

## Assess the frequency and severity of adverse drug reactions due to errors in drug intake at a tertiary care hospital

G. Shivaprakash<sup>1</sup>, Praveen Ravi<sup>2</sup>, Sanjay Hadigal<sup>2</sup>, L. C. Pallavi<sup>3\*</sup>

<sup>1</sup>Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India,

<sup>2</sup>Department of Pharmacology, Kasturba Medical College, Manipal University, Mangalore, Karnataka, India,

<sup>3</sup>Department of Physiology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

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**\*Correspondence to:**

Dr. L. C. Pallavi,

Email: [pallavilcu@gmail.com](mailto:pallavilcu@gmail.com)

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### ABSTRACT

**Background:** Drug-related problems are an important cause of morbidity and mortality and a significant burden on healthcare resources. There are few studies to account for errors in drug intake leading to adverse drug reactions (ADRs). This study was pursued with the objective of determining the frequency and severity of the ADRs resulting from erroneous drug intake, the expenses incurred in treating the same.

**Methods:** The study was a prospective, cross-sectional, observational study. The study subjects were patients with ADRs due to errors in drug intake and from self-medication. All the information regarding the ADR were collected as per ADR reporting form issued by Central Drugs Standard Control Organization. Causality was assessed by both Naranjo and the WHO criteria for causality assessment. Direct cost of all the medications, hospital charges (admission, bed charges, consultations paid, treatment charges, investigations, and conveyance charges) were recorded to find the financial burden due to error in drug intake.

**Results:** The study showed that nearly 30% of the ADRs were due to errors in drug intake and the major contributing factor is self-modification either by discontinuation or missed doses. Major drugs that are implicated in these ADRs were that of metformin and insulins among anti-diabetic drugs and amlodipine and atenolol among antihypertensives. These two groups contributed to 18 (62%) of the total 29 ADRs. Organ system commonly involved was central nervous system and that was followed by musculoskeletal system. The average direct cost incurred in the management of these ADRs was Rs. 5773 for non-serious adverse events (SAE's) and Rs. 11,400 for SAE's.

**Conclusion:** Proper education about the importance of compliance and damaging consequences of self-modification of drug dosage in patients who are on treatment for chronic disorders like diabetes and hypertension will be an effective strategy to prevent many of these ADRs.

**Keywords:** Errors, Adverse drug reactions, Self-medication

### INTRODUCTION

Drug-related problems are an important cause of morbidity and mortality and a significant burden on healthcare resources. A high rate of adverse drug reactions (ADRs) has been demonstrated in hospitalized patients potentially leading to death. 10-17% of the visits to the emergency department (ED) are related to the ADR.<sup>1,2</sup>

There is a general worldwide trend in promoting self-determined irrational medication to improve the access to treatment while minimizing health care costs. However, self-medication, including drug misuse or abuse, significant

drug interactions, and ADRs contributes significantly to hospital admissions. Moreover, reckless self-medication leading to ADRs accounts for 1% of admissions in the ED. Hence, obtaining a complete self-medication history is the key to identifying potential ADRs and preventing medication errors.<sup>3</sup>

These admissions constitute a significant cost burden. It has been estimated that at any one time equivalent of up to seven 800 bed hospitals may be occupied by patients admitted with ADRs. Moreover, the expenses incurred in managing these admissions are calculated to be £466 million annually in the UK. Most of the ADRs are predictable from the known

pharmacology and many represented known interactions and are therefore likely to be preventable.<sup>4</sup>

This study was pursued with the objective of determining the frequency and severity of the ADRs resulting from erroneous drug intake and the expenses incurred in treating those ADRs.

### **Primary objective**

To assess the frequency and severity of ADR's due to errors in drug intake.

### **Secondary objectives**

1. To assess direct cost of such ADR's
2. To assess avoid ability of the ADR due to drug interactions.

## **METHODS**

### **Study design**

A prospective cross-sectional observational study was conducted for 2 months at a tertiary care teaching hospital in Mangalore.

### **Study participants**

Patients with ADRs due to errors in drug intake at emergency, medicine, and medical intensive care unit departments were enrolled for the study. All the patients above the age of 18 years and who gave consent were included in the study. Illiterate patients, patients unable to participate because of neuropsychiatric disorders, all poisoning cases, and drug intake due to addictions were excluded. The study was conducted after approval from the institutional ethics committee and after obtaining the informed consent from the patients.

The ADR is defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function, in accordance with International Conference on Harmonization tripartite guidelines.<sup>5</sup>

Errors in drug intake are defined in the protocol as faults in:

- Ordering wrong dose/frequency/drug interactions by irrational combinations
- Dispensation by pharmacist
- Drug administration – faulty administration of drugs by the nurse (wrong dose and wrong technique) and self-medication by the patient.

Definition of self-medication whether intentional or unintentional in the study protocol:

- To take the drugs without relevant prescription (sold without prescription, ancient prescription of prescribed for another person)
- Self-modification of treatment
- Self-discontinuation of treatment.

