RESEARCH ARTICLE

Polypharmacy and potential drug-drug interactions among geriatric patients

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ABSTRACT

Background: Polypharmacy is common and increasing among geriatric patients. Polypharmacy has been strongly associated with drug-drug interactions (DDIs). Polypharmacy and DDIs represent potential health hazards for the elderly. Aim and Objective: This study aims to analyze the polypharmacy and associated potential DDIs (pDDIs) among geriatric patients. Materials and Methods: A total of 484 geriatric (age \geq 65 years) patients, who have fulfilled the selection criteria, were included in the study. Polypharmacy was assessed from prescriptions. pDDI was assessed using computer-based checks online available on the internet. Results: A total of 111 patients (22.93%) were prescribed \geq 6 drugs simultaneously – polypharmacy. Six patients were prescribed \geq 10 drugs (hyperpolypharmacy) simultaneously. A total of 191 (39.46%) prescriptions have at least one pDDI – 98 (20.24%) prescriptions, 63 (13.02%) prescriptions, and 30 (6.20%) prescriptions have 1–2 pDDI, 3–5 pDDI, and \geq 6 pDDI, respectively, with total pDDIs were 578. The statistically significant association has been found between the polypharmacy and pDDI (<0.0001). Conclusion: The study has identified the polypharmacy as highly significant predictor for pDDIs. Rational prescribing along with the use of information technology can be helpful to improve medication safety in high-risk population like geriatric patients.

KEY WORDS: Polypharmacy; Potential Drug-drug Interactions; Geriatrics

INTRODUCTION

Polypharmacy can be defined as either the concomitant use of multiple drugs or the administration of more medications than are indicated clinically.^[1] Multiple medication use has been strongly associated with drug-drug interactions (DDIs) and adverse drug reactions.^[2] DDI is a situation in which a drug affects the activity or is affected by another drug when

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administered together. This may be synergistic, antagonistic, or may produce a new effect which neither drug produces alone. DDIs have a higher probability of occurrence in patients with polypharmacy.^[3]

Polypharmacy is common and increasing among elderly patients. Different surveys reveal that elderly patients take an average of two to nine prescription and non-prescription medications each day.^[4-6] In SWEOLD surveys, the prevalence of polypharmacy increased 3-fold over a decade from 18% in 1992 to 42% in 2002 and led to increase in potential DDIs (pDDIs).^[7] A study done among 814 patients in two teaching hospitals showed that polypharmacy and high-level polypharmacy were prescribed in 366 (45.0%) and 370 (45.5%) patients, respectively.^[8] A study from the US reported that 30.3% of patients were at risk of pDDIs

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in day care unit.^[9] A South Indian study also identified and reported high prevalence of pDDIs.^[10]

The geriatric population of India is estimated at 104 million, 53 million females and 51 million males, and is continuously increasing.^[11] This figure is expected to rise to more than 300 million, constituting 20% of India's total population, by 2050. Common morbidities faced by the geriatrics include hypertension, arthritis, osteoporosis, and diabetes mellitus among others. Most of these coexist with other morbidities. Polypharmacy and DDIs represent potential health hazards for the elderly. Therefore, polypharmacy and DDIs deserve attention and the mechanisms behind should be investigated further.

Objectives of the Study

The objectives of the study were as follows:

- To study polypharmacy among geriatric patients attending the outpatient department
- To study pDDIs among geriatric patients attending the outpatient department.

MATERIALS AND METHODS

Туре

This was a prospective and cross-sectional study.

Site

This study was conducted at the Department of Pharmacology, GMERS Medical College and Hospital, Dharpur, Patan.

Study Duration

This study duration was April 2018–December 2018.

Ethical Clearance

The study protocol was presented in the Institutional Ethics Committee (IEC), GMERS Medical College and Hospital, Dharpur, Patan. The study protocol was approved by IEC (No.: MCD/Patan/IEC/12/2018).

Sample Size

All the geriatric patients, attending to the outpatient department during the period, were included in the present study, who had fulfilled the following selection criteria.

Inclusion Criteria

Patients with age more than 65 years of both genders who had attended the outpatient department. (Geriatric/elderly population is defined as persons of ≥ 65 years of age).^[12]

Exclusion Criteria

As such, there were no specific exclusion criteria.

Collection of Data

Patients were recruited in the study on pro rata basis and all the patients participating in the study were explained clearly about the purpose and nature of the study in the language they can understand. Written informed consent was obtained from the patients before their enrolment to the study. All information to accomplish objectives was collected by studying the patients' treatment record and by personal interview of each of the study participants' case record form (CRF). The CRF was comprised of details regarding sociodemographic profile: Present history including symptoms, drug therapy, and other relevant information.

