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**Research Article**

# POTENTIAL DRUG INTERACTIONS AMONG ELDERLY OUTPATIENTS IN A TERTIARY CARE HOSPITAL – A CROSS SECTIONAL STUDY

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**A B S T R A C T**

**Background:** The elderly, with multiple co-morbidities are exposed to indiscriminate drug prescribing, making them vulnerable the risk for potential drug-drug interactions. The objective of this study was to determine the prevalence and factors associated with potential drug interactions in elderly outpatients.
**Methodology:** This hospital-based cross-sectional study enrolled outpatients aged ≥60 years, and their prescriptions examined. Drug data was entered onto a software program to identify and grade potential drug interactions.
**Results**: Among 140 subjects studied, the prevalence of polypharmacy (≥5 drugs/day) was 69.3% (average 6.4 drugs/person). The prevalence of potential drug interactions was 79.3%. Of 559 potential interactions identified, 33(5.9%) were major, 411 (73.5%) moderate and 115 (20.6%) minor. The number of total potential interactions ranged between 1 and 25 per subject (average =4/person). Patients on polypharmacy ($p<0.005$), with diabetes mellitus ($p=0.045$) and/or hypertension ($p<0.05$) and those reporting side-effects ($p=0.039$) had a higher prevalence of potential drug interactions. The most common drug and combination implicated in interactions were aspirin and aspirin with calcium carbonate.
**Conclusion**: The prevalence of potential drug interactions in the study population was high. There is a need to educate physicians regarding the potential for drug interactions and the dangers of polypharmacy to ensure better prescribing practice.



## INTRODUCTION

The number of elderly people in India is steadily on the rise and is expected to form 20 percent of the population by 2050.[1] The prevalence of chronic disease including diabetes mellitus and hypertension among older persons is high, rising with age. This makes the older population more likely to be on chronic multiple drug therapy, often life-long.

Drug-drug interactions (DDIs) are defined as the pharmacologic or clinical response to the administration of a drug combination which is different from that anticipated from the known effects of the two agents when given alone [2]. Not only do they constitute a common cause of adverse drug reactions, but amount to significant hospitalization, morbidity and death among the elderly.[3,4,5] With the introduction of newer drugs into the market at a rapid pace, the situation may worsen, thus making the task of identifying new clinically significant drug interactions a priority task. Approximately 70% of DDIs are clinically relevant and 3-5% of all inpatient medication errors can be blamed on them. [6, 7]

Older people are generally more frail and sensitive to adverse drug reactions. As the number of drugs consumed by them is higher when compared with other age groups, they are more vulnerable to potential drug-drug interactions [8]. A review of several studies indicated that patients aged > 65 years use, on average, two to six prescribed medications, and 1–3.4 non-prescribed medications [9]. The potential hazards of 'polypharmacy' (defined as the concomitant use of five or more drugs [10]) have been known for some time and indiscriminate polypharmacy has been identified as a major medical problem in some developing countries. This phenomenon poses a significant challenge to the World Health Organization's action program on essential drugs [11]. There is lack of adequate data on polypharmacy and the prevalence of potential drug interactions in the elderly in our country.

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Chronic multiple diseases, increasing multi-specialist services with lack of coordination between the specialties and the practice of self-medication could potentially add to the problem. This study aims to estimate the prevalence of polypharmacy and potential drug interactions among the elderly visiting the outpatient service of a tertiary care hospital along with the factors associated with such interactions, with hope to inform the physician population about better and more rational drug prescribing in the future.

## MATERIALS AND METHODOLOGY

***Study Design and setting**:* The present study was a cross sectional study conducted in the outpatient department (OPD) of a 1200-bed hospital in Bangalore, which has an average outpatient attendance of 1379 every day, during the period of March 2017 to June 2017. The study was conducted in the outpatient departments (OPDs) of Medicine, Chest Medicine, Cardiology, Endocrinology, Geriatrics and Urology. Using an estimated prevalence (of potential drug interactions) of 25% (from previous studies), a precision of 7.5% and a confidence of 95%, the estimated sample size was estimated to be 128, rounded off to 140 subjects based on anticipated non-response of 10%. Ethical approval was obtained from the institutional ethics committee prior to start of the study.

***Inclusion and exclusion criteria**:* The elderly outpatients aged 60 or above, who consumed two or more medications simultaneously and could produce a prescription of their previous visit indicating the medications they have been currently taking, were included in the study. Patients who were seriously ill, who were unable to give the required information or patients with serious mental illnesses were excluded from study.