### **Data collection methodology**

A study nurse and the post graduate from each department were trained to report all the suspected ADR due to errors in drug intake to the principal investigator. The principal investigator also checked the daily ADR registries in the pharmacovigilance register in the hospital. Any potential ADR suspected to be due to errors in drug intake were enrolled for the study. When the patient was categorized to be having the ADRs, demographic details like age, sex, education level of all the patients were collected. All the relevant data like presenting complaints with its duration, past history like underlying disease, its duration, current status of the disease with its treatment, drug history apart from allopathy like concomitant herbal, homeopathic, unani were recorded.

All the information regarding the ADRs were collected as per ADR reporting form issued by Central Drugs Standard Control Organization (CDSCO) and were recorded.<sup>6</sup> Causality was assessed by both Naranjo and WHO criteria for causality assessment.<sup>7,8</sup> This was done by the expert committee which included, two consulting physician, clinical pharmacologist, and the investigator. Only those ADRs with causality of possible, probable and definite were analyzed.

The severity of the ADRs was assessed by CTCAE grading. In addition to the information in the CDSCO format, other relevant information such as prescriptions, dispensed medications, and its compatibility with the ordered ones, mode of administration, self-modification of dose with dates and self-discontinuation with dates were also collected.

Outcomes of all ADRs due to errors in drug intake were documented as:

- Recovered
- Recovered with sequelae
- Recovering
- Continuing
- Fatal
- Required admission.

Direct cost of all the medications, hospital charges (admission, bed charges, consultations paid, treatment charges, investigations, and conveyance charges) were recorded to find the financial burden due to error in drug intake. Treatment charges were recorded as per patient's information and by referring latest edition of Current Index of Medical Specialties.<sup>9</sup>

Avoid ability of ADR with respect to drug-drug interactions were assessed based on the definitions by Hallas et al.<sup>10</sup>

- Definitely avoidable-the ADR was due to a drug treatment procedure inconsistent with present day knowledge of good medical practice
- Possibly avoidable-the ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice
- Unavoidable-the ADR couldn't have been avoided by any reasonable means.

## RESULTS

The demographics and details with regard to ADRs were noted.

Among the 90 ADRs that were reported in a period of 2 months, 29 (30%) of them were due to errors in drug intake. The majority of the patients reporting the ADRs were older people aged more than 45 years. Most of the patients were literate and 59% were employed. 23% of them had annual income of less than one lakh, but the majority was insured medically. Most of them belonged to the upper class in the socioeconomic status (Table 1).

72% of the drugs implicated in ADRs were the drugs used for treating chronic conditions like diabetes mellitus and hypertension (Table 2). Metformin, insulin were the common drugs among anti-diabetic medications and amlodipine and atenolol among anti-hypertensives. Hyperglycemia and rise in blood pressure due to error in intake of these medication led to adverse events. ADRs such as headache, dizziness, blurring of vision, sweating, shivering, urinary tract infections, and fatigue were associated with anti-diabetic group and events like headache, giddiness, visual disturbance, leg pain, with anti-hypertensive agents. One episode of stroke was observed due to sudden stoppage of aspirin in one patient. One adverse event each was observed with salbutamol stoppage leading to wheezing, diarrhea with excess intake of anti-microbial agent amoxicillin and hallucination with tramadol. ADRs like ankle edema, drowsiness, weight gain were observed due to self-modification of dose of levothyroxine. Among the systems involved, ADRs involving central nervous system were the most common (69%) among all ADRs followed by the musculoskeletal system such as sciatica, tingling and numbness in the limbs. In the 29 ADRs reported 4 were serious adverse events (SAEs). Among the SAEs, 3 involved central nervous system and one involved vascular system.

The average direct cost incurred to ADRs due to error in drug intake was Rs. 5773 for non SAE's and Rs. 11,400 for SAE's. The costs studied here were the direct costs of all medications and the hospital charges like consultations, investigations, and conveyance.

**Table 1: Demography.**

Characteristics	Percentage	p value
Age (years)		
≥45	72	0.016*
<45	28	
Sex		
Male	52	0.853
Female	48	
Education		
Illiterate	10	0.000**
Literate	90	
Employment		
Unemployed	41	0.353
Employed	59	
Annual income		
<1 lakh	23	0.029*
>1 lakh	77	
Socioeconomic status		
Upper class	93	0.000**
Lower class	7	
Insurance		
Yes	86	0.000**
No	14	

Values expressed as percentage. Chi-square test was applied and  $p \leq 0.05$  considered significant. \* $p < 0.05$ , \*\* $p < 0.001$

No ADRs were reported due to drug-drug interactions and hence the avoid ability of ADR with respect to drug-drug interactions by the definitions of Hallas et al. could not be done.

All the patients recovered and there were no deaths in all the 29 ADRs. None of the ADRