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Drug-Drug Interactions among Elderly Patients at Hospital Discharge: A Cross-Sectional Descriptive Study

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Abstract:

Background: The presence of multiple comorbidities makes prescription of multiple drugs essential in the elderly. Thisis attended with an increased risk of potential drug-drug interactions (DDIs). *Aim and objectives:* To determine the number of DDIs, their severity, and the common DDIs detected in the prescriptions written for elderly patients of a tertiary care teaching hospital and identify any difference in terms of gender. *Material and Methods:* This was a cross-sectional study. Every prescription was screened for potential DDIs using the Lexicomp® software. The detected DDIs were classified as X, avoid combination; D, consider therapy modification; and C, monitor therapy as per the Lexicomp® criteria. *Results:* The data from 124 patients discharged from the General Medicine department of a tertiary care hospital were evaluated. Of these, 67.7% (82/124) were females. A total of 39 category X-DDIs, 71 category D-DDIs, and 349 category C-DDIs were seen. There was a significant positive correlation between the number of drugs prescribed and the number of DDIs detected ($p < 0.001$). *Conclusion:* Our study showed that DDIs were common among elderly patients. A large number of DDIs belong to category C, which requires only monitoring of therapy. Careful planning of the treatment regimen at the time of hospital discharge can decrease the number of drugs prescribed and, thereby, the number of potential DDIs can be decreased.

Keywords: Elderly, Prescription, Drug Interaction

Introduction:

Appropriate prescribing of drugs and medication management is important in the care of elderly patients [1]. The presence of multiple co-morbidities in the elderly necessitates, many times, the prescription of multiple drugs [2]. Polypharmacy is attended with an increased risk of potential drug-drug interactions. The risk is further increased due to the likely care of the elderly patient by physicians of different specialties, wherein, one physician may be unaware of all the drugs being prescribed by the other unless a thorough medication review is conducted [3]. The fact that drug-related problems are a major cause of morbidity among the elderly patients highlights the importance of this issue [4]. Use of technology, in the form of online drug-interaction detection software/websites, is encouraged. These not only alert the physician to the presence of potential Drug-Drug Interactions (DDIs) in a prescription but, also, provide extensive information regarding the interactions which help the physician decide on the future course of action [5]. However, not all drug interactions require prescription modification [6, 7]. Also, some interactions which are marked as serious may not require treatment modification if the drugs have been prescribed with the knowledge of the interaction, adopting appropriate steps to avoid a possible adverse outcome. The

objective of this study was to describe the DDIs present in the prescriptions written for elderly patients of a tertiary care teaching hospital with regard to the number of DDIs, their severity, and the common DDIs detected; any difference in terms of gender was also evaluated.

Material and Methods:

This was a cross-sectional, descriptive study conducted at Kasturba Medical College, Mangalore, a tertiary care teaching hospital. Ethical approval was obtained from the Institutional Ethics Committee, Kasturba Medical College, Mangalore, before initiation of the study. The study was conducted in accordance with the Indian Council of Medical Research National Ethical Guidelines for Biomedical and Health Research Involving Human Participants and the Declaration of Helsinki. The study data were obtained from the hospital discharge prescriptions written for elderly patients (one prescription per patient) in the General Medicine wards. The data were collected over a period of 6 months (February to July 2016) by convenience sampling. Patients ⩾ 65 years of age were considered as elderly [8]. The following data were collected: age of the patient, gender, diagnosis and number of co-morbidities, and drugs prescribed during hospital discharge. No other personally identifiable information was collected, and data confidentiality was maintained. Prescription of ⩾ 5 drugs was considered as polypharmacy.

Every prescription was screened for potential DDIs using the Lexicomp® software [9]. The detected DDIs were classified as X, avoid combination; D, consider therapy modification; and C, monitor therapy, as per the Lexicomp® criteria [9].

Statistical analysis:

The data was recorded in a Microsoft Excel file and then transferred to a Statistical Package for Social Sciences (SPSS) file. SPSS version 11.5 (IBM Corp, Chicago, USA) was used for the statistical analysis. The data has been presented as numbers, percentages, median and interquartile range. We used median values for analysis since the data was not normally distributed as determined using the Shapiro-Wilk test. Mann-Whitney U test was used to compare the continuous variables, and Chi-square test was used for the categorical variables. Kendall rank correlation coefficient was used to determine the relation between gender, the number of co-morbidities, the number of drugs prescribed, and the number of DDIs in each category (X, D, and C). *P*-value <0.05 was considered statistically significant.