***Data Collection:*** Out patients aged >60 were approached in the OPD while they were waiting to consult their physician. Following written informed consent, information was collected from the eligible patients. A self-administered questionnaire was developed and validated by circulation among experts in the field. Following pilot testing and suitable modification, the questionnaire was given to consenting study subjects. Study investigators conducted face to face interviews using the questionnaire for those patients who were either unable or unwilling to fill it themselves. Information regarding demographic details, existence of co morbidities, the current prescription that the patient was on, side effects reported by the patients and number of doctors that the patients was visiting was collected.

***Study tools:*** Drug related information was entered onto a software package on the website www.drugs.com. (http://www.drugs.com/drug_interactions.php).This enables identification and grading of potential interactions according to their severity. Drug interactions were graded as major, moderate and minor. Major interaction**s** were those which were highly clinically significant, with the risk of the interaction outweighing the benefit of combination. Moderate interactions implied that such combinations should be avoided, or used only under special circumstances. Minor interactions were of minimal clinical significance.

***Data analysis:*** Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) version 18.0 software. The data were analyzed for prevalence of potential interactions and possible associations with gender, polypharmacy and other factors. The most commonly prescribed drugs, the most common drugs associated with interactions and the most commonly prescribed drug combinations associated with interactions were obtained from the data collected. Descriptive data were presented as mean + standard deviation (SD), factors associated with drug interactions were studied using the Chi Square test. A p-value of $<0.05$ was considered as statistically significant.

## RESULTS

***Description of the study population***

A total of 140 subjects aged 60 years and above were included in the study, of which 73(52.1%) were males. 81(57.85%) subjects belonged to the age group of 60-65 years and 30 (21.4%) of them were >70 years of age. The detailed demographic data of the population studied is given in table 1.
Among the 140 subjects, the prevalence of few specific morbid conditions were noted. 21(15%) of the patients had diabetes mellitus only, 36(25%) had Hypertension (HTN) only and 50 (35.7%) had a combination of both DM and HTN. Other morbidities seen included Gastritis (7.85%), Asthma/COPD (19.3%) and Hyperlipidemia (15%).

***Drug intake***

The total number of drugs taken by each subject (n=140) ranged between 2 and 17 with an average of 6.4 drugs per subject studied. The most commonly prescribed drugs were Amlodipine (5.2% of subjects), Metformin (5.1%), Atorvastatin (4.3%), Aspirin (4.2%) and Vitamin D3 (4%). 97(69.3%) subjects were found to be on polypharmacy (i.e. taking five or more drugs). Figure1 shows the distribution of subjects based on the number of drugs taken each day.

***Prevalence and factors associated with potential drug interactions***

111(79.3%) out of 140 subjects studied had a risk of having drug interaction(s). The severity of the potential drug interactions was further assessed and graded as major, moderate and minor. Of 559 potential interactions indentified,33 (5.9%) were major, 411(73.5%) moderate and 115(20.6%) minor. The average number of potential interactions of any grade per person was estimated to be the number of total potential interactions in each subject ranging from 1 to 25. Most subjects who had potential for interactions (73%) had the potential for between 1-5 interactions, while 22% had the potential for 6-10 interactions and fewer than 3% had the potential for 20 or more interactions.

Many factors were assessed as having a possible association with the risk of drug interaction, including age, gender, polypharmacy, consumption of non-prescribed medicines, visiting multiple doctors/departments and the presence of co-morbidities. 80.8% of the male patients and 77.6% of the female patients had a potential for some form of interaction (*P>0.05, NS).* It was found that the prevalence of interactions rose with age, with the highest prevalence in the subjects above 70 years of age, but this was not statistically significant.
Certain drugs and drug combinations were identified to be of greater importance due to the greater prevalence of drug interactions associated with them. Drug combinations resulting in maximum number of interactions in order include Aspirin & Calcium Carbonate; Aspirin & Amlodipine; Aspirin & Insulin;

Amlodipine & Calcium Carbonate and Atorvastatin & Clopidogrel.

The prevalence of potential drug interaction among those subjects who reported taking five or more drugs each day (polypharmacy) was 88.7%, which was significantly different from the prevalence among those who took less than 5 drugs each day. ($p<0.005$) A significant association was observed between potential drug interaction and reported side effects ($p=0.039$) and the presence of diabetes mellitus ($p=0.045$) and / or hypertension ($p<0.05$) (Table 2).

## DISCUSSION

This study aimed at assessing the prevalence of and factors associated with potential drug interactions among the elderly outpatient population was conducted in a tertiary level 1200-bed hospital in Bangalore city, with an average of 1379 out patients every day**.**

The study focuses on estimating the prevalence of potential drug interactions. These are interactions that may not have occurred as yet, but which pose a risk to the patient. Therefore, it becomes the need of the hour to identify such interactions, which are preventable, before they turn into adverse drug reactions, causing tremendous disastrous consequences.

