

PREDICTORS ASSOCIATED WITH ADVERSE DRUG REACTIONS AMONG GERIATRIC PATIENTS IN AN OUTPATIENT CLINIC

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ABSTRACT

Objective: The process of aging involves an individual's structural and functional depravity of their organ systems often results in compromised pharmacological principles of the prescribed drugs. Multimorbidity and polypharmacy along with change in pharmacokinetic and pharmacodynamic responses of drugs predispose the elderly to adverse drug reactions (ADRs). The present study was aimed to identify and report the characteristics and incidence of ADRs among geriatrics in an outpatient clinic.

Methods: This was a 6-month prospective hospital-based observational study among patients of either sex aged 60 years and above visiting an outpatient clinic at the study site. The suspected ADRs were categorized according to the Will's and Brown classification system. Causality of these ADRs was verified by applying the WHO-UMC criteria and the Naranjo's scale. Severity and preventability of the ADRs were classified using the modified Hartwig and Siegel scale and modified Schumock and Thornton scale, respectively. Multivariate logistic regression was used to determine the risk factors for developing ADRs.

Results: Among the 365 patients monitored, 57 (15%) patients experienced 60 ADRs. Therapeutic classes of drugs frequently associated with ADRs were the drugs used in hypertension (27 [45%]). Patients presenting with amlodipine (9 [15%]) induced pedal edema were observed with the highest frequency of ADRs. Polypharmacy (OR: 1.619, 95% confidence interval: 0.957–2.741, p=0.021) was observed as the influential risk factor for ADRs.

Conclusion: Pharmacist's services and involvement in geriatric patient's centered care can be associated with their improved health, quality of life and economic outcomes, a reduction in medicine-related adverse events, and limiting the morbidity and mortality in this age band.

Keywords: Geriatrics, Outpatient, Adverse drug reactions.

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INTRODUCTION

The 21st century has witnessed a significant and distinctive global demographic phase called "population aging" [1]. India is in its point of demographic transition and the aging population is growing faster [2]. Indian elderly represents 12.8% of the entire global elderly population [3]. Aging is an intricate process which is associated with several physiological changes of the organ systems exposing them to multiple chronic comorbidities such as hypertension, diabetes, dyslipidemia, and depression [4] which lead to the rigorous use of multiple drugs, in turn, call for extensive treatment regimens [5]. The use of multiple drugs in a patient is known as polypharmacy [6] and is soundly associated with multiple negative health consequences which include increased health-care costs due to the increase in harmful drug interactions [7], adverse drug reactions (ADRs) [8,9], functional impairment, etc., leading to unnecessary expenses in health care.

Globally, studies conducted have suggested ADR-related hospital admissions at a rate of 10% and 11% in geriatrics [10,11]. They account for almost two-thirds of all drug-related hospital admissions and emergency department visits [12,13]. ADRs result in increased health-care costs [14]. The previous studies have found that those presenting with an ADR have an extended hospital stay and succeeding outpatient health service use which is of higher rate than those without ADRs [15,16]. In a developing country like India, the coverage of insurance policies is limited and thus increasing out of pocket medical expenses resulting in economic burden. They have important consequences and one-third of such events are preventable or ameliorable. Hence, active

pharmacovigilance (PV) surveillance activities, spontaneous reporting of ADRs, and conducting observational studies are important tools for identification, evaluation, and prevention of ADRs, minimalizing the financial burden on the victims.

PV is a hoard of activities in relation to the detection, assessment, understanding, and prevention of ADRs caused by medications. Drug safety and PV remain an active and rational discipline. PV studies need to be scrutinized in the older age group due to polypharmacy, which is a source of ADRs, prompting to hospital visits. In severe cases, this may lead to hospital readmissions resulting in additional treatment cost to cure the ADRs.

PV plays a pivotal role in confronting the risks posed by the increasing range and potency of medicines and to a greater extent in geriatrics, all of which carries an inexorable and sometimes an unpredictable source of harm. Hence, this study aims to assess the causative drugs, severity, and various factors responsible for causing an ADR and assess their preventability, causality, predictability, and severity in geriatric patients visiting an outpatient setting of a tertiary care hospital.

METHODS

This prospective observational study was carried out in elderly patients visiting a geriatric outpatient clinic of a tertiary care hospital in Bengaluru. Ethical clearance was obtained from the Institutional Ethics Committee. The study was conducted for a period of 6 months from October 2017 to April 2018. Patients of either sex, above 60 years visiting the clinic, were enrolled in the study. Those

undergoing treatment with anticancer drugs, receiving hospice care, and those not willing to participate in the study were excluded from the study.