Results:

The data of 124 patients who were discharged from the General Medicine ward of the hospital during the study period were evaluated. Of these, 67.7% (82/124) were females. The male patients were older compared to the females, but the difference was not statistically significant (74.50 [IQR, 69.75−77.25] and 72.00 [IQR, 67.75−76.00] years, respectively; $U = 1362.00$; $p = 0.057$). The number of co-morbidities, drugs per prescription, and category X, D, and C DDIs for the entire study sample were 2 (IQR, 1−3), 6 (IQR, 4−8), 0 (IQR, 0−0), 0 (IQR, 0−1), 1 (IQR, 0.75−3), respectively. The number of DDIs considering all the categories together was 2.5 (1–5), minimum being 0 and maximum being 26. The number of patients with at least one category X, D, C DDIs was 20.2% (25/124), 30.7% (38/124), 75.8% (94/124), respectively. The maximum number of category X,

D, C DDIs recorded per prescription was 5, 8, and 23, respectively. The maximum number of drugs prescribed in a single prescription was 17.

The median (IQR) age, number of co-morbidities, and the number of drug prescribed in those without a DDI compared with those with at least one DDI was 70.5 (68−76) years, 1 (1−2.75), 4 (2.25−4) and 73 (68−77) years, 2 (1−3), 7 (5−9), respectively. The number of drugs prescribed was significantly higher in those with a DDI (p <0.001).Table 1 shows the number of DDIs in the study sample based on polypharmacy and the number of co-morbidities.

The number of comorbidities was significantly higher in males compared with females (2.5 [1.75−4] versus 1 [0.75−3], $p = 0.006$). There was no significant difference in the number of drugs prescribed or category X, D, and C DDIs based on gender (Table 2).

Multiple regression was run to predict the number of DDIs from age, gender, number of co-morbidities, and the number of drugs prescribed (Table 3). The variables statistically significantly predicted the number of DDIs, F (4, 119) = 46.058, $p< 0.001$, $R^2 = 0.608$. Only the number of drugs prescribed added statistically significantly to the prediction, $p <0.001$.

Table 4 shows the correlations between the number of drugs prescribed, category X, D, and C DDIs. A moderate positive correlation was also seen between the number of co-morbidities and the number of drugs prescribed ($\tau = 0.362$, $p<$ 0.001).

Table 1: Number of Drug-Drug Interactions per Prescription Based on the Number of Drugs Prescribed and Number of Co-morbidities (n=124)

Parameters	Category X DDI Median (IQR)*	Category D DDI Median (IQR)*	Category C DDI Median (IQR)*
<5 drugs per prescription	0 (0−0)	0 (0−0)	0 (0−1)
⩾5 drugs per prescription	0 (0−1)	0 (0−1)	3 (1−5)
Co-morbidities ⩽1	0 (0−0)	0 (0−0)	1 (0−2)
Co-morbidities >1	0 (0−0)	0 (0−1)	3 (1−5.75)

**A median value of 0 signifies that majority of the subjects had no drug-drug interactions*
DDI: drug-drug interaction; IQR: interquartile range

Table 2: Drug-Drug Interactions Present in Prescriptions Written for Elderly Patients on Hospital Discharge Based on Gender

Parameters	Male (n = 42) Median (IQR)^	Female (n = 82) Median (IQR)^	*p*-value*
Number of co-morbidities	2.5 (1.75−4)	1 (0.75–3)	0.006
Number of drugs prescribed	6.5 (4−8)	6 (4–8.25)	0.782
Drug-drug interactions			
Category X	0 (0−0)	0 (0−0)	0.417
Category D	0 (0–1)	0 (0–1)	0.948
Category C	2 (0.75–6)	1.5 (0.75–3)	0.451

**Based on Mann-Whitney U test*
^A median value of 0 signifies that majority of the subjects had no drug-drug interactions
IQR: interquartile range; Category X: avoid the drug combination; Category D: consider therapy modification; Category C: monitor therapy.

Table 3: Multiple Regression Analysis of Factors Predicting the Number of Drug-Drug Interactions (n = 124)

Factor	Unstandardized coefficient	Standard error	*p*-value
Constant	−8.352	3.31	0.013
Age	0.660	0.042	0.121
Gender	−0.186	0.539	0.730
Comorbidity	0.015	0.180	0.934
Number of drugs	1.156	0.100	0.000

Table 4: Correlations between the Number of Drugs Prescribed and Each Category of Drug-Drug Interactions in the Elderly Patients