With increasing trends of polypharmacy, and given the multiple diseases the elderly receive medications for, there is a high risk for inappropriate prescription for the elderly, the issue being further aggravated by the rising incidence of multi-specialist care and the tendency to visiting multiple providers for the same ailment.

This study has been carried out in an outpatient setting, which accounts for a large proportion of the patient load seen in any health care institution. There is limited data in the Indian setting on potential drug interactions in the outpatient department and it is hoped that the results of this study can serve as foundation for further studies.

The elderly are also the victims of multiple comorbidities, the commonest being hypertension and diabetes mellitus. A total of 140 patients aged 60 years and above were included in the study, of whom 71(50.7%) were noted to have diabetes mellitus (DM) which is a highly prevalent condition globally. The prevalence in our study is higher than that reported by Kirkman *et al* [12], where the prevalence of diabetes mellitus ranged between 20-33%. The difference could be attributed to the racial differences in the population, the difference in the diagnostic criteria that may be considered in the different studies.

86 (61.4%) subjects had hypertension (HTN) and 50 (35.7%) had a combination of both DM and HTN. This is comparable to the study done by Lena *et al*.[13] on health and social problems of elderly in Karnataka, where the prevalence of hypertension was found to be 59.1%.

It is the high prevalence of these chronic diseases, with their associated co-morbidities and high dependence on multiple drugs to fight the same, which paves the opportunity for potential drug interactions, more than the rest of the community.

The number of drugs taken by a patient in the study group ranged between 2 and 17 with an average of 6.4 drugs per person. Similar to our study, another study done in Germany among older primary care patients, the participants consumed an average of 3.7 prescribed medicines each day [14]. Furthermore, in another review conducted, it was demonstrated that patients aged > 65 years use on average two to six prescribed medications, and 1–3.4 non-prescribed medications. [9]

In a study done in two teaching hospitals in India, out of 814 patients studied, polypharmacy was present in 366 (45.0%)[15]. Previous studies conducted among hospitalized elderly patients have revealed the prevalence of polypharmacy ranging from 20 to 60%, based on different criteria in the selection of patients and collection of medication data [16-20]. Indiscriminate polypharmacy has been identified as an emerging medical problem and has been named as an obstacle to the World Health Organization's action program on essential drugs [11]. Other studies have also clearly shown that the risk of ADRs (including interactions) is related to the number of medicines taken [21–23] and that the elderly receive more medicines, sometimes inappropriately [24, 25].

79.3% out of 140 subjects studied had a risk of having drug interaction(s). This is a significantly high figure as compared to previous studies. It might be that subjects studied in the outpatient setting were more likely to have potential interactions due to increased accessibility to more doctors and relative lack of coordination between the various departments, as compared to an inpatient setting. In a study conducted in Indian inpatient set up, only 8.3% of 1510 prescriptions showed the potential for one or more drug interactions, all being severe [26] .In various other studies on frequency of potential drug interactions, rates have been reported ranging from 4-46% [27-33], depending on nature of patients studied, method of assessment of interactions and the study setting.

Of 559 potential interactions indentified,33 (5.9%) were major, 411(73.5%) moderate and 115(20.6%) minor. This is similar to the study done by Sabin *et al* where of 402 potential DDIs, 12.2% were major, 69.9% were moderate and 17.9% potentially minor [34].

From this study it was found that the most common drug associated with interaction was Aspirin. The next most common drugs were (in order of decreasing frequency) Calcium Carbonate, Amlodipine, Insulin and Metoprolol. In a study done in Puducherry in inpatient seting, the most common drugs responsible for Potential drug interaction was Alprazolam followed by Aspirin, Zolpidem, Nifedipine and Insulin[35] .

Though the drug responsible for maximum drug interactions depends vastly on the prescription patterns in that area, the high prevalence of potential drug interactions, especially in the outpatient setting as compared to inpatient, aggravates the risk to the elderly, as they are less likely to be monitored and any drug interaction less likely to be detected.

Certain factors were identified to predispose the patients to increased risk of interactions. One such factor which was found to have a significant association with DDI was polypharmacy, p-value being <0.005. Previous studies done by Johnel *et al* [36] and Carbonin *et al*[23] also reported a similar association, that showed increasing number of drugs showed increased number of potential drug interactions.
Presence of diabetes mellitus (p-value= 0.045), Hypertension (p-value<0.005) or the presence of both (p-value =0.01) also

had a significant association with potential drug interactions, likely to be consequent to the large number of drugs prescribed in these conditions.

