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ADVERSE DRUG INTERACTIONS IN ELDERLY HOSPITALIZED PATIENTS: A PROSPECTIVE ANALYSIS

Aswathi Susan George, M. Ramesh * and Juny Sebastian

Department of Pharmacy Practice, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, Sri Shivarathreeshwara Nagar, Mysuru - 570015, Karnataka, India.

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Correspondence to Author:
Dr. M. Ramesh

Professor and Head,
Department of Pharmacy Practice,
JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University,
Sri Shivarathreeshwara Nagar,
Mysuru - 570015, Karnataka, India.

E-mail: mramesh@jssuni.edu.in

ABSTRACT: Objective: To determine the incidence, characteristics, predictors and cost associated with the management of adverse drug interactions (ADIs) in elderly population. **Methods:** The prospective, intensive and interventional study included all patients taking at least two medications who were elderly admitted to medicine or surgery wards of a tertiary care hospital and were followed untill discharge. ADIs were identified using standard references. **Results:** A total of 1992 drug-drug interactions were detected from 659 patients over the nine month study period. Incidence of Drug-Drug Interactions (DDI) and ADI was 59.05% and 7.34% respectively. About 5.9% of DDIs resulted in adverse reactions. Of the total Adverse Drug Reactions (ADRs) detected, 31.5% (89 ADIs in 82 patients) of ADRs were due to DDIs. Pharmacodynamic interactions accounted for 73.5% of DDIs. There was significant association between occurrence of ADIs with three or more diagnosed diseases, three or more chronic diseases, administration of >10 medications and >7 days of hospital stay. The total direct cost associated with the management of ADIs was INR 15, 638/- of which moderate interactions accounted for the maximum (INR 13, 572/-). **Conclusion:** Clinicians need to be aware of most common ADIs occurring in the clinical practice and should be cautious in using the medications especially in elderly patients as they are more susceptible to ADIs. Clinical pharmacist can play a vital role in the detection, prevention and management of ADIs which can result in improved therapeutic outcomes and decreased unnecessary healthcare expenditure.

INTRODUCTION: Drug-drug interactions (DDIs) are a predictable and preventable type of adverse drug event (ADE) which occurs when an interacting agent affects the pharmacokinetics or pharmacodynamics of an index drug and exacerbates a known untoward event of the index drug. This can lead to an increase in toxicity or reduction in therapeutic efficacy of the index drug [1-3].

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Preventable drug interactions are the cause of approximately 20 - 30% of all adverse drug reactions (ADRs), of which 70% requires clinical attention and 1 - 2% is even life threatening and also account for one-half of all ADR costs [1, 4].

The issue of DDIs need more attention in elderly hospitalized patients due to severity of disease, chronic diseases, comorbid conditions, polypharmacy, complex therapeutic regimen and frequent modification in therapy [5, 6]. Several factors increase the complexity of management of drug interactions in elderly people such as age-related physiological changes in pharmacokinetic and pharmacodynamic characteristics, polypharmacy, impairment in many organ functions particularly

liver and kidney, multiple disorders, inter individual variability, frailty, reduced homeostasis, psychological factors, inadequate nutritional status, unintentional noncompliance and increased sensitivity to drug effects, leading to a higher percentage of ADR [7 - 9]. Iatrogenic complications which are one of the major problems affecting the elderly may be primarily attributed to polypharmacy [2].

It has been reported that the actual risk of DDI increases from 16% with three medications to 72% with six medications and 100% with seven or more medications [10]. Thus for elderly patients, poly-pharmacy complicates drug therapy, increases economical burden and is a challenge for healthcare professionals [11]. Although DDIs are one of the most significant problems with drug prescribing, most physicians are not fully aware of all major and clinically important drug interactions or underestimate the risk of co-administration of multiple drugs [12].