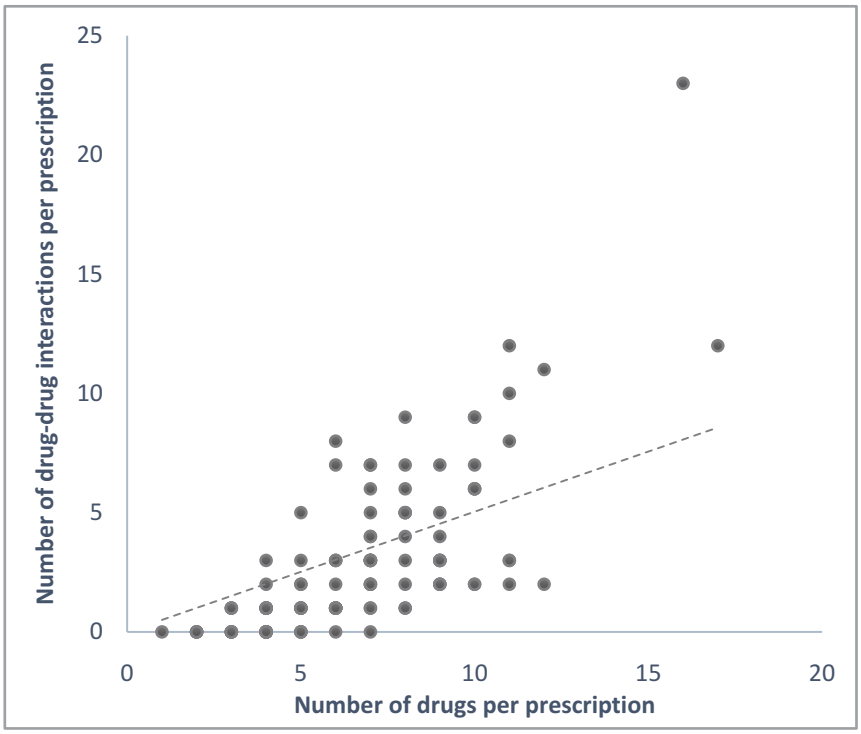
Correlation parameters*		Number of drugs prescribed	Category X DDI	Category D DDI	Category C DDI
Number of drugs prescribed	Correlation coefficient	1.000	0.271	0.318	0.616
	p-value	.	<0.0001	<0.0001	<0.0001
Category X DDI	Correlation coefficient	0.271	1.000	0.141	0.172
	p-value	<0.0001	.	0.092	0.026
Category D DDI	Correlation coefficient	0.318	0.141	1.000	0.244
	p-value	<0.0001	0.092	.	0.001
Category C DDI	Correlation coefficient	0.616	0.172	0.244	1.000
	p-value	<0.0001	0.026	0.001	.

**Correlation was determined using Kendall's tau-b (τb) correlation coefficient*
Category X: avoid the drug combination; Category D: consider therapy modification; Category C: monitor therapy.

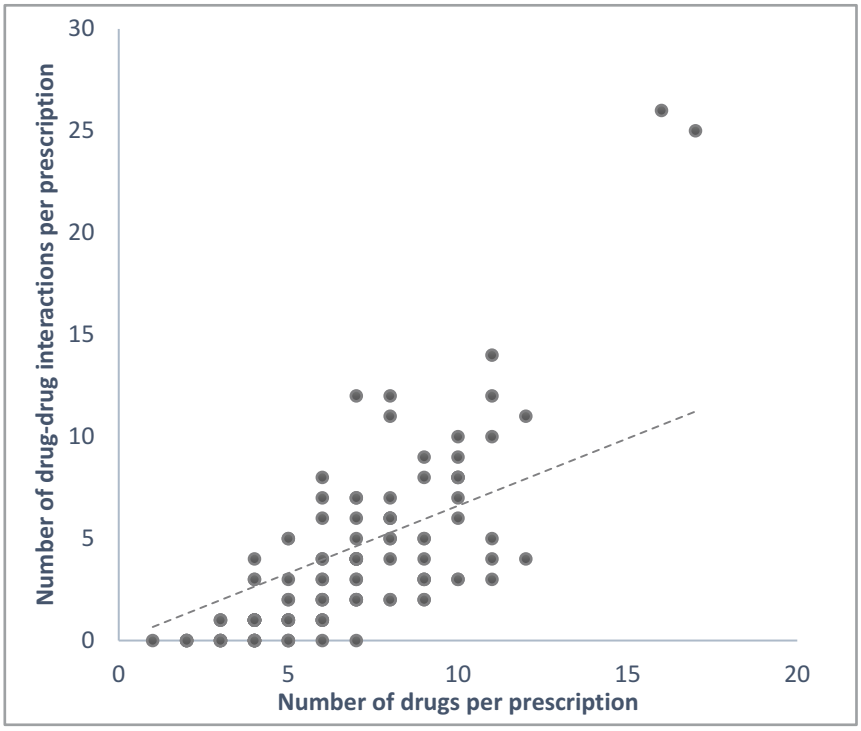
Figure 1a shows the moderate positive correlation between the number of DDIs and the number of drugs prescribed ($p < 0.001$). Figure 1b shows the moderate positive correlation between the number of drugs prescribed and the number of category C DDIs ($p < 0.001$). The correlation between the number of drugs prescribed and category X and D DDIs was low but statistically significant ($p < 0.001$ for both).