Polypharmacy

As such, there is no accepted definition for polypharmacy as per the number of the drugs prescribed simultaneously. There are studies which suggest that the risk for drug interactions and inappropriate medication increased greatly when six or more different medications were prescribed simultaneously.^[13,14] There are other studies which have defined the use of 10 or more different medications as excessive polypharmacy/hyperpolypharmacy.^[15,16] Hence, for the present study, polypharmacy status was categorized into three groups: (i) Non-polypharmacy – prescription of 1-5 drugs; (ii) polypharmacy – prescription of 6-9 drugs; and (iii) hyperpolypharmacy – prescription of ≥ 10 drugs.

DDIs

pDDIs were assessed using computer-based checks online available on the internet (Drug Interaction Checker by Medscape).^[17] The website categorized the pDDI among all drugs prescribed in a prescription as follows:

- Mild/Minor pDDI: Minimally clinically significant. Interaction is unlikely to be clinically relevant
- Moderate: Moderately clinically significant. Use it only under special circumstances or close monitoring required
- Serious: Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.

Statistical Analysis

The data were entered into Microsoft Office Excel and analyzed by MedCalc statistical software. Quantitative variables were described using the mean and standard deviation after checking normality of data which were tested using Kolmogorov test. Qualitative variables were described using the absolute (N) and relative (%) frequencies. Comparisons among subgroups were performed using Fisher's exact test. The binary logistic regression model was used to analyze the association of the occurrence of pDDIs with specified risk factors, including age, sex, number of drugs, and number of fixed drug combinations. The output of logistic regression was expressed as adjusted odds ration with 95% confidence intervals. P < 0.05 was considered as statistically significant.

RESULTS

A total of 484 geriatric (age ≥ 65 years) patients, who have fulfilled the selection criteria, were included in the study. A majority of the patients belonged to the age group of 65–74 years with the mean age of 69.82 ± 5.14 years [Table 1]. Out of total 484 patients, a majority of the patients (63.43%) were male [Table 2].

On analysis of prescription of the patients, a total of 111 patients (22.93%) were prescribed ≥ 6 drugs simultaneously – polypharmacy. Among these 111 patients, 6 patients were prescribed ≥ 10 drugs (hyperpolypharmacy) simultaneously. The mean number of drugs prescribed was 4.29. As per the prescription of different classes of drugs, 326 patients (67.36%) were prescribed ≤ 4 different classes of drugs, while 155 (32.03%) patients and 3 (0.61%) patients were prescribed 5–9 and ≥ 10 different classes of drugs. Out of total 484 prescriptions, 117 (44.01%) prescriptions at least contain 1 fixed-dose combination (FDC) [Table 3].

The pDDIs were assessed using Drug Interaction Checker bv Medscape (https://www.reference.medscape.com/ drug-interactionchecker). All the drugs prescribed in a prescription were entered into online system for assessing the pDDI in a particular prescription. It was found that 293 (60.54%) prescriptions did not have any pDDI while 98 (20.24%) prescriptions, 63 (13.02%) prescriptions, and 30 (6.20%) prescriptions have 1–2 pDDI, 3–5 pDDI, and ≥ 6 pDDI, respectively, with total pDDIs were 578 [Table 4]. On classification of pDDI based on their severity [Table 5], mild/minor pDDIs were 102 (17.65%), moderate pDDIs were 463 (80.10%), while serious pDDIs were 13 (2.25%). Coprescription of aspirin and enalapril has been found out to be the most common drug pair involved in serious pDDI [Table 6].

The present study also tried to found out predictors of pDDIs using multivariate logistic regression analysis [Table 7]. The statistically significant association has been found between the polypharmacy and pDDI (<0.0001). Age, gender, and number of prescribed FDC do not show significant association with pDDI.

DISCUSSION

Geriatric patients usually have a range of comorbidities which often lead to the prescription of multiple medications.

Table 1: Distribution of patients according to age		
Age in years	Patients, n (%)	
65–74	398 (82.23)	
75–84	77 (15.91)	
>85	9 (1.86)	
Minimum age (years)	65	
Maximum age (years)	90	
Mean age (years)	69.82±5.14	

Table 2: Distribution of patients according to gender			
Gender	Patients, n (%)	Mean age (years)	
		Mean±SD	
Male	307 (63.43)	69.92±5.13	
Female	177 (36.57)	69.79±3.88	

Table 3: Distribution of patients according to different parameters of prescribed drugs

Variables	Patients, n (%)
Number of prescribed drugs	
1–5 (non-polypharmacy)	373 (77.07)
6–9 (polypharmacy)	105 (21.69)
≥ 10 (hyperpolypharmacy)	6 (1.24)
Number of prescribed drug classes	
<u>≤</u> 4	326 (67.36)
5–9	155 (32.03)
≥10	3 (0.61)
Number of prescribed fixed-dose combinations	
0	271 (55.99)
1	189 (39.05)
2	23 (4.75)
3	1 (0.21)