Moreover, the share and size of elderly population is increasing over time which is becoming a major concern for a developing country like India as it pose a mounting pressure on various socio-economic fronts especially in the field of healthcare [13,14]. Though there is a substantial amount of literature on adverse drug interactions, it is difficult to accurately estimate their incidence, mainly because of different study design, populations, frequency measures and classification systems [15]. However, minimising or avoiding adverse drug reactions in elderly persons is a rational goal on both personal and socioeconomic levels. The knowledge of the incidence and predictors of DDI-related ADRs could aid in the development of preventive practices and policies [16].

Ethical Clearance: The ethical clearance for the study was obtained from the local institutional ethical committee.

MATERIALS AND METHODS: All patients admitted to the general medicine and surgery wards were screened on a daily basis to enroll in to the study. Elderly patients receiving more than one drug and admitted for more than a day was the inclusion criteria to enroll subjects in to the study. Patients who satisfied the study criteria were enrolled and followed till the day of discharge. Patient's demographic details, present and past medical history as well as current medications were collected from various sources and documented. Prescribed medications were classified according to the first level of anatomical therapeutic chemical (ATC) classification system as recommended by World Health Organization (WHO).

The medications of all those patients who were enrolled into the study were subjected to analysis for potential DDIs. Potential DDIs were identified using the online version of computerized interaction detection system such as Micromedex®, Medscape® and Drugs® and Stockley's Drug Interaction textbook to promote greater sensitivity in the study. Only potential DDIs rated as contraindicated, major, moderate or minor by at least any two of the DDI-checkers were included in the analysis.

Patients were monitored intensively for occurrence of ADRs. The causal relationship between the suspected drug and the reaction was established by using the Naranjo's scale [17]. The reported ADR was categorized as adverse drug interaction (ADI) where the suspected drug is involved in the DDI. The DDIs which led to ADIs were classified as pharmacokinetic (absorption, distribution, metabolism or elimination) and pharmacodynamic (synergism / additive effect or antagonism) interactions and their percentage values were calculated. The onset of ADIs was classified into either rapid (the effect of interaction occurred within 24 hours of administration) or delayed (the effect occurred if the interacting combination is administered for more than 24 hours, that is, days to weeks).

ADIs were categorized into various system organ classes as per the WHO Adverse Reactions Terminology (WHO-ART) and their respective percentage values were calculated. The causality of ADI was established using the Drug Interaction Probability Scale (DIPS). Based on this scale, each of the ADIs was classified into any one of the categories as highly probable, probable, possible and doubtful. The severity of the DDIs that led to ADIs was classified into either contraindicated, major, moderate or minor.

Predictors of ADIs: Using multivariate logistic regression analysis, predictors of ADI among the study population were determined. The variables tested for identification of predictors includes age, gender, duration of hospital stay, total number of diagnosed diseases, total number of chronic diseases and total number of drugs administered during hospitalization. The statistical analysis was performed using SPSS version 21.

RESULTS:

Patient Characteristics: Of the 8977 patients admitted to the medicine and surgery wards, 1131 (12.6%) were elderly. Of the 1131 elderly patients admitted, 1116 (98.7%) patients met the study criteria. The demographic details of the study population and the patients who experienced ADIs are presented in **Table 1**.

