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RESEARCH ARTICLE

Drug–Drug Interaction Profiles of Common Polypharmacy Regimens in Geriatric Populations

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Abstract: ***Background***: The term polypharmacy which can be defined as the concomitant use of a number of drugs is a problem that is gaining traction in geriatric population as more people with different chronic conditions continue to grow. Though it is one of the requirements when treating the disease, polypharmacy is the cause of a high probability of drug-drug interactions (DDIs) that might result in adverse drug reactions, failure to cure, and even hospitalization. ***Purpose***: The aim of the research was to measure the prevalence, trends, and clinical implications of potential DDIs in older outpatients on polypharmacy, as well as identify important predictors of high-risk interactions. ***Methods***: It was a cross-sectional observational study on 250 geriatric outpatients aged 65 years and above at a tertiary care centre. The patients who received 5 or above medications were chosen. Drug interactions were identified using the Lexicomp, Micromedex and Drugs.com. The interactions were described in terms of the mechanism (pharmacodynamics/pharmacokinetic) and severity (major, moderate, minor). The statistical analysis was performed with the help of SPSS (v27.0) and the logistic regression was applied to identify factors that predict major DDIs. ***Results***: 1, 247 potential DDIs have been identified and 82 percent of patients are affected. 32 percent, medium of 51 percent, and minor of 17 percent were major dealings. Most common interacting classes were antihypertensives, antidiabetics, anticoagulants and psychotropics. Increased scores in comorbidity and polypharmacy (10 or more drugs) were significant predictors of major DDIs ($p < 0.01$). ***Conclusion***: Clinically significant DDIs are highly common in geriatric polypharmacy, particularly in individuals with a high co-morbidity count. Screening of computerized interaction, pharmacist-led interventions, and routine medication review are the measures that should be implemented to improve drug safety and maximize therapy in elderly patients.

Keywords: Geriatric populations, polymharmacy regimens, drug- drug interaction.

INTRODUCTION

The world is aging at an alarming rate and the number of adults above the age of 65 years and above is the fastest growing demographical population in the world today. The population of people with age 65 and above is projected to rise by more than 1.5 billion by 2050 (World Health Organization, 2010, p.1). With higher life expectancy, there is a rise in chronic multimorbidity, a condition where people have many long-term conditions as cardiovascular disease, diabetes mellitus, osteoarthritis, chronic kidney disease, and neurodegenerative disorders [2]. This clinical complexity is bound to result in polypharmacy as it is conventionally described as taking more than five medications at the same time [3].

Although polypharmacy may be clinically warranted as a treatment of multimorbidity, it greatly predisposes geriatric patients to drug-drug interactions (DDIs), adverse drug reactions (ADRs) and hospitalizations (4). The aging process is linked to physiological alterations, which alter the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (drug-receptor sensitivity and response) of drugs and makes older people more prone to drug-related damage [5]. Research has approximated 30-60 percent of older adults to have at least one clinically significant DDI, 15-20 per cent of which result in severe adverse effects including falls, bleeding, renal failure or delirium [6]. Besides, the interactions associated with polypharmacy are also a cause of about 10 15% of inadvertent hospital admissions in older adults [7].

DDIs can either be pharmacodynamic (due to additive, synergistic or antagonistic effects of drugs at their intended site of action), or pharmacokinetic (when one drug changes the metabolism or bioavailability of another) (usually by cytochrome P450 [CYP450] enzyme inhibition or P-glycoprotein transport inhibition). Considering warfarin, patients taking NSAIDs and warfarin are at risk of increased bleeding due to both pharmacokinetic competition at the protein binding location and pharmacodynamic enhancement of the anticoagulant effect [9]. On a similar note, combination of ACE-blockers and potassium-sparing

deuretics like spironolactone may be results in the fatal hyperkalemia [10]. These illustrations becomes the most complicated contact of the drug mechanisms in seniors with a vast number of medications.

Several reports have reported that the prevalence of potentially harmful DDIs is high in geriatric practice. A European cohort study with large scale revealed that more than half of elderly patients belonging to eight or more medications were subjected to at least one major DDI [11]. The rate of ADRs that can be avoided as a result of drug interactions is even greater in developing regions, where medication reconciliation systems are frequently underutilized [12]. Some of the factors that lead to this are broken deliveries of healthcare, self-medication, poly-prescribing by various specialists, and inaccessibility to pharmacist-led medication review [13]. Moreover, age-associated cognitive impairments and lack of health literacy increase the risks of misusing drugs and engage in poor adherence, which increases the risk of detrimental interactions [14].