The other significant factor was the reporting of any side-effects by the patient, p-value being 0.039. The implication of this would be that those side-effects reported by the subjects were probably due to the potential drug interactions, which turned into adverse drug reactions.

The high incidence of potential drug interactions in the elderly, secondary to polypharmacy and long term comorbidities, warrants a challenge and a word of caution to all physicians, to approach the prescriptions judiciously, and avoid any unnecessary prescriptions. Though polypharmacy is often the result of need in elderly, physicians should familiarize themselves with the drug interactions of the common drugs and common combinations they prescribe in such patients, as much as possible. Beers criteria, updated in 2012 is a frequently used method for evaluating appropriateness of prescribing in elderly [37]. Further, with the availability of reliable software on the internet, to check for any potential drug interactions, physicians or pharmacists can easily incorporate the practice of cross-checking for interactions, at every opportunity.

## CONCLUSION

The prevalence of polypharmacy and potential drug interactions was found to be high, in the elderly in the study. Also a significant association was found between polypharmacy, the presence of diabetes mellitus and/or hypertension and the reporting of side effects with the potential of having a drug interaction. The use of easily available software programs to check for potential drug interaction, minimizing the drugs prescribed to a patient, a constant watch for drug side effects and the improvement of coordination between prescribing physicians is essential in avoiding potentially harmful drug interactions among elderly patients.

**Table 1** Description of the study population

| Demographic Variables | Male (N:73) | Female(N:67) |
|---|---|---|
| **Age** | | |
| 60-65 years | 42(57.5%) | 39(58.2%) |
| 66-70 years | 11(15.1%) | 18(26.9%) |
| More than 70 years | 20(27.4%) | 10(14.9%) |
| **Marital status** | | |
| Never married | 0(0%) | 7(10.4%) |
| Currently married | 65(89.04%) | 27(40.3%) |
| Widowed/ Separated | 8(10.95%) | 33(49.25%) |
| **Place of Residence** | | |
| Urban | 46(63.01%) | 50(74.6%) |
| Rural | 20(27.4%) | 13(19.4%) |
| Semi-urban | 7(9.6%) | 4(5.97%) |
| **Occupation** | | |
| Employed | 34(46.6%) | 57(85.1%) |
| Retired | 25(34.2%) | 8(11.9%) |
| Unemployed | 14(19.2%) | 2(2.9%) |
| **Highest Education** | | |
| No formal education | 21(28.8%) | 20(29.85%) |
| School | 32(43.8%) | 41(61.2%) |
| Graduate | 13(17.8%) | 5(7.5%) |
| Post graduate | 7(9.6%) | 1(1.5%) |
| **Speciality Visited at Hospital At Time of interview** | | |
| Medicine | 34(46.6%) | 37(55.2%) |
| Chest medicine | 7(9.6%) | 6(8.95%) |
| Cardiology | 2(2.7%) | 3(4.5%) |
| Endocrinology | 15(20.5%) | 8(11.9%) |
| Geriatrics/ Senior citizen clinic | 1(1.4%) | 5(7.5%) |
| Other | 14(19.2%) | 8(11.9%) |

**Table 2** Factors associated with potential drug interactions in the study population

| Sl. no | Factor | Chi-square value | P value | Significance* |
|---|---|---|---|---|
| 1 | Gender | 0.219 | 0.640 | NS |
| 2 | Age | 1.314 | 0.518 | NS |
| 3 | Polypharmacy | 16.898 | <0.005 | S |
| 4 | Consuming drugs without prescription | 2.4 | 0.118 | NS |
| 5 | Visiting more than 1 doctor for same ailment | 0.710 | 0.399 | NS |
| 6 | Reporting side effects | 4.252 | 0.039 | S |
| 7 | Diabetes mellitus present | 7.828 | 0.045 | S |
| 8 | Hypertension present | 14.261 | <0.005 | S |
| 9 | Both DM and HT present | 10.253 | 0.01 | S |

** NS = not significant, S= statistically significant*

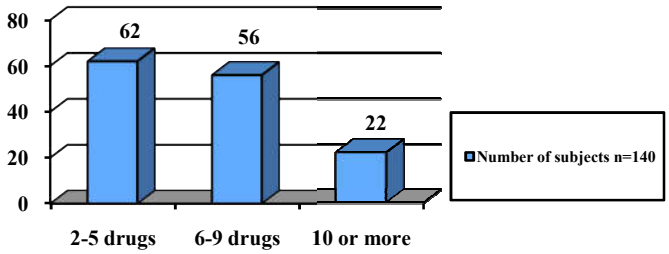


**Fig 1** Distribution of subjects by number of drugs taken per day (n=140*)*

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