EXPLORING THE PATTERN OF POLYPHARMACY AND PROPORTION OF DRUG TO DRUG INTERACTIONS AND ADVERSE DRUG REACTIONS IN THE ELDERLY

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ABSTRACT

BACKGROUND

The geriatric population is increasing as a result of advanced medical facilities. This population also faces a number of medical health challenges. They tend to receive multiple medications often leading to Drug-Drug Interactions (DDIs) Adverse Drug Reactions (ADRs) and other clinical consequences, which compromises their quality of life if not endangering it as well. There are few Indian studies focusing on this problem. Hence, this study was undertaken with the aim to assess the polypharmacy pattern, proportion of DDIs and adverse drug reactions in the geriatric population in a tertiary care hospital.

MATERIALS AND METHODS

This was a cross-sectional study wherein data from 201 geriatric inpatient's prescriptions were collected. The prescriptions were assessed for demographic details such as age, gender, comorbidities and drugs prescribed. All prescriptions were evaluated for polypharmacy, DDIs and ADRs. DDIs were assessed using Micromedex software. Patients were stratified into groups and DDIs were compared between the groups, gender and also with number of drugs used.

RESULTS

There were 201 patients with a mean age of approximately 70 years. Polypharmacy occurred in 73.63% of them with mean number of drugs being 6.23. The number of drugs used increased significantly with age (p=0.0001). Hypertension was the most common comorbidity. Polypharmacy was strongly associated with hypertension and dyslipidaemia. A total of 129 (64.17%) patients accounted for 425 potential DDIs. The most common drug involved in DDIs was aspirin. A subset analysis of ADRs showed an occurrence of 50.68% with 10.81% being definitely avoidable.

CONCLUSION

Elderly individuals are at increased risk of being on polypharmacy. This comes with the risk of several potential DDIs, which in turn may lead to adverse drug reactions, which results in morbidity. Doctors involved in the care of the elderly should be aware of these facts and exercise caution while adding any new drug.

KEYWORDS

Adverse Drug Reactions, Drug Interactions, Elderly, Polypharmacy.

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BACKGROUND

Care of the elderly is an integral part of a physician's job, which poses several challenges. Judicious and appropriate use of medications is one among them. It is predicted that by the year 2030 half of the world's population will comprise of people over the age of 65 years.[1] As per National Policy on older persons adopted by Government of India, an elderly person or geriatric is defined as one who is of age 60 years or above. According to official population projections, the number of Indian elderly will rise to approximately 140 million by 2021.[2]

With increasing age, there is a higher likelihood of elderly patients being prescribed more medications due to their increasing health problems. Multimorbidity is a term used to define a condition where 2 or more illnesses exist in the same person.[3] Studies have shown that the risk of polypharmacy rises with increasing age.[4] Ageing can alter the pharmacokinetic functions right from absorption to excretion.[1]

The WHO defines polypharmacy as the concurrent use of five or more medications.[4] Though, these drugs are often necessary for treating the multiple health problems, they also pose a danger in the form of drug interactions and subsequent Adverse Drug Reactions (ADRs). Drug-Drug Interaction (DDI) refers to modification of response to one

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drug by another drug when they are administered simultaneously. Studies have confirmed polypharmacy as one of the major risk factors in precipitation of DDIs.[5] The modification is mostly quantitative, i.e. the response is either increased or decreased in intensity, but sometimes it is qualitative, i.e. abnormal or a different type of response is produced. The possibility of DDI arises whenever a patient receives more than one drug and chances increase with number of drugs taken.[6] There are numerous potential DDIs that can result in toxicity and even lead to life-threatening situations.

According to one study, 14.4% of all hospital admissions in the elderly are medication related and among the increased risk factors for admissions were ADRs and polypharmacy.[7]

The clinical outcome of polypharmacy includes medication nonadherence leading to treatment failure, inability to perform activities of daily living, cognitive impairment, increased risk of falls, urinary incontinence, risk of malnourishment and financial burden.[8]

While polypharmacy is unavoidable at times, certain interventions can improve rational drug use. Clinical pharmacist intervention in the form of evaluating drug regimens in conjunction with treating physicians reduced inappropriate drug prescriptions consistently over a period of one year and possibly ADRs as well.[9]

Majority of the adverse side effects in the elderly are type A that is potentially preventable.[10] Several countries in caring for the elderly have developed lists of inappropriate medications which are periodically updated. It would be useful to consult the Beers Criteria list and STOPP/START criteria while prescribing medications to the elderly.[11]

Indian data regarding prevalence of drug-drug interactions in geriatric age group is scanty. Hence, this study was undertaken with the aim to assess the polypharmacy pattern, proportion of DDIs and adverse drug reactions in the geriatric population in a tertiary care hospital.

