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Potentially inappropriate medications, drug-drug interactions, and prescribing practices in elderly patients: a cross-sectional study

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SUMMARY

OBJECTIVE: To evaluate potentially inappropriate medications, potential drug-drug interactions, and prescribing practices in elderly ambulatory patients.

METHODS: We carried out a cross-sectional study on 275 elderly patients attending different outpatient departments. We used the Screening Tool for Older Person's Prescriptions criteria version two to identify potentially inappropriate medications, IBM Micromedex, to categorize potential drug-drug interactions as major and moderate. World Health Organization prescribing indicators were used to evaluate prescribing practices.

RESULTS: The prevalence of potentially inappropriate medications in 275 prescriptions was 21.9%. Diclofenac was the most common inappropriate drug (n=23). Metoprolol is the second most inappropriate drug (n=12). Amlodipine and clopidogrel, aspirin and furosemide, and aspirin and spironolactone together accounted for 71.42% of major interactions (n=15). Atorvastatin and clopidogrel was the most common moderate drug-drug interaction in our study (n=24). The average number of drugs per encounter, the percentage of drugs with a generic name, and the percentage of drugs from the essential drugs list must be improved.

CONCLUSION: There is a need to provide awareness through education about the explicit criteria to identify potentially inappropriate medications and prescribing indicators that aid in rational prescribing in the elderly.

KEYWORDS: Aged. Drug interactions. Potentially inappropriate medication list. STOPP. Inappropriate prescribing.

INTRODUCTION

The aging population across the world is increasing. By 2050, 16% will be elderly, compared to 9% in 2019[1]. Increasing age is a risk factor for chronic diseases and comorbidities. Subsequently, the need to administer drugs to manage them also increases. As a result, the chances of polypharmacy increase and may contribute to drug-related problems such as potential drug-drug interactions, adverse drug reactions, inappropriate prescribing.

Inappropriate prescribing in the elderly is a global concern. The global prevalence of potentially inappropriate prescribing ranges from 13–35%[2]. It is directly linked to substantial morbidity, mortality, and wastage of health resources[3]. The physician's poor choice of medication is a significant cause of ADRs among older people[3]. These adverse effects of inappropriate prescribing need to be prevented, owing to the problem's seriousness. Potentially inappropriate prescribing tools are developed to achieve this goal.

Potential drug-drug interactions due to inappropriate prescribing is another severe problem. Approximately 3–26% of adverse reactions related to hospital admissions are due to drug-drug interactions[4]. Clinically significant drug-drug interactions may occur with narrow therapeutic index, microsomal enzyme inhibitors, severely ill patients, compromised renal and hepatic

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function, and older adults with polypharmacy[5]. The drug-drug interactions can be categorized as major and moderate based on the severity of the interaction. Major drug-drug interaction is life-threatening, whereas moderate interaction exacerbates the patient's clinical condition[IBM]. So, there is a need to promote the rational use of drugs. It helps to eliminate polypharmacy, inappropriate prescribing, and any drug-drug interactions.

Congruent with this, the present study aimed to evaluate the inappropriate prescribing in the elderly using Screening Tool to Older Person's Prescriptions (STOPP) criteria version 2.0, potential drug-drug interactions and their management using IBM Micromedex database, and the rational use of drugs with the help of core drug use indicators by World Health Organization.

METHODS

We conducted a cross-sectional study on elderly patients attending different outpatient departments in a tertiary care hospital. The study was conducted for six months (01/08/2019–31/01/2020). We used a simple random sampling technique to select geriatric patients. Each geriatric patient was allotted a number at the beginning of the consultation with the doctor and using a random number generator, and they are selected randomly. The estimated sample size was 270 (margin of error=5%, 95%CI, population size=900, response distribution=50%).

We included elderly patients (age ≥65 years), prescribed with at least one drug, and excluded inpatients and patients who cannot spare their time due to time constraints. Our study was approved by the Institutional Human Ethics Committee (VIPT/IEC/89/2019). We clearly explained the aim of the study to each participant and obtained written informed consent from them.

Study instruments

We used the Screening Tool for Older Person's Prescriptions criteria version 2.0 to identify potentially inappropriate medications. IBM Micromedex®3 was used to categorize drug-drug interactions (DDI) into major and moderate. Major DDI was any interaction that may be life-threatening and (or) requires medical intervention to minimize or prevent serious adverse effects. Moderate drug interaction was any interaction that may result in exacerbation of the patient's condition and (or) require an alteration in the therapy.

The WHO prescribing indicators help measure the appropriate use of drugs and general prescribing tendencies within a given setting independent of the specific diagnosis. The five indicators measure the degree of polypharmacy, tendency to prescribe by generic name, tendency to prescribe antibiotics, the widespread use of the costly form of drug therapy, and the degrees to which national practices conform to national drug policy.

Data analysis

We calculated frequency and percentages for qualitative data. Based on the normality assumption using the Shapiro-Wilk test, we represented the quantitative data as mean and standard deviation or median and interquartile ranges. A χ^2 test was used to find the association between polypharmacy and inappropriate prescribing. The level of significance was considered at $p<0.05$. Jeffrey's Amazing Statistics Program (JASP, version 0.12.1.0) was used for statistical analysis.