The technological innovations have made it possible to use clinical decision support systems (CDSS) and drug-interaction database like Micromedex, Lexicomp, and Drugs.com Interaction Checker in order to identify potential DDIs prior to causing clinical damage [15]. Nonetheless, even though they are available, there is still a lack of integration into the daily clinical practice. Clinicians tend to miss or ignore warnings because of over-reliance on automated alerts, failure to review medication regularly, and alert fatigue [16]. Thus, the multidisciplinary method involving proactive, technological screening, pharmacist monitoring, and physician education is crucial in the patient care of older adults regarding medication safety management.

New principles like deprescribing, which is the gradual reduction of prescribed drugs when the harm is greater than the good, are becoming relevant in reducing the risks of polypharmacy [17]. On the same note, the pharmacogenomic testing is an emerging instrument that can be used to identify patients who have genetic variations in metabolism of drugs (e.g., polymorphisms in the CYP2D6, CYP3A4 enzymes), and provide a personalized approach to prevent DDIs [18].

Although a lot of research has been done, the majority of the studies involve independent interactions or a particulartherapeutic classes as opposed to polypharmacy profiles in geriatric patients in practice. Additionally, local information about the trend, intensity, and clinical significance of DDIs within health care environments on an outpatient basis are unavailable especially in understaffed healthcare systems.

In this study, the authors will examine the prevalence, trends and clinical impacts of drug-drug interactions in regularly used polypharmacy in geriatric patients. It also aims at determining demographic and clinical risk factors in relation to high-risk interactions and determining the possibility of technology-assisted screening in preventing DDI. This paper offers an evidence-based contribution to enhance safer prescribing and better clinical outcomes as well as enhance the role of pharmacists in geriatric medications management by explaining the interaction landscape of polypharmacy in geriatrics.

MATERIALS & METHODS

Study Design

The research purpose was to determine the prevalence, nature and clinical importance of the possible drug-drug interactions (DDIs) among geriatric outpatients with polypharmacy. A cross-sectional observational research was done in this connection. The research was conducted during the period between January and September, 2024, and at Geriatric Medicine and Internal Medicine unit of a teaching hospital which is a tertiary care unit.

The choice of this design is determined by the fact that the trends of prescribing and DDI profiles can be compared within the real-life environment of the no intervention being done and, consequently, determine the scope of risks of polypharmacy as it occurs under the normal clinical conditions.

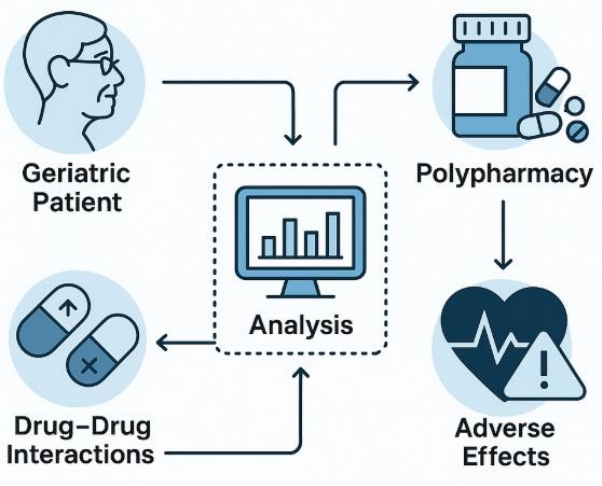

Fig.1. Drug-drug interaction analysis

As can be seen in this figure 1, the idea of drug-drug interaction (DDI) analysis in geriatric polypharmacy is based on the premise that combination therapy can cause undesirable healthcare conditions in elderly individuals.

Study Population

Inclusion Criteria

1. Out the patient clinics, patients, 65 and above.
2. Patients with 5 or more polypharmacy threshold.
3. The capacity to offer an informed consent or a legal surrogate to the same.

Exclusion Criteria

1. The patients were the palliative care patients and the acute hospitalized patients.

2. Patients who are taking short term pain killers or antibiotic within less than 7 days.
3. Incomplete drug history or the absence of the desire to do so.

The enrolment of all the participants, whom the total amounted to 250, was accomplished with the assistance of a systematic random sampling that was grounded on the inclusion criteria. The previously performed research informed the size of the sample that quoted prevalence of clinically significant prevalent DDIs among the elderly (power= 80, 0.05 = 0.05) [11].