TABLE 1: DEMOGRAPHIC DETAILS OF THE STUDY POPULATION AND THE PATIENTS WHO EXPERIENCED ADI

Characteristics		Number of patients [n (%)]	
		Study population (n = 1116)	Patients with ADI (n = 82)
Gender	Male	669 (59.9)	54 (65.9)
	Female	447 (40.1)	28 (34.1)
Age (years)	60-69	654 (58.6)	42 (51.2)
	70-79	353 (31.6)	33 (40.2)
	80-89	93 (8.3)	7 (8.5)
	≥90	16 (1.4)	Nil
Duration of hospital stay (days)	≤7	689 (61.7)	8 (9.8)
	8-14	294 (26.3)	37 (45.1)
	15-21	88 (7.9)	18 (22)
	22-28	25 (2.2)	7 (8.5)
	> 28	20 (1.8)	12 (14.6)
Number of diagnosed diseases	One	479 (42.9)	17 (20.7)
	Two	331 (29.7)	25 (30.5)
	Three	176 (15.8)	20 (24.4)
	Four	109 (9.8)	12 (14.6)
	Five	15 (1.3)	3 (3.7)
	Six	5 (0.5)	4 (4.9)
	Seven	1 (0.1)	1 (1.2)
Number of chronic diseases	One	423 (37.9)	28 (34.1)
	Two	248 (22.2)	22 (26.8)
	Three	63 (5.6)	13 (15.9)
	Four	14 (1.3)	6 (7.3)
	Five	1 (0.1)	1 (1.2)
	Nil	367 (32.9)	12 (14.6)
Number of drugs	2-5	283 (25.4)	1 (1.2)
	6-10	594 (53.2)	23 (28.1)
	11-15	210 (18.8)	43 (52.4)
	16-20	26 (2.3)	13 (15.9)
	> 20	3 (0.3)	2 (2.4)

Incidence of ADIs: The overall incidence of potential DDIs was found to be 59.05% (659 out of 1116 patients experienced DDIs) and the average number of DDI in a patient was 1.78. Out of 1992 DDIs, 117 (5.9%) DDIs led to ADIs which were caused by 69 drug pairs (index drug and interacting agent). Out of the total number of enrolled patients, 259 (22.93%) patients experienced 283 ADRs. The average number of ADR per patient was 1.09. Of the total patients who experienced ADRs, 89 (31.45%) ADRs were due to DDIs and were observed in 82 (31.66%) patients. Out of the total 1116 enrolled patients, 82 (7.35%) patients experienced ADIs. Of the 89 identified ADIs, 70 were caused by one DDI, 13 were caused by two DDIs, five were caused by three DDIs and one was caused by four DDIs.

In a case, two ADIs were caused by one DDI. The average number of ADIs per patient was 1.09 and the average number of DDI in an ADI was found to be 1.31.

Types of Interactions Leading to ADIs: Of the 117 DDIs which led to ADIs, 31 DDIs were pharmacokinetic and 86 were pharmacodynamic interactions of which none of the DDIs were attributed to antagonistic interaction. Synergistic interaction [n = 86, (73.5%)] contributed to the majority of interactions which led to ADIs. The summary of the types of interactions leading to ADIs are shown in **Table 2**.

TABLE 2: TYPES OF INTERACTIONS LEADING TO ADIs

Type of interaction		Number of interactions n (%)		
		Medicine Ward	Surgery Ward	Total
Pharmacokinetic (n = 31)	Absorption	3	0	3 (2.6)
	Distribution	6	2	8 (6.8)
	Metabolism	8	4	11 (9.4)
	Excretion	4	5	9 (7.7)
Pharmacodynamic (n = 86)	Synergistic	60	25	86 (73.5)
	Antagonistic	0	0	0
Total		81	36	117

ATC Codes of Drug Implicated in ADI and System Organ Class (SOC) Associated with ADIs: Most of the ADIs belonged to the SOC metabolic and nutritional disorders [n = 46, (51.7%)], followed by psychiatric disorders [n = 14, (15.7%)], Gastrointestinal system disorders [n = 10, (11.2%), and Central and peripheral nervous system disorders [n = 6, (6.7%)].

Causality Assessment of ADIs: Majority of the ADIs were probable (56.4%) as per the causality assessment scale and 42.7% were possible and the causal association was doubtful in one case. 79.5% of the ADIs were moderate in severity, 14.5% were major and seven cases were minor in severity.

Intervention and Management of ADIs: All the 117 interactions which led to ADIs were brought into notice of the concerned physician. In all cases, the suggestion was accepted while change in drug therapy was incorporated in 73 (62.4%) interactions. The details of the management of ADIs are presented in **Table 3**.