Appropriate consent was obtained from the patients before the data pertaining to patient demographics, diagnosis, prescribed medications, treatment durations and indications for each drug was recorded. Case notes and other relevant medical records along with patient interview were reviewed for the likelihood of occurrence of an ADR. Patients' who presented with suspected ADRs were followed up every 2 weeks for a minimum period of 8 weeks. The nature of the suspected ADR, suspected medications, and relevant clinical information was recorded. The suspected ADRs were categorized according to Wills and Brown classification system. Causality of ADRs was verified by applying the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale and Naranjo's criteria. ADR severity and preventability were classified using modified Hartwig and Siegel scale and modified

Schumock and Thornton scale, respectively. Patients who presented with ADRs were also reviewed for their management and outcomes.

Collected data of the suspected drug were categorized and presented according to system organ classification. The suspected ADRs were reported to the treating physician. Patient details were analyzed using descriptive statistics. Risk factors for ADRs were determined at $p < 0.05$ by investigating the effects of age, gender, number of diseases, and number of drugs prescribed. Multivariate logistic regression was used to evaluate the influence of these risk factors on the development of ADRs. All statistical calculations were performed using the Statistical Package for the Social Sciences Version 22.0 for Windows®. $p < 0.05$ was considered statistically significant.

RESULTS

Over the study period, 365 (male = 61% and female = 38.6%) patients who visited the geriatric clinic were assessed. Most of the patients visiting the clinic were between the age groups of 60 and 69 years (55.3%). Two hundred and two (55.34%) patients had at least 1-2 diseases. Two hundred and forty-eight (67.9%) patients had at least 1-5 drugs in their prescription and only 10 (2.7%) patients were observed to have more than 10 drugs in their prescription (Table 1).

Of the 365 patients who were monitored, 57 (15%) patients experienced an ADR. A total of 60 suspected ADRs were noted in these patients. Antihypertensives (27 [45%]) and antidiabetics (7 [11.5%]) were the common drugs causing the suspected ADRs. The most common ADRs due to the antihypertensives (45%) were pedal edema (9) due to amlodipine (9), hyperkalemia, and cough. The suspected ADRs due to antidiabetics were hypoglycemia (2) and pruritis (2) due to insulin (Table 2).

The causality of the suspected ADRs was assessed using the WHO-UMC criteria where 78.4% of the reactions were classified as probable, Naranjo's scale, in which 90% of the suspected adverse reactions are probable (Table 3).

Table 1: Demographic variables of participants

Patient characteristics	Number	%
Sex		
Male	224	61
Female	141	38.6
Age		
60-69	202	55.3
70-79	132	36.2
>80	31	8.5
Number of diagnosis		
1-2	202	55.34
3-4	160	43.83
>5	3	0.8
Number of concurrently prescribed medications		
1-5	248	67.9
6-10	107	29.4
>10	10	2.7

Table 2: Spectrum of different ADRs and drug (s) implicated

Therapeutic class	Number of ADRs (n=60) (%)	ADRs (n)	Causative drugs (n)
Antihypertensives	27 (45)	Pedal edema (9), hyperkalemia (3), cough (3), hyponatremia (2), hypokalemia (1), ototoxicity (1), headache (1), dyslipidemia (1), giddiness (1), bradycardia (1), itching (1), gynecomastia (1), orthostatic hypotension (1), insomnia (1)	Amlodipine (9), furosemide (4), losartan (3), olmesartan (3), metoprolol (2), spironolactone (2), atenolol (1), ramipril (1), telmisartan (1), torsemide (1)
Antidiabetics	7 (11.5)	Pruritis (2), hypoglycemia (2), insomnia (1), headache (1), flatulence (1)	Insulin (2), metformin (2), glimepiride (1), sitagliptin (1), voglibose (1)
Analgesics	3 (5)	Constipation (2), hematuria (1)	Tramadol (2), ibuprofen (1)
Antibiotics	3 (5)	Diarrhea (2), dyspepsia (1)	Azithromycin (1), cefpodoxime (1), nitrofurantoin (1)
Antiplatelets	3 (5)	Hematemesis (2), tinnitus (1)	Aspirin (3)
Antipsychotics	3 (5)	Blurring of vision (1), drowsiness (1), headache (1)	Zolpidem (1), lorazepam (1), clonazepam (1)
Anticoagulants	2 (3.3)	Epistaxis (1), melena (1)	Nicoumalone (2)
Bronchodilators	2 (3.3)	Epistaxis (1), tachypnea (1)	Budesonide (1), Salbutamol (1)
Antihyperlipidemic	2 (3.3)	Hyperglycemia (1), itching (1)	Atorvastatin (1), Rosuvastatin (1)
Antitubercular	2 (3.3)	Nausea (2)	Combination of rifampicin, isoniazid, ethambutol (2)
Thyroid supplements	2 (3.3)	Giddiness (1), hyperglycemia (1)	Levothyroxine (2)
Antivirals	1 (1.7)	Malaise (1)	Lamivudine (1)
Cardiac glycoside	1 (1.7)	Bradycardia (1)	Digoxin (1)
Mood stabilizer	1 (1.7)	Hypothyroidism (1)	Lithium (1)
Vitamin supplements	1 (1.7)	Itching (1)	Vitamin B12 (1)

ADRs: Adverse drug reactions

Thirty-nine (65%) of the suspected reactions were mild in severity according to the modified Hartwig and Siegel's severity scale (Table 4).