Ethical Considerations

The research design was also considered and it has to be approved by the Institutional Ethics Committee (IEC Approval No: GMC/GERI/2024/07). The purpose of the study was explained to all the respondents who signed the informed consent, the role and participation would be voluntary and confidentiality.

Data Collection

The structured case record form (CRF) also was used to collect data and it contained:
a. Demographics Age, sex, BMI, smoking/alcohol history.
b. Comorbidities, Charlson Comorbidity Index (CCI). Diagnoses.
c. Drugs Name, dosage, route, frequency and duration-Generic.
d. Prescriber data: Data regarding the number of various prescribers that were engaged in the regimen.
The actual interview of the patient and reading of the prescription were conducted to ensure that appropriate and correct prescription of medication was done.

Drug Interactions Recognition and Location.

1. Interaction Screening Tools.

Three available drug-interaction databases were used to process the medication list of each patient and give possible DDIs.
a. Lexicomp Drug Interactions
b. Micromedex Drug-Reax System
c. Interaction Checker Drugs.com.
It was necessary to consider the interactions only after being verified with at least two of the three instruments to be specific and decrease false [15].

2. Mechanism Classification System

Generally, they are generally found at a molecular level.
Pharmacokinetic Interactions: interactions that alter the bioavailability, distribution, metabolism or elimination (e.g. CYP450 inhibition/induction, a change in renal clearance).
Pharmacodynamic Interactions Pharmacologic or physiologic Additive, synergistic or antagonistic pharmacologic interaction with pharmacological target or physiology.

3. Classification by Severity

Any DDI was classified as one of the following examples in the scale of severity applied by lexicomp and Micromedex:
a. Major: It can cause death, or it can lead to a direct medical intervention (e.g. warfarin -NSAID).
b. Moving: Can also contribute to the further worsening of the clinical/dosage adjustment.
c. Minor: Clinical innocence, and self-limiting, in general.
4. Grades of Clinical Documentation.
This was to report of the quality:
a. Set: backed up by some clinical studies or a meta-analysis.
b. Most probable Case report or pharmacological.
c. Potential: there is no sufficient evidence or the hypothesis.

Data Analysis

1. Quantitative Analysis

In brief, potentiality of DDIs was identified among patients. This was in order to find the following descriptive statistics:
Mean patient drug per capita. Table 1 severity-wise, mechanism and drug class Frequency and percentage of DDIs.

2. Statistical Analysis

The SPSS v27.0 (IbM Corp.) was used to perform the analysis of data.
Continuous (i.e. number of drugs, age) variables were of the shape of mean value and SD. Frequencies and percentages were categorical variables (e.g. sex, type of interaction).

Inferential statistics:

Pearson correlation (r) was used to determine the associations between the frequency/severity of DDIs and the number of medications. Chi-square test i.e. gender and presence of DDI was used to compare the categorical variables. The independent predictors of the major DDIs that adjusted the confounding variables (age, comorbidity index and number of prescribers) were estimated with multivariate logistic regression.
The p-value that was found to be below 0.05 was considered significant.

Therapeutic Drugs Categories and Evaluated courses.

The drugs were categorized as per the Anatomic Therapeutic Chemical (ATC) system of classification as:
a. The Cardiovascular: ACE-inhibitors, beta-blockers, duretics, statins.
b. Drug of Antidiabetic: Metformin, sulfonylurea, DPP-4.
c. Antiplatelets and the Anticoagulant:Few are Warfarin, aspirin, clopidogrel.
d. Antipsychotics, benzodiazepine CNS drugs, SSRIs.
e. GIT and renal medication: Phosphate binders, proton pump inhibitor.

To determine the suitability of such interactions between the elderly patients, interactions among these groups and among them were studied through Beers Criteria (2019) [19].

The validation and quality control.
This would then need a senior pharmacist and clinical pharmacologist to check and ensure that data entry and analysis are accurate. Duplicates were also cross checked and ambiguous DDI classifications were expertly judged.

They were to perform pilot test first (n = 25) because the CRF would be subjected to establish that the processes of finding DDI are valid. The conclusion analysis did not involve pilot data.

RESULTS & ANALYSIS

1. Demographics and Clinical Characteristics.

The geriatric patients under analysis were equal in number 250 patients (58 females and 42 males), the average age of geriatric patients was 71.4 with a standard deviation of 6.2. The mean number of comorbidities (4.1) along with the standard deviation of comorbidities (1.3) of the patients was observed to be high in the burden of chronic disease as well as the mean comorbidity index (CCI) of the patients was 3.8 with a standard deviation of 0.9.
Top chronic conditions were the hypertension (76%), type 2 diabetes (61%), coronary artery disease (40%), osteoarthritis (32%) and chronic kidney disease (22%).