A total of 39 category X DDIs, 71 category D DDIs, and 349 category C DDIs were recorded. The maximum number of category X, D, and C DDIs were seen in patients with respiratory disorders (21/39, 28/71, and 115/349, respectively). The median number of DDIs per prescription was 2.5 (1–5).

The most common category X DDI observed was the administration of a combination of sympathomimetic bronchodilators (formoterol+ budesonide and formoterol). Administration of the combination of anticholinergic drugs as inhalers was also a common DDI identified. Apart from the respiratory drugs, a combination of domperidone with other QT interval-prolonging drugs was a common category X DDI identified in this study. Combination of domperidone with other QT interval-prolonging drugs also formed the most common category D DDI followed by administration of clopidogrel with a proton pump inhibitor. The combination of two sympatho-mimetic bronchodilators (budesonide + formoterol and ipratropium + salbutamol) was the most common cause for category C DDIs as well.



a)



b)

Fig. 1: Correlation between the number of drugs prescribed and the number of drug-drug interactions per prescription (a) and the number of category C drug-drug interactions (b)

Discussion:

Our study showed that the median (IQR) number of DDIs per prescription in the elderly patients discharged from the hospital was 2.5. The percentage of patients with a DDI which potentially required avoiding a drug or modifying the drug regimen was 20.2%. Majority of the patients in our study sample were females. Male patients had a higher number of co-morbidities although the age was the same compared with females. The age distribution is like other studies conducted in India, although, males were more predominant in these studies [10, 11].

The percentage of prescriptions which contained at least one category X, D, or C DDIs was 20.2%, 30.7%, and 75.8%, respectively. This pattern is like that seen in another study conducted at a tertiary care hospital in Goa, which included all adult patients, but the percentage of DDIs were lower with the percentage of category X DDI being 2.3% [12]. The high numbers of DDI in our study may be due to the fact that only elderly patients were studied. A study done among elderly patients in Puducherry showed the percentage of mild, moderate, and severe DDIs to be 17.2%, 79.3%, and 3.4% [10]. However, the DDI assessment method used was different in this study which partly accounts for the differences seen.

We found a significant positive correlation between the number of drugs prescribed and the number of DDIs, and this was true for all the category of DDIs, with the strength of the correlation being moderate and increasing in the order of category X, D, and C. A study conducted among institutionalized elderly patients in Brazil showed a significant relationship between the number of drugs prescribed and the presence of DDIs [13]. Many other studies have also shown a similar positive correlation between the number of medications prescribed and the number of DDIs seen [2, 12]. In our study, the prescriptions written for patients with respiratory diseases accounted for a large percentage of the DDIs. This is different than what was seen in other studies [10, 12]. This difference may be due to the difference in the local disease patterns, the treatment protocols followed, and the prescribers' practices. Two common DDIs seen in our study were the combination of sympathomimetic bronchodilators and combination of drugs with QT prolonging effect, one of the drugs being domperidone.

The combination of sympathomimetic broncho-dilators increases the risk of cardiovascular disease and, hence, should be avoided [9]. Similarly, studies have shown that the combination of domperidone, which is a drug with high risk for QT prolongation, with other drugs with QT prolonging effect, can significantly increase the risk of development of cardiac arrhythmias [14]. Hence, alternative drugs should be used.

Our study has limitations. It was a single center study with small sample size, therefore, the DDI pattern and the diseases and drugs predominantly associated with DDIs may be different in the general population. Also, the DDIs were detected using the LexiComp software; it is known that not all DDIs detected are of clinical relevance or require modification of the prescription [15]. This is particularly true for category C DDIs, which accounted for the majority of the DDIs in this study.

Conclusion:

Our study showed that DDIs are common among elderly patients. Many DDIs belong to category C, which requires only monitoring of therapy.

A positive correlation is seen between the number of co-morbidities and drugs prescribed and the number of DDIs; no gender-based difference was seen in the number of DDIs. Careful planning of the treatment regimen at the time of hospital discharge can decrease the number of drugs prescribed and, thereby, the number of potential DDIs can be decreased.

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