Table 4: Number of pDDI among all the patients			
Number of pDDI	Patients, n (%)		
0	293 (60.54)		
1–2	98 (20.24)		
3–5	63 (13.02)		
≥6	30 (6.20)		

pDDI: Potential drug-drug interaction

Table 5: Distribution of pDDI based on severity					
pDDI	Males	Females	Total	P value*	
	n	n	n (%)		
Mild pDDI	66	36	102 (17.65)	0.50	
Moderate pDDI	279	184	463 (80.10)	0.20	
Serious pDDI	11	2	13 (2.25)	0.15	
Total pDDI	356	222	578 (100.00)		

*Fisher's exact test. pDDI: Potential drug-drug interaction

The use of multiple medications may increase the potential for DDIs.^[18] With this background, the present study was carried out to assess the polypharmacy and related pDDIs in our hospital setup. A total of 484 geriatric patients were included in the study.

On categorization of prescription for the polypharmacy status, polypharmacy (prescription of 6–9 drugs) has been found in 105 (21.69%) patients while hyperpolypharmacy (prescription of \geq 10 drugs) has been found in 6 (1.24%) patients. The mean number of drugs prescribed was 4.29. There is no universal definition of polypharmacy available in the literature. Many authors define "polypharmacy excessive and unnecessary drug use," while many other authors define polypharmacy based on the number of drugs prescribed.^[19,20]

For the present study, we defined polypharmacy as a prescription of six or more different drugs because there are studies available which suggest that prescription of six or more drugs increases the risk of pDDI as well as of inappropriate prescribing.^[13,14] If we use more rigorous

Table 6: Drug pairs involved in serious pDDI					
Drug pairs	Number of pDDI	Effect of drug interaction			
Aspirin+Enalapril	6	Diminished renal function, diminished antihypertensive effects of enalapril			
Diclofenac+Enalapril	1	Diminished renal function, diminished antihypertensive effects of enalapril			
Omeprazole+Clopidogrel	2	Diminished antiplatelet effect of clopidogrel			
Aspirin+Ramipril	1	Diminished renal function, diminished antihypertensive effects of ramipril			
Ibuprofen+Enalapril	1	Diminished renal function, diminished antihypertensive effects of enalapril			
Aspirin+Ibuprofen	2	Increased toxicity of aspirin, diminished effects of aspirin			

pDDI: Potential drug-drug interaction

definition - polypharmacy as prescription of five or more drugs, the level of polypharmacy was increased from 22.93% (n = 111) to almost double (44.01%, n = 213). Almost a similar level (39.4%) of polypharmacy (prescription of five or more drugs) has been found in a study done by Slabaugh et al.[21] A study done among 814 patients in two teaching hospitals showed that polypharmacy and hyperpolypharmacy were prescribed in 366 (45.0%) and 370 (45.5%) patients, respectively.^[8] A study by Rakesh et al. shown higher rate of polypharmacy (prescription of five or more drugs) of 66.2% as compared to the present study.^[22] The lower level of polypharmacy in the present study as compared to other studies as there was low level of chronic diseases such as hypertension (22.72%) and diabetes mellitus (19.83%) in the present study population as compared to the study done by Rakesh et al. - hypertension (75.4%) and diabetes mellitus (51.6%). In the present study, the mean number of drugs prescribed was 4.29 which falls in the range of reported value of 3.7-7.9 by different studies.^[23-25]

Apart from financial burden, there are many negative outcomes of polypharmacy, such as adverse drug events, poor adherence, drug interactions, medication errors, and geriatric "syndromes" – urinary incontinence, cognitive impairment, and loss of balance leading to falls/fractures.^[18,26] There are literatures available which suggest that polypharmacy is significantly associated with increase in adverse drug events. Risk of adverse drug events is 15% with two medications, but this risk is increased to 58% and 82% with 5 medications and \geq 7 medications, respectively. Addition of further medications leads to greater increase in incidence of adverse drug events as well as drug interactions.^[27-29]

In the present study, 191 (39.46%) prescriptions have at least one pDDI – 98 (20.24%) prescriptions, 63 (13.02%) prescriptions, and 30 (6.20%) prescriptions have 1–2 pDDI, 3-5 pDDI, and ≥ 6 pDDI, respectively, with total pDDIs were 578. According to severity of pDDI, different types of pDDI were – mild/minor pDDI (17.65%), moderate pDDI (80.10%), and serious pDDI (2.25%). The similar pattern of pDDI was found in a study done by Salwe *et al.*^[30] In that study, the most common pDDI was of moderate grade (76.8%) while