MATERIALS AND METHODS

This was a cross-sectional study wherein the inpatient records of 201 elderly patients admitted to the medical wards of a tertiary care hospital was reviewed for medication details after obtaining clearance from ethics committee of this institution. Demographic data, associated comorbidities, potential DDI and adverse drug reactions were assessed. DDI were assessed using Micromedex Software. A severity scale was used to classify DDIs. A mild DDI was one where the risk of adverse outcome appeared small, moderate DDI was one where the administration of the drug combination was to be avoided unless benefit outweighed risk and a major DDI was one which was to be avoided.[12]

Patients were stratified age wise into different groups, namely between 60 to 69 years, 70 to 79 years, 80-89 years and above 90 years. Those on 5 or more drugs were considered to be on polypharmacy according to the WHO definition.[4] The DDIs were compared between the groups and also between the genders. Further a subset were analysed for adverse drug reactions.

Adverse drug reactions are classified as follows based on Hallas et al classification (1990).[13,14]

Definitely Avoidable- When the drug treatment procedure is inconsistent with present day knowledge of good clinical practice.

Possibly Avoidable- When the ADR could be avoided with efforts exceeding obligatory demands.

Unavoidable- Could not have been avoided by any means. The severity of ADRs was classified as mild, moderate and severe based on Modified Hartwig, Seigel and Schneider scale (1992).[14,15] Mild ADRs are self-limiting and resolve with time and without treatment. Moderate ADRs are those, which require therapeutic intervention and prolonged hospital stay by 1 day, but resolved in less than 24 hours or change in drug therapy. Severe ADRs were those that were life-threatening or caused prolonged hospital stay or intensive medical care.

Based on a previous study by Bhojan et al in 2013 who observed that the DDI among geriatric age group was 68.6%, in the present study, expecting 95% confidence level and 10% relative precision, a minimum of 181 subjects were required. Descriptive statistics were analysed and presented in terms of mean, standard deviation and percentage. Chi-square test was used to study the association of age and gender with polypharmacy and DDIs. SPSS version 20 was used to analyse the data.

RESULTS

A total of 201 prescriptions were analysed. There were 57.21% (n=115) male patients and 42.78% (n=86) female patients in this study. The age of this population ranged from 60 to 93 years. The mean age of the patients was 69.19 ± 6.99 years. The distribution of patients in the different age groups was as follows. There were 54.22% (n=109) in 60-69 years age group, 36.31% (n=73) in 70-79 years age group, 8.45% (n=17) in the 80-89 years age group and 0.99% (n=2) in those 90 years and above (Bar diagram 1).

The number of drugs used per patient ranged from a minimum of 1 to a maximum of 14 drugs. Going by the definition of polypharmacy used by us, 73.63% (n=148) of patients were on it. The mean number of drugs per patient in the entire population was 6.23 ± 2.54, whereas it was 7.24 ± 2.15 in the polypharmacy group. The gender distribution among patients receiving polypharmacy was 66.27% (n=57) in female patients and 79.13% (n=91) among male patients. This is represented in bar diagram 2. The mean number of drugs used per person was 7.74 in females and 6.94 in males in the polypharmacy group.

After analysing age and number of drugs administered by Pearson Chi-square test, we found that p was significant at less than 0.0001. This tells us that there is statistically significant association between age and number of drugs administered with association increasing with age; however,

p was found to be 0.03 between gender and number of drugs, which was insignificant considering alpha level as 0.01.

Multimorbidity was prevalent in 89.55% of patients. The mean number of comorbidities in the polypharmacy group was 2.59 and 3.07 in the non-polypharmacy group and 2.72 overall. This was possibly due to a patient with a single comorbidity being on multiple drugs. The commonly associated comorbidities were hypertension, diabetes, infections and cerebrovascular and cardiovascular disease. This is represented in table 1. There was a strong relationship between number of drugs used and presence of hypertension and dyslipidaemia with statistically significant correlation of less than 0.001 and 0.004, respectively. This correlation didn't occur with the other comorbidities.

The major classes of drugs prescribed in decreasing order were antihypertensive drugs, anti-diabetic medications, antibiotics, antiplatelet drugs, GI protectants, antilipid medications and levothyroxine. Other than these drugs were classified as miscellaneous drugs (Table 2).

There were 129 (64.17%) patients who had potential DDIs and a total of 425 DDIs. Among them, 2 (0.47%) of the drug combinations were minor, 262 (61.64%) were of moderate type and 161 (37.88%) were major. The mean DDI per person was 2.11 ± 2.44. The most common drug involved in contributing to it was aspirin followed by insulin and clopidogrel.

After analysing age and number of potential DDIs by Pearson Chi-square test, we found that p was 0.92, which was insignificant; likewise, 'p' was equal to 0.49 on comparing with gender, which too was insignificant.

Occurrence of potential DDIs was more in the polypharmacy group of patients; it was 66.82% in patients on 5-9 medications and 24.24% in patients on 10-14 medications, whereas 8.94% had DDIs in non-polypharmacy group with 1-4 medications (Table 3). Pearson's correlation value between number of drug used and DDI showed, r=0.02, which means that there was a weak relationship between drug and DDIs; and there was no statistically significant correlation (2 tailed significant value = 0.972)

A subset of 146 patients was evaluated for adverse drug reactions.

There were 74 (50.68%) patients who developed ADRs. The total number of ADRs was 148, among which 88.51% (n=131) were unavoidable, 10.81% (n=16) were definitely avoidable and 0.67% (n=1) was possibly avoidable. Mild ADRs were 83.10% (n=123) followed by moderate in 16.21% (n=24) and severe in 0.67% (n=1). This is represented in table 4.The most common drug causing ADR was aspirin followed by furosemide, telmisartan, clopidogrel and amlodipine. The commonest ADR was gastritis and minor bleeding.

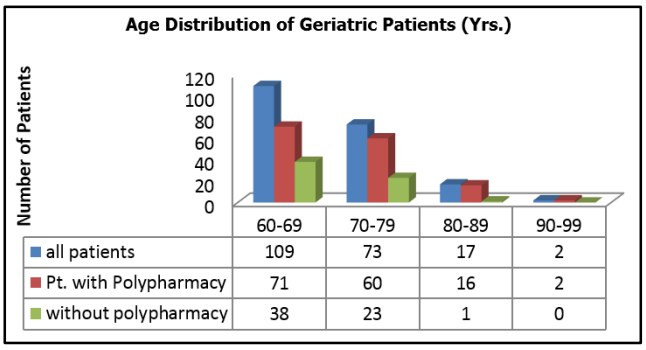

Figure 1. Age Distribution of Geriatric Patients (Yrs.)

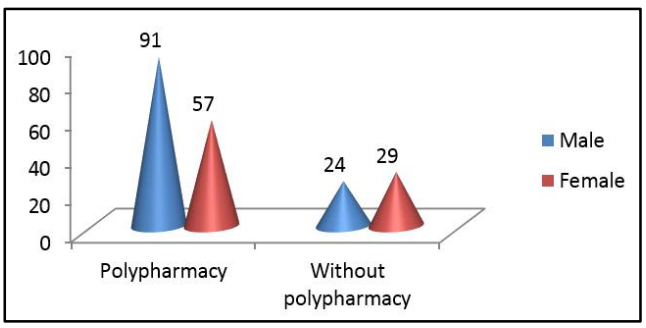

Figure 2. The Number of Drug Used Per Patient

Disease	Number of Patients	Percentage
Hypertension	122	60.69%
Diabetes mellitus	113	56.21%
Infections	111	54.95%
Vascular disorders	103	51.24%
Dyslipidaemia	24	11.94%
Thyroid disorders	23	11.44%
Neuropsychiatric diseases	17	8.45%
Respiratory diseases	12	5.97%
Renal diseases	06	2.98%
Musculoskeletal diseases	06	2.98%
Anaemia	05	2.48%
GI diseases	05	2.48%

Table 1. Major Comorbidities

Class of Drugs	Number	Percentage
Antihypertensive drugs	273	21.78%
Antidiabetic medications	150	11.97%
Antibiotics	137	10.93%
Antiplatelet drugs	119	9.49%
GI protectants	97	7.74%
Antilipid medications	52	4.15%
Levothyroxine	23	1.83%
Miscellaneous	402	32.08%
Total No. of Drugs	**1253**	**100%**

Table 2. Major Classes of Drugs Used

Number of Drugs	Number of DDIs	Percentage
1-4	38	8.94
5-9	284	66.82
10-14	103	24.24
Total	**425**	**100**

Table 3. Proportion of DDI in Relation to Number of Drugs

Severity of ADR	Number	Percentage
Mild	123	83.10
Moderate	24	16.21
Severe	1	0.67
Total	**148**	

Table 4. Severity of ADRs

DISCUSSION

Previous literature on polypharmacy in the elderly has documented different occurrence rates. While some studies have taken into consideration the number of drugs used to define the condition others have considered inappropriate drug prescription.[4,16] The occurrence of polypharmacy was very similar in the study by Bilal Ahmed done in Pakistan in 2014 (70%) as compared to our study (73.63%) even though they have studied the geriatric population in ambulatory care.[4] The rate is similar in another Asian country as well.[17] Other studies have recorded lower occurrence rates probably because they have considered inappropriate drug usage as a criterion and have been done in other countries where prescription protocols may differ.[18,19,20]

Polypharmacy occurred slightly more often among male as compared to female patients (66.27% versus 79.13%) and the mean number of drugs used by female and male patients were 7.74 and 6.94, respectively. One study found males were more likely to be exposed to polypharmacy[1] while another study did not find any gender-based difference.[19] We too found no significant gender difference. The number of drugs administered increased with age. This finding concurred with other studies.[21,22]

The commonest drug used in polypharmacy in one study was GI agents (18), while in our study, they were antihypertensives since hypertension was the most common comorbidity in this study.

A large percentage of our patients were multimorbid (89.55%) with hypertension and diabetes being the most common comorbidities. A study done by Aubert et al in Swiss primary care settings found that polypharmacy was strongly associated with hypertension, diabetes mellitus, chronic kidney disease and cardiovascular diseases.[23] In our study, we found a strong association exists between hypertension and dyslipidaemia with polypharmacy.

We found 64.17% of our study sample with potential DDIs, which was much higher than in a large study conducted by Bjorkman in six European countries on[1601] elderly persons attending outpatient departments and found 46% with this risk.[24] Many of our patients were admitted with infections (55.22%). Prescribing antibiotics to the elderly who are already at the risk of polypharmacy increases the chances of drug interactions.[25] This may explain the higher risk of DDIs in our study.

Age, gender and number of drugs used had no bearing on the occurrence of DDIs in this study. One study found that DDIs increased with age, but the population under consideration were all adults aged above 18 years unlike only the elderly as in our study.[26] According to another study, the risk of DDIs increased with increasing number of drugs with 11% risk while being on 2-4 drugs and 81% on ≥15 drugs.[2] However, this study too was done in adults of all ages.

Aspirin either in high or low doses should be avoided in combination with antithrombotic agents and methotrexate since it has been documented to have either severe adverse effects or absence of therapeutic effect.[24] The other important drug involved in DDIs was clopidogrel. Interactions with both these cardiovascular drugs can have serious implications in terms of adverse cardiac outcomes.[27]

The subgroup analysed for ADRs showed quite a high occurrence of ADRs (50.68%). However, most of them were mild and only a few were moderate (16.21%) or severe (0.67%) in intensity. This kind of pattern was seen in another study conducted in Kashmir in 2016.[14] Aspirin was the most common drug causing ADR, and since it is not possible to stop it in most cases, one should be careful with drug interactions while adding other medications.

CONCLUSION

A large percentage of our population were on polypharmacy probably since ours is a tertiary care centre where patients have access to consultations by various specialists. This in turn may lead to many potential drug interactions, which may result in adverse drug reactions. Treating physicians are often not aware of the clinical effects of polypharmacy nor do they exercise knowledge regarding drug interactions. The primary care consultant needs to carefully prune the prescriptions in order to avoid unnecessary medications and this is to be done periodically on a day-to-day basis in order to avoid inappropriate prescribing.

The concept of clinical pharmacologist working with clinicians is not a very popular one in India though some centres are becoming increasingly aware of this. Coordination between treating doctors and clinical pharmacologists is likely to improve the quality of prescriptions and help in reducing drug interactions and side effects and develop rational drug use.

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