TABLE 3: MANAGEMENT OF ADIs

Management of ADIs	Number of interactions (%) (n = 117)
Fate of index drug	
Drug withdrawn	43 (36.8)
Dose altered	13 (11.1)
Change in frequency	4 (3.4)
No change	57 (48.7)
Fate of interacting agent	
Drug withdrawn	4 (3.4)
Dose altered	0
Change in frequency	0
No change	113 (96.6)

Out of 82 who experienced ADIs, in 62 (75.6%) patients the outcome of intervention was observed to be 'improved therapeutic outcome' and in 20 (24.4%) patients there was 'no change in therapeutic outcome'. Symptomatic treatment was given for 40 (48.8%) patients while 42 (51.2%) patients received no treatment.

Of the total patients who experienced ADIs, the most common consequence of ADIs was 'worsened disease condition' [40 (48.8%)] followed by 'increased cost of therapy' [42 (51.2%)] patients. The details of the predictors of ADI are presented in **Table 4**.

TABLE 4: PREDICTORS OF ADI

Predictors	Number of patients (n = 659)		Odds Ratio (95% CI)	*p* value
	ADI+ (n = 82)	ADI- (n = 577)		
Gender				
Female	28	251	-	-

Male	54	326	0.67 (0.41-1.09)	0.12
Age (years)				
60-69	42	312	-	
70-79	33	195	1.25 (0.77-2.05)	0.37
80-89	7	58	0.89 (0.38-2.09)	1.00
≥90	0	12	-	-
Duration of Hospital stay				
≤ 7 days	8	378	-	-
8-14 days	37	150	11.65 (5.30-25.61)	<0.01
15-21 days	18	36	23.62 (9.60-58.12)	<0.01
22-28 days	7	9	36.75 (10.95-123.33)	<0.01
> 28 days	12	4	141.75 (37.46-536.35)	<0.01
Number of diagnosed diseases				
One	17	211	-	-
Two	25	171	1.81 (0.94-3.47)	0.07
Three	20	111	2.23 (1.12-4.44)	0.02
Four	12	76	1.96 (0.89-4.29)	0.12
Five	3	7	5.31 (1.26-22.45)	0.04
Six	4	1	49.64 (5.25-469.3)	<0.01
Seven	1	0	-	-
Number of chronic diseases				
Nil	12	140	-	-
One	28	229	1.42 (0.70-2.89)	0.39
Two	22	165	1.55 (0.74-3.25)	0.27
Three	13	37	4.09 (1.72-9.72)	0.002
Four	6	6	11.66 (3.25-41.79)	<0.01
Five	1	0	-	-
Number of drugs				
2-5	1	62	-	-
6-10	23	353	4.04 (0.53-30.45)	0.22
11-15	43	149	17.89 (2.41-132.82)	<0.01
15-20	13	12	67.16 (8.01-562.83)	<0.01
>20	2	1	124.00 (5.53-2777.30)	0.004

Direct Cost Associated with ADIs: An increased cost of therapy due to ADIs was incurred for 42 patients and total direct cost associated with ADIs was INR 15,638. The average cost associated with major, moderate and minor interactions were INR 132.1, INR 202.6 and INR 153.25 respectively.

DISCUSSION: Although many studies were conducted regarding the incidence, characteristics and predictors of potential DDIs, very few studies have been performed with respect to DDIs which led to ADRs. Elderly population are more vulnerable to ADIs due to age related physiological changes, increased number of diseases and consequently increased number of medication use.

The cost implicated in the management of ADIs account for a considerable portion of the healthcare expenditure. Therefore, vigilance in the area of DDI related ADRs is important in a developing country like India especially in population with low socioeconomic status.

In our study, the incidence of potential DDIs was found to be 59.05%. This is in concordance with the study conducted by Rahmawati F. *et a*l., [18] on elderly population where the incidence of potential DDIs was 65%. Another study conducted by Moura C. *et al*., [19] on general population showed that 37% of the study population experienced potential DDIs. This variation may be due to the difference in the study population.