Table 1. Demographic and Clinical Characteristics (n = 250)

Parameter	Mean ± SD / %
Age (years)	71.4 ± 6.2
Female (%)	58%
Mean CCI score	3.8 ± 0.9
Mean number of comorbidities	4.1 ± 1.3
Mean number of prescribed medications	8.3 ± 2.6
Hypertension	76%
Type 2 Diabetes Mellitus	61%
Coronary Artery Disease	40%
Osteoarthritis	32%
Chronic Kidney Disease	22%

2. Polypharmacy Drugs Patterns and Usage.

Between 5 and 14 medication (mean = 8.3) was prescribed to patients. Antihypertensives (82%), antidiabetics (67%), anticoagulants/antiplatelets and CNS-active agents (38%), were the most common classes of drugs used.

The biggest prescription was made up of cardiovascular drugs (ACE inhibitors, beta-blockers, calcium channel blockers, and statins, 42, 24 and 18 percent, respectively).

3. Drug-Drug Interactions Prevalence and Distribution.

There were 250 patients that yielded 1,247 possible DDIs. Mean number of DDIs/patient was 4.99 + 2.2 and 82 percent of the patients had at least one interaction. Amongst all the DDIs identified, 32 percent were major, 51 percent were moderate, and 17 percent were minor (Table 2 and figure 2).

Table 2. Classification of Drug–Drug Interactions by Severity

Severity Category	Frequency (n)	Percentage (%)	Example Interaction
Major	399	32%	Warfarin + NSAIDs → Bleeding risk
Moderate	636	51%	ACE inhibitor + Spironolactone → Hyperkalemia
Minor	212	17%	Metformin + PPIs → Reduced absorption
Total	**1,247**	**100%**	—

Patients prescribed **≥10 medications** exhibited significantly higher DDI prevalence ($p < 0.001$).

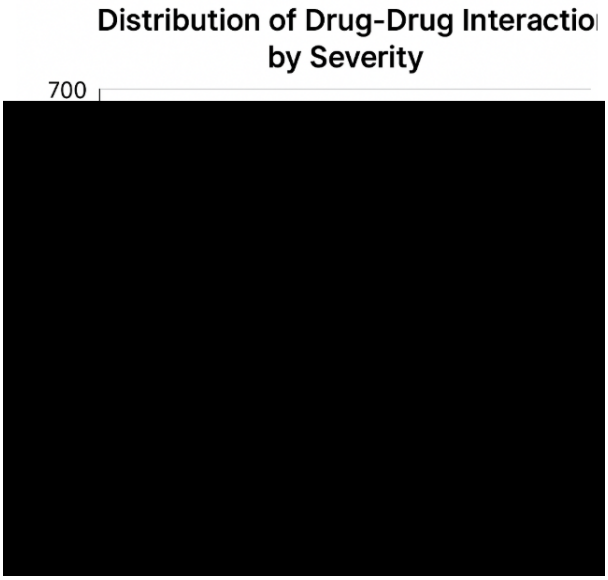

Fig.2. Distribution of drug drug interaction by severity

4. Mechanistic Classification of Interactions

Pharmacokinetic processes explained 61% of all DDIs and pharmacodynamic interactions were 39% shown the table 3 and figure 3.

The most frequent pathway of pharmacokinetic interaction was a CYP450 enzyme modulation (mostly CYP3A4 inhibition or induction). Well-known cases were simvastatin + amlodipine (CYP3A4 inhibition resulting in statin toxicity) and warfarin + metronidazole (CYP2C9 inhibition causing the excess anticoagulation).

Table 3. Mechanistic Distribution of Drug–Drug Interactions

Mechanism Type	Frequency (n)	Percentage (%)	Common Example
Pharmacokinetic	760	61%	Simvastatin + Amlodipine
Pharmacodynamic	487	39%	Benzodiazepine + Opioid
Total	**1,247**	**100%**	—