Of the 60 ADRs noted, 10 (16.65%) were classified under the metabolic and nutritional disorders and 10 (16.65%) were categorized under body as a whole general disorder according to the system organ class affected (Table 5).

Multivariate logistic regression was used to analyze the predictors of the suspected ADRs. Predictors which were determined were gender (female), number of diseases (>1), and polypharmacy (>5 drugs). Polypharmacy showed significance in the present study ($p=0.021$); $p<0.05$ was considered statistically significant (Table 6).

DISCUSSION

ADR poses a major threat to the health-related quality of life in frail elderly patients. With the advancement in age, the prevalence of drug use increases proportionally along with multiple comorbidities, thereby exposing geriatrics to an increased risk of drug-induced harm.

The present study observed 57 (15%) patients had ADRs which was similar to the study conducted by Mandavi *et al.*, in 2010, where 10% of elderly patients experienced an ADR. A total of 60 ADRs occurred in these patients [17]. These findings were similar to the study conducted by Figueiredo *et al.* in a Brazilian teaching hospital where 50 (21.1%) patients presented with 62 ADRs [18].

The study observed that patients were between the age groups of 60 and 69 ($n=202$; 55.3%), 70–79 ($n=132$; 36.2%), and >80 ($n=31$; 8.5%). It was observed that the ADRs were primarily seen in 35 (61.4%) patients aged between 60 and 69 years. Among the patients, 18 (75%) of them were female. A study performed by Harugeri *et al.* disclosed typical results where 184 (33.4%) patients were between the same age group. One hundred and thirty-five (35.9%) female patients presented with ADRs [3].

Geriatrics has high levels of disease burden and a corresponding increase in medication utilization. The study indicated that 23 (40.4%) patients who developed the ADRs had two diseases where 45% of them were prescribed with 1–5 drugs. Mandavi *et al.* conducted a study between 2009 and 2011 indicated similar results with 41% of the patient having two disease conditions with 11% of patients taking 6–10 medications [17]. Multiple diseases make patients more vulnerable to ADRs due to the use of many drugs [19]. They have higher prevalence of chronic disease and comorbidities, often requiring more medication to multiple illnesses, thus increasing ADR risk. The average number of drugs per prescription in our study was 4.84 which are higher than the WHO optimal level of ≤ 3 , indicating polypharmacy [20]. A higher rate of polypharmacy was seen in a study by Nandagopal *et al.*, in Hyderabad, with an average of 7.02 [21]. Although the average in our study was lesser, it still requires that caution be taken to diminish the potentially higher risk of adverse health outcomes among the elderly.

In our study, hypertension (203 [55.6%]) and diabetes mellitus (168 [46%]) were the two most commonly occurring chronic conditions. While the findings in our study were analogous to a study conducted by Nagaraju *et al.*, in Bengaluru [22], they were not the same as when compared to a study by Mahesh *et al.* where diseases of the cardiovascular system (39.13%) and endocrine system (25%) were mostly reported [23].

The study revealed that the most common category of drugs that caused the ADRs was antihypertensives ($n=27$; 45%). The most prevalent drug which was involved in the response was amlodipine which manifested 9 (15%) of the reactions. The observations were undeviating with other studies where antihypertensives were often related with ADRs in the elderly. Our study showed that antihypertensives were the most commonly prescribed drug class followed by antidiabetics. In comparison to this, a study by Nandagopal *et al.* revealed that

antidiabetics (21.9%), followed by antibiotics (17.78%), were frequently prescribed [21].

Table 3: Causality assessment of suspected ADRs

Assessment	n (% of ADR) (n=60)
WHO-UMC scale	
Probable	47 (78.4)
Possible	13 (21.6)
Naranjo's causality	
Probable	54 (90)
Possible	6 (10)
Karch and Lasagna's scale	
Probable	38 (63)
Possible	18 (30)
Conditional	4 (6.66)

ADRs: Adverse drug reactions

Table 4: Assessment of severity, preventability, and predictability of suspected ADRs (n=60)

Parameters	n	%
Modified Hartwig and Siegel's severity scale		
Mild	39	65
Moderate	20	33.33
Severe	1	1.66
Modified Schumock and Thornton's preventability scale		
Definitely preventable	1	1.66
Probably preventable	47	78.33
Not preventable	12	20
Predictability scale		
Predictable	46	76.66
Not predictable	14	23.33