In our study, the incidence of ADI with respect to the study population was 7.3%. This finding was consistent with the findings of Neto PRO *et al*., [15] and Skvrce NM *et al*., [16] where the incidence of DDI related ADRs was found to be 6.5% and 7.8% respectively.

In the present study, the incidence of ADI with respect to the total number of ADR was 31.45% which suggests that about one-third of the ADRs were caused due to DDIs. But, only 5.9% of the total number of DDIs led to ADIs.

In the present study, pharmacodynamic interactions accounted for majority [73.5% (n = 86)] of the total DDIs that led to ADIs. All those pharmacodynamic interactions that led to ADIs were due to synergism. This may be because of concurrent use of drugs that may have synergistic effect. For example, hyperkalemia caused by digoxin and spironolactone or somnolence/dizziness caused by alprazolam and tramadol.

In our study, major portion [79.5% (n = 93)] of DDIs that were responsible for ADIs were due to moderate interactions whereas major interactions accounted for 14.5% (n = 17). This finding is comparable to the study conducted by Raut A *et al*., [8] where major portion of DDIs leading to ADRs were due to moderately severe (65.62%) interactions and 34.37% of interactions were major in their severity. It is obvious that major and moderate interactions are more likely to cause the adverse consequences when compared to minor interactions. Clinicians need to be cautious while using multiple regimens especially that have potential for major and/or moderate interactions.

Causality assessment of DDIs leading to ADIs as assessed by using the DIPS showed that 50 (42.7%) interactions were 'probable', 66 (56.4%) interactions were 'possible' and one (0.9%) interaction was 'doubtful'. This finding reveals that almost half of the interactions had a good causal association with the occurred event. The onset of ADIs was rapid in five (5.6%) cases and delayed in 84 (94.4%) cases. In four cases of rapid onset, the interaction was due to nervous system agents (ATC-N) resulting in somnolence or dizziness. Drugs acting on the cardiovascular system (ATC-C) and nervous system (ATC-N) were most commonly implicated in the occurrence of ADIs. Similar findings were seen in the study carried out by Skvrce NM *et al*., [16] where ATC code 'N' was involved in most DDIs leading to ADRs followed by ATC code C (27%). Another study conducted by Busca C [5] *et al*., revealed that cardiovascular medicines (ATC-C) were associated with higher risk of ADRs caused by DDIs. Elderly patients have a greater risk of cardiovascular and nervous system disorders due to which they are prescribed with more number of drugs belonging to ATC codes C and N and therefore there is a higher risk of drug interactions due to these agents.

In our study, most of the ADIs belonged to the system organ class 'metabolic and nutritional disorder' [n = 46, (51.7%)] followed by 'psychiatric disorder' [n = 14, (15.7%)], 'gastrointestinal system disorders' [n = 10, (11.2%)] and 'nervous system disorders' [n = 6, (6.7)]. The system organ class 'metabolic and nutritional disorders' were commonly seen in elderly patients as majority of them were treated with cardiovascular agents which have a high tendency of causing electrolyte abnormalities. Also, elderly patients have limited regenerative abilities and increased drug sensitivity which makes them more prone to metabolic and psychiatric disorders. This finding is in contrast with the findings observed in the study conducted by Skvrce N. M. *et al*., [16] wherein it was reported that most ADRs caused by DDI, belonged to the class 'gastrointestinal system disorders' (24.3%), 'nervous system disorders' (14.5%), 'investigations' (11.8%), and 'psychiatric disorders' (11.2%). This may be due to the difference in disorders treated in the study population.