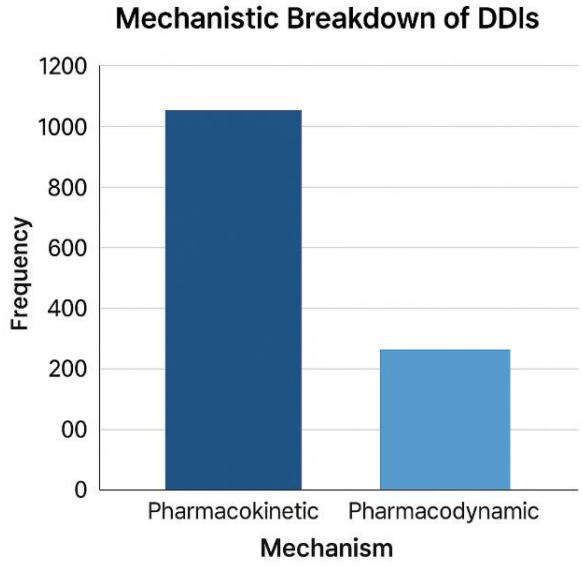

Fig.3. Mechanistic breakdown of DDIs

5. Drug Classes which are Most Frequently Involved in DDIs

This was found to be the case when drug classes were analyzed, with the most frequent culprits being antihypertensives, antidiabetics, anticoagulants, and psychotropics.

Table 4. Drug Classes Most Frequently Involved in Major DDIs

Drug Class	Frequency (n)	Percentage (%)	Representative Drug Pairs
Cardiovascular drugs	175	44%	ACE inhibitor + Spironolactone
Anticoagulants/Antiplatelets	96	24%	Warfarin + NSAIDs
CNS agents	70	18%	Benzodiazepine + Antidepressant
Antidiabetic agents	36	9%	Metformin + Contrast agents
GI agents (PPIs, laxatives)	22	5%	PPI + Clopidogrel

The most common major DDI (12% of all major interactions) was warfarin-NSAID, and the next common major DDI was ACE inhibitor-spironolactone (9%) and benzodiazepine-SSRI (7%) shown the table 4.

Correlation and Risk Factor Analysis.

A positive relationship between number of prescribed drugs and frequency of DDIs was found to be strong and positive ($r = 0.72$, $p < 0.001$).

Multivariate logistic regression revealed that polypharmacy (10 or more drugs), greater CCI score (more than 4), and more than two prescribers were independent predictors of the major DDI phenomenon ($p < 0.01$) shown the table 5.

Table 5. Predictors of Major Drug–Drug Interactions (Multivariate Logistic Regression)

Variable	Odds Ratio (OR)	95% CI	p-Value
Polypharmacy (≥10 drugs)	3.5	2.1–6.3	<0.001
CCI >4	2.8	1.6–4.9	<0.01
≥2 Prescribers	2.1	1.3–3.8	0.02
Female gender	1.2	0.8–1.9	0.21 (ns)

These results show that polypharmacy and comorbidity burden are the most decisive predictors of the risk of DDI among the elderly.

DISCUSSION

The current research indicates that potential DDIs are very common (82 percent) in geriatric patients who are under polypharmacy as it has been documented in previous studies [6, 4]. The reality that on an average, there are five DDIs per patient accentuate the clinical cost of multi-drug regimens among the elderly.

The extensive contribution of pharmacokinetic interactions (61 percent) is the most common, especially through CYP450, which is a manifestation of the complexity of metabolism in older physiology. A decrease in hepatic enzyme activity, renal clearance, and changes in body composition have been identified to lead to unpredictable pharmacokinetic, which increases the chances of drug accumulation and toxicity [5].

Cardiovascular and CNS agents were the most common agents to major interactions which were consistent with global data of high-risk combinations of antihypertensives, anticoagulants, and psychotropics [10]. The usual warfarin-NSAID interaction as in this study, is a dual-risk interaction of either pharmacodynamic or pharmacokinetic. These combinations may lead to severe bleeding, and clinical attention and regular INR surveillance may be required [9].

CONCLUSION

This paper identifies the clinical importance and high occurrence of drug-drug interactions among elderly patients with polypharmacy. The results highlight the increasing pharmacological burden of older adults with an average of almost five and eighty-two percent of participants having at least one potential DDI. The dominance of both pharmacodynamic and pharmacokinetic interactions, which are mainly regulated by the enzymes of cytochrome P 450 and the changes in the cardiovascular and the central nervous systems showsthat the complexity of risks of the simultaneous medication are used in the older generation. Categorically, polypharmacy among geriatrics is a problem of severe concern over medication safety. Early detection, deprescribing and integration of pharmacist knowledge are proactive mechanisms that can ensure the prevention of avoidable drug-related harm. The pharmacotherapy of the elderly needs to be optimized in a manner that the need of the therapy subsists, and safety as well as longevity coincide with better living quality.

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