ADRs: Adverse drug reactions

Table 5: System organ classification associated with ADRs (n=60)

System organ class	Number of ADRs (n=60)	%
Metabolic and nutritional disorders (800)	10	16.65
Body as whole general disorders (1810)	10	16.65
Gastrointestinal system disorders (0600)	9	15
Central and peripheral nervous system disorders (0410)	6	10
Respiratory system disorders (1100)	6	10
Endocrine disorders (0900)	3	5
Skin and appendage disorders (0100)	3	5
Psychiatric disorders (0500)	3	5
Platelet, bleeding, and clotting disorders (1230)	2	3.33
Cardiovascular disorders, general (1010)	2	3.33
Vision disorders (0431)	1	1.65
Urinary system disorders (1300)	1	1.65
Application site disorders (1820)	1	1.65
Vascular (extracardiac) disorders (1040)	1	1.65
Reproductive disorders, male (1410)	1	1.65
Hearing and vestibular disorders (0432)	1	1.65

ADRs: Adverse drug reactions

Table 6: Predictors associated with the suspected ADRs

Risk factor	Odds ratio (multivariate logistic regression)	95% CI		p-value
		Lower limit	Upper limit	
Gender (female)	1.176 (0.658–2.104)	0.658	2.104	0.584
Number of diseases (>1)	0.581 (0.292–1.154)	0.292	1.154	0.121
Polypharmacy (>5 drugs)	2.313 (1.134–4.719)	1.134	4.719	0.021***

CI: 95% confidence interval, degree of freedom (df) = 1. p<0.05 was considered statistically significant

According to the systems organ classification, 16.65% of the ADRs affected the metabolic and nutritional disorders. The findings were similar to the study conducted by Harugeri *et al.* where 33.2% of the metabolic and nutritional disorders were precipitated due to the ADRs [3]. The disorders included hypoglycemia with insulin, hypokalemia with diuretics, and hyperkalemia with spironolactone.

The most commonly identified ADR was pedal edema due to amlodipine presented in 15% of the patients. The findings were nearly similar to the study by Mandavi *et al.* where 21.1% of the patients presented with peripheral edema due to amlodipine [17]. Reported frequency rates for edema with calcium channel blocker therapy are quite varied ranging from 5% to 70%.

To improve the validity of the analysis, causality assessments were implemented using the WHO-UMC criteria and the Naranjo algorithm. Based on the WHO-UMC criteria, 47 (78.4%) ADRs were probable and 54 (90%) presented probable with respect to the Naranjo's. Pirmohamed *et al.* in the United Kingdom in the year 2004 employed the Naranjo's scale to analyze the causality of the ADRs, where 68.73% of them were probable [24].

Severities of the ADRs were evaluated using modified Hartwig and Siegel's severity scale where 33.33% of ADRs were moderate in severity. The previous studies exhibited similar results at 48.83% of moderate severity. The ADRs of moderate severity had predominance in the gastrointestinal system. Due to which, few of the patients required hospitalization, but the study was limited to only outpatients, length of hospitalization was not analyzed. Modified Schumock and Thornton scale were employed to evaluate the preventability of the ADRs. The present study revealed that 47 (78.33%) ADRs were probably preventable. Most drugs were affecting the gastrointestinal system and the cardiovascular system. According to the predictability scale, 46 (76.66%) reactions were predictable.

Female gender, chronic diseases, and number of drugs (≥ 5) were identified as the risk factors for developing ADRs which were consistent with literature [25-28]. The present study showed odds of 2.31 among those with multiple medications in developing ADRs. This was consistent with a study conducted by Nguyen *et al.* where subjects using ≥ 9 medications were 2.33 times more likely to develop a reaction indicating a positive relationship between the number of medications and ADRs [29]. High prescribing rates, although associated with severity of illness and severe morbidity, may also increase the occurrence of ADRs [30]. This necessitates a need to develop and implement strategies to minimize ADRs and increase safety among the elderly.

CONCLUSION

Older people are a heterogeneous population, with high levels of morbidity and polypharmacy. As the benefits of medications are always accompanied by harmful effects, it is not surprising that they are at increased risk of developing ADRs. The diagnosis of ADRs in these patients can be challenging. Patients in outpatient care and some post-acute settings have complex medication regimens, at times prescribed by multiple clinicians with far less monitoring compared with hospitalized patients. There exists scarce evidence regarding the ADRs in outpatient clinics.

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AUTHORS' CONTRIBUTIONS

All authors have made substantial contributions to the conception and design, acquisition of data, analysis, and interpretation of data. All authors have approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors report no conflicting interests with respect to this study. No sources of funding were subjected during the conduction of this study.

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