In the present study, out of 117 DDIs that led to ADIs, all were brought into the notice of the concerned healthcare professional and where required sought for change in drug therapy as appropriate. Suggestions were given regarding the change in index drug or interacting agent and where the interacting drugs could not be changed, appropriate treatment for the management of ADIs were suggested. Suggestion was accepted in all cases, and change in drug therapy was incorporated in 73 (62.4%) interactions whereas in 44 (37.6%) interactions there was no change in drug therapy. In cases where no change was incorporated, either the interaction effect was minor in severity or an appropriate treatment was initiated for the management of ADIs. The outcome of intervention was observed to be 'improved therapeutic outcome' in 62 (75.6%) of the total 82 patients who experienced ADI. 'No change in therapeutic outcome' was observed in 20 (24.4%) patients. This finding suggests that pharmacist intervention can result in improved therapeutic outcome of the patients who experienced ADIs.

ADIs were managed either by suggesting the necessary changes required in the index drug or interacting agent and / or by suggesting

symptomatic treatment. Changes were more commonly incorporated in the index drug than the interacting agent as the suspected drug that caused the event was preferred to be altered to improve the outcome of management of ADIs. Symptomatic treatment was provided in 40 (48.8%) patients whereas no treatment was provided in 42 (51.2%) patients. In patients where no treatment was provided, the index drug or interacting agent was altered or the interaction effect was minor which does not require treatment.

The consequences of ADIs observed in our study included 'worsened disease condition' [n = 40, (48.8%)] and an increase in the cost of therapy [n = 42, (51.2%)]. This finding suggests that ADIs are important cause of increased burden of disease and unnecessary healthcare expenditure. There is a greater opportunity for pharmacist to minimize and / or prevent such adverse consequences through early detection, prevention and management of potential DDIs that lead to ADIs.

The study showed that there is an increase in odds ratio from 11.65 [95% CI (5.30 - 25.61), $p < 0.01$] in patients whose hospital stay was 8-14 days to 141.75 [95% CI (37.46 - 536.35), $p < 0.01$] in patients whose hospital stay was more than 28 days. This suggests that there is an increase in the risk of ADIs with increase in the duration of hospitalization owing to increased duration of drug exposure and/or exposure to additional/new drug therapy. This finding is consistent with the finding of Busca C. *et al*., [5] where there was a statistically significant association between ADIs and the length of hospital stay.

Also, our study found that diagnosis of three or more diseases, presence of three or more chronic diseases and consumption of more than 10 drugs were associated with the risk of ADIs. There was no significant difference with regard to gender [OR = 0.67 (0.41 - 1.09), p = 0.12]. It is obvious that the use of multiple medications owing to the presence of multiple conditions increase the risk of patients developing ADIs. The study conducted by Neta PRO *et al*., [20] revealed that patients who presented six or more diseases and those who took five or more drugs had a significantly higher risk of DDI-related ADRs. Although the findings of number of diseases and number of drugs as predictors in the Neto PRO *et al*., study [20] differ from our study findings, the finding of gender as predictor was similar to our study where it was reported that there was no association between either of the gender and the risk of ADIs.

In our study, the direct cost implications were observed in 42 patients. The total direct cost incurred was INR 15,683/-. Of which moderate interactions accounted for INR 13,572/-. The interaction effect of majority of the moderate interactions were electrolyte disturbances and the lab charges used to estimate the serum electrolytes accounted for the increase in cost due to ADIs caused by moderate interactions. When compared to medication cost to treat the ADIs, direct cost associated with lab charges, owing to frequent monitoring, was the major reason for the increased cost in the management of ADIs. Our study findings demonstrate that ADIs are important cause of increased burden of healthcare expenditure.

CONCLUSION: Elderly patients are more susceptible to adverse drug interactions. ADIs are important cause of increased burden of disease and unnecessary healthcare expenditure. Clinicians need to be aware of most common ADIs occurring in the clinical practice and should be cautious in using the medications especially in elderly patients. Intense monitoring of elderly patients for potential DDI and its early detection and prevention may result in improved therapeutic outcomes and decreased unnecessary healthcare expenditure. Clinical pharmacist can play a vital role in the detection, prevention and management of ADIs.

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