy leads to an increased incidence of DDIs.The incidence of DDIs in the elderly has been reported to be two to three times higher than in the younger patients.

Major ploypharmacy was common in the hospitalized patients in our study as 45% of the study patients received more than 11 drugs, 31.66% patients received more than 6 drugs, 19.16% received 16 drugs and 2.5% received more than 21 drugs and least 1.66 % patients received less than 5 drugs. The results were comparable with study carried out by Lohani SP et al [19] as 89% of the study patients received more than 5 drugs, 43% received more than 10 drugs and 16% received more than15 drugs during hospital stay.

Multimorbidity is associated with higher mortality, increased disability, a decline in functional status and a lower quality of life. Most commonly prescribed drugs were Cardiovascular 22.60%, Antihypersecreatory 21.50%, Antibiotic 20.13%, Antiemetic 14.24%, Antihyperlipidemic 7.80%, Antiplatelets 7.26%, Antidiabitic 6.43% were found to be most commonly involved class in the hospitalized elderly patients. The result was similar with the Indian studies conducted by M.Sonal Sekhar et al [20] showing that CVS 19.8%,Antibiotic 11.3%, antiplatelet 9.09% and the study results were slightly differ with the study of Yone de Almeida Nascimento et al [21] showing that CVS 34.9%,Antiplatelet 4.6% and Anti diabetic 6.2% in studies respectively. Maximum number of patients involved in this study had multimorbidity. IHD (12.5%) were most prevalent disease with comorbidity, HTN (15.83%), anemia (11.66%) which was differ from the study conducted by Francesc Formiga et al [13] in Spain.

The aging of the population and increasing complexity of medication regimens used to treat ambulatory patients and a fragmented health care system with multiple prescribers treating the patients make the occurrence of serious DDIs even more likely [10].

A drug interaction pair typically consist of the

- Object drug
- Precipitant drug

The activity of object drug is altered the drug causing this change is the precipitant drug.
The outcome can be harmful if the interaction causes an increase in the toxicity of the drug. A reduction in efficacy due to an interaction can sometimes be just as harmful as an increase [10].

The relationship between medication prescribed and actual DDIs were found that DDIs increased as number of drugs increased in therapy. These results are similar with study carried out in Brazil by Raquel S. Mendes-Netto et al. [22] which shows 100% DDIs in class with maximum numbers of drugs prescribed i.e. 6 to 7, 88.8% DDIs in 4 to 5 drugs, 39% DDIs in 2 to 3 drugs.

This study found 32 DDIs were actual and 224 were potential. According to severity assessment 65.62% of actual DDIs were moderate and 34.37% were major which was slightly similar to the study conducted by Hui-Ling et al [14] which shows 64.95% moderate DDIs and 7.2% major DDIs. Azithromycin, Digoxin were frequently involved in actual major DDIs.

Furosemide, digoxin, aspirin, clarithromycin were frequently responsible for potential DDIs. Study conducted by Richard M. Goldberg et al. [23] shows the similar drug involved in potential DDIs.

5. CONCLUSION

The elderly population consumes a disproportionate share of prescription and drugs as compared to younger persons. These factors, combined with age related changes in pharmacokinetic and pharmacodynamic parameters that make the elderly population more susceptible to drug interactions. Therefore, when the elderly receive the drug therapy, it must be necessary for the well-defined goals and given at the lowest effective doses to achieve. Drug-drug interactions may be avoided with the discontinuation of drugs that do not achieve the desired end points or that are no longer needed. Although the number of drugs increased from hospital admission to discharge by the number of major, moderate and minor, DDIs per patient increase. Despite of these results, it is important to realize that 86.6 % potential DDIs were found as major and moderate. It was observed that DDIs were occurred due to drug pair which was administered simultaneously. To avoid those conditions prescribing drugs with a low risk for DDIs as well as careful monitoring is important measures to prevent harm associated with DDIs. Increased awareness and interventions aimed at reducing exposure and minimizing the risks associated with potentially adverse drug combinations in the elderly are needed. The management of clinically relevant DDIs can be improved by physicians' advice of clinical pharmacists.

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