Table 7: Predictors of pDDI (multivariate logistic regression analysis)						
Variables	Groups	Patients with pDDI	Patients without pDDI	Wald	Odds ratio (95% CI)	P value
Age	≤70	148	207	1.91	0.73	0.17
	>70	44	85			
Gender	Male	116	191	0.14	1.08	0.71
	Female	76	101			
Number of drugs	≥ 6	143	286	39.41	16.64	< 0.0001*
	1-5	49	6			
Number of fixed-dose combinations	≤ 1	183	277	0.69	0.66	0.4080
	>1	9	15			

* P<0.0001: Highly significant association. pDDI: Potential drug-drug interaction

serious/severe pDDI was 6.98% of total pDDI. In the study done by Teka *et al.*, 62.2% of the patients were exposed to at least one pDDI – contraindicated (3.6%), major (32.9%), and moderate (25.7%).^[31] The other studies by Pasina *et al.*^[32] and Lea *et al.*^[33] reported a prevalence of 63.5% and 60.5% pDDI and DDIs, respectively. There are also other studies focusing on elderly outpatients which shown comparatively lower prevalence of pDDI.^[34,35] All these studies suggest that the prevalence of pDDI may be different according to patients selection, more common in inpatients setup as compared to outpatients.

The present study has identified the polypharmacy highly significant predictor for the occurrence of pDDI (<0.0001). There are many studies available which have also identified high number of prescribed medications as an important predictor of pDDI in elderly population.^[36-39] As there is an increase in number of prescribed medications, there is an increase in risk of pDDI, which has been proven in one of the studies from Brazil. They reported that the risk of pDDI was 39%, 88.8%, and 100% when patients are taking 2–3, 4–5, and 6–7 medications, respectively.^[40] In case of polypharmacy, there are also increases chances of inclusion of one or more unnecessary drugs in prescription which may further increase the risk of avoidable pDDI. In one of the studies, it has been found that nearly half of elderly patients were prescribed at least one medication that was unnecessary medically.^[41]

The pDDIs reported in the present study as well as in other studies are actually theoretical. The actual clinical DDIs are quiet low as compared to pDDI.^[31] Although polypharmacy may play an important role in occurrence of DDIs, there are many factors, such as comorbidities, age of patients, therapeutic range, and dosage of the drugs, which are also contributed in DDI.^[42] In geriatric population, there are the presence of many comorbidities which may lead to the prescription of polypharmacy that does not necessarily mean inappropriate. The medications are prescribed for different diseases or to achieve the different purposes such as to achieve synergism, reduce the resistance, and combat adverse drug reactions of other drugs. Hence, it is very difficult to avoid the use of many medications in elderly patients. It is unnecessary to avoid important medications because of the risk of theoretical pDDI. Chances of DDI can be minimized using other alternative medications which are involved in least pDDI in a particular prescription.

Although pDDI may be theoretical, health-care professional must be aware regarding this to prevent hazardous DDIs. The DDIs due to polypharmacy can be reduced by different educational programs, but it is time consuming as well as close monitoring may be required. It is also not possible for health-care professional to remember each and every DDIs. In addition, there are chances of frequent multiple changes in a treatment regimen.^[43] Ultimately, health-care professional should reduce the number of prescribed medications, plan

simple dosing schedule, if possible, minimize frequent changes in prescription, and periodic review of whole treatment regimen. In the era of information technology, the use of internet and specific software to detect the DDIs can be helpful to overcome the limit of memorizing each and every DDI. Increasing health-care professionals' awareness as well as sensitize higher authorities regarding polypharmacy and related dangerous drug interactions may be helpful in limiting the irrational prescribing and this will ensure medication safety of the geriatric patients.

There are certain limitations of the present study such as involvement of outdoor patients of single department only. The present study also has not included monitoring of adverse drug reactions or other parameters as a measure of actual clinical DDIs. The study with multiple specialties with all types of patients – indoor as well outdoor departments – along with rigorous monitoring of all drug-related events may be planned to overcome these limitations. However, the present study provided insight into the prevalence of pDDI in geriatric patients in a resource-constrained setting, like us. As with other studies, the present study has identified polypharmacy as a highly significant risk factor for the occurrence of pDDI in geriatric patients.

CONCLUSION

The findings of the present study reveal that geriatric patients are at risk of prescription polypharmacy because of the presence of comorbidities. Nearly 40% of the study prescriptions have at least one pDDI. The study also has identified the polypharmacy highly significant predictor for pDDI. Rational prescribing along with the use of information technology can be helpful to improve medication safety in high-risk population like geriatric patients.

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