RESULTS

The mean age of elderly patients was 65.90±5.48 years. Males are higher (53.10%) than females. There are 108 patients with comorbidities (39.27%). A total of 1140 drugs were prescribed, and 23 potentially inappropriate medications were distributed across 60 prescriptions. The prevalence of potentially inappropriate medications in 275 prescriptions was 21.9%. Hypertension is the most common comorbidity (45.37%). The majority of the prescriptions contain less than five drugs (65.09%). The majority of the patients (65.09%) visited the department of general medicine (Table 1).

Table 1. Socio-demographic and clinical characteristics of patients.

Characteristic	Frequency (%)
Age (in years)	65.90±5.48
Gender	
Male	146 (53.10)
Female	129 (46.90)
Comorbidities (n=108)	
Hypertension	46 (45.37)
Diabetes Mellitus	37 (36.11)
Hypertension and Diabetes	18 (16.67)
Coronary Artery Disease	02 (1.85)
Others	05 (4.63)
Number of drugs	
<5 drugs	179 (65.09)
≥5 drugs	96 (34.91)
Type of Department	
General Medicine	127 (46.18)
Endocrinology	59 (21.45)
Ortho	43 (15.64)
Pulmonology	26 (9.45)
Others	20 (7.27)

Diclofenac was the most common inappropriate drug (n=23), and Metoprolol is the second most inappropriate drug (n=12). The most commonly prescribed class of inappropriate drugs was Non-Steroidal Anti-Inflammatory Drugs-Diclofenac, Piroxicam, Ibuprofen (Table 2).

We identified 21 major drug-drug interactions (DDI) and 74 moderate interactions. Amlodipine and clopidogrel, aspirin and furosemide, and aspirin and spironolactone together accounted for 71.42% of interactions (n=15). Atorvastatin and clopidogrel was the most moderate drug-drug interaction in our study (n=24) (Table 3).

Table 4 outlined the prescribing indicators along with the World Health Organization reference value. The average number of drugs per encounter, the percentage of drugs prescribed by generic names, and the percentage of drugs from an essential drug list were not within the reference range. We observed a statistically significant association between inappropriate medications and polypharmacy ($p<0.001$), type of department ($p=0.03$).

DISCUSSION

A drug-drug interaction contains an object drug and a precipitant drug. Object drug is a medication that has its therapeutic effect modified by the drug interaction process. The precipitant drug is the medication that affects the pharmacodynamics and pharmacokinetics of the object drug[6]. For example, in the major drug interaction between amlodipine and clopidogrel, amlodipine is the precipitant drug and it decreases the antiplatelet effects of the object drug.i.e., clopidogrel by inhibition of CYP3A-mediated clopidogrel activation[7]. The risk of increased antithrombotic events can be reduced by cilostazol[8].

Drug-Drug interactions can be minimized by choosing alternative drugs that are not affected by the precipitant drug. For example, concurrent use of clopidogrel and CYP3A4 metabolized statins like atorvastatin will result in high on-treatment platelet reactivity[7]. However, substituting the atorvastatin with pravastatin or rosuvastatin that is not metabolized by CYP3A4 will avoid the interaction[9]. We can manage drug interactions by

Table 2. List of potentially inappropriate medications according to screening tool of older person's prescriptions criteria version 2.0.

Name of the drug(s)	Class of the drug(s)	Frequency (n)	Reason for Inappropriateness
Diclofenac	Non-Steroidal Anti-inflammatory Drugs (NSAID)	23	Inappropriate in moderate to severe hypertension as it increases the risk of exacerbation of hypertension
Metoprolol	Beta-Blocker	12	Inappropriate in Diabetes mellitus as it increases the risk of masking hypoglycaemic symptoms
Cinnarizine	1st generation anti-histamine	4	Prolonged use increases the risk of sedation and anticholinergic side effects; Duplication of the drug is inappropriate
Amitriptyline & Amlodipine	TCA; Calcium Channel Blocker	4	Concurrent use increases the risk of severe constipation
Pheniramine Maleate	1st generation anti-histamine	3	Prolonged use increases the risk of sedation and anticholinergic side effects
Telmisartan and Losartan	Angiotensin Receptor Blockers	2	Duplication of the drug class
Chlordiazepoxide (n=2) & Clobazam (n=1) & Clonazepam (n=1)	Benzodiazepines	4	Long-acting benzodiazepine increases the risk of sedation, confusion, impaired balance, falls.
Prednisolone	Systemic Corticosteroid	2	Systemic corticosteroid instead of inhaled corticosteroid for maintenance therapy in moderate to severe COPD is inappropriate
Glibenclamide	Sulfonyl Urea	2	Increased risk of prolonged hypoglycemia
Propranolol (n=1) and Atenolol (n=1)	Beta Blockers	2	Inappropriate in Diabetes Mellitus as it increases the risk of masking hypoglycaemic symptoms
Diclofenac & Piroxicam	NSAID	1	Duplication of the drug class
Hyoscine Butyl Bromide	Anticholinergic	1	Inappropriate in patients with chronic constipation as it exacerbates the constipation

TCA: Tri cyclic antidepressant.

Table 3. Potential drug-drug interactions (major & moderate) that requires a change in the prescription of the elderly patients.

Interaction	Mechanism	Frequency
Major Interactions		
Amlodipine+Clopidogrel	Decreased antiplatelet effect and increased risk of thrombotic events	5
Aspirin+Furosemide	Reduced diuretic effectiveness and possible nephrotoxicity	5
Aspirin+Spironolactone	Hyperkalaemia and possible nephrotoxicity	5
Amitriptyline+Diclofenac	Increased risk of bleeding, including intracranial haemorrhage	2
Ibuprofen+Hydrochlorothiazide	Possible nephrotoxicity	1
Diclofenac+Hydrochlorothiazide	Possible Nephrotoxicity	1
Domperidone+Hydroxychloroquine	Increased risk of QT-interval prolongation, including torsades de pointes	1
Enalapril+Losartan	Increased risk of adverse events, including hypotension, syncope, hyperkalaemia, and changes in renal function	1
Moderate Interactions		
Atorvastatin+Clopidogrel	High-on treatment platelet reactivity	24
Aspirin+Metoprolol	Results in increased blood pressure	16
Azithromycin+Theophylline	Increased serum theophylline concentrations	8
Metoprolol+Metformin	May increase or decrease the blood-glucose-lowering effect of the antidiabetic agent, and may decrease or obscure signs and symptoms of hypoglycemia	7
Glimepiride+Metoprolol	May increase or decrease the blood-glucose-lowering effect of the antidiabetic agent, and may decrease or obscure signs and symptoms of hypoglycemia	7
Diclofenac+Telmisartan	May result in renal dysfunction and/ or increased blood pressure.	6
Aspirin+Atenolol	May result in increased blood pressure	3
Diclofenac+Losartan	May result in renal dysfunction and/ or increased blood pressure.	3

Table 4. World health organisation prescribing indicators.

Name of the indicator	Frequency/ Percentage (%)	WHO reference value (%)
The average number of drugs per encounter	4.23	<2
Percentage of drugs prescribed by generic name	71.85	100
Percentage of encounters with an antibiotic prescribed	18.51	<30
Percentage of encounters with an injection prescribed	4.44	<20
Percentage of drugs from Essential drug list or formulary	96.32	100

avoiding the combination directly, dose adjustment, monitoring for early detection, improved computerized screening systems, proving information about patient risk factors like comorbidities[7].

We compared the indicators of our study with three other studies[10-12]. Comparatively, the percentage of drugs prescribed from the essential drugs list was high in our study (96.32%). The average number of drugs is nearly equal, except for Jyosthna et al.[11] (6.7), who reported polypharmacy. Abdulah et al.[12] reported a higher percentage of prescribed by generic name (98.09%). Jyosthna et al.[11] reported a very high percentage of encounters with an injection (67.5%), which is nearly 15 times of our study.

World Health Organization prescribing indicators measure the appropriate use of medicines. The indicators are aimed to assess the extent of polypharmacy, prescriber's tendency to prescribe medicines using a generic name, frequency of with antibiotics and injections are prescribed, and to assess whether prescribing practices complies with national drug policy[13].

The advantage of using these indicators is, they will give an overview of irrational prescribing irrespective of diagnosis[13].

Inappropriate prescribing results in prescribing medications with higher risk than benefit. For example, cinnarizine is a potentially inappropriate medication; if prescribed to treat menopausal symptoms because it is ineffective[14]. Drugs-to-avoid lists include medications that should be avoided in any circumstance, doses that should not be exceeded, and drugs to avoid in patients with specific disorders[15]. STOPP criteria version 2.0 provides a drugs-to-avoid list for the elderly and is widely accepted as an evaluation tool for potentially inappropriate medications.

A study in a Brazilian hospital reported Omeprazole, Furosemide, Clonazepam, Spironolactone as the most common inappropriate medications at home and the hospital[16]. Three studies[17-19] from Japan reported Benzodiazepines as the most commonly observed potentially inappropriate medication according to STOPP criteria version 2. There are proven interventions to reduce the inappropriate medications in the elderly such as educational interventions[20], pharmaceutical interventions[21], medication review[22], computerized systems[23]. The use of drug reference software such as Micromedex or Lexicomp will aid in good prescribing.

CONCLUSIONS

NSAIDs, Diuretics, and Beta-Blockers are the most commonly observed potentially inappropriate drugs. The major and moderate drug interactions that require a change in the therapy can be minimized using a drug-to-avoid list or criteria. Awareness, accountability of prescribing, and drug utilization evaluation can contribute to the rational use of drugs.

AUTHORS' CONTRIBUTIONS

VM: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – reviewing & editing. **KCB:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **PS:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **KK:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **SR:** Data curation, Investigation, Resources, Writing – original draft, Writing – reviewing & editing. **RMK:** Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – reviewing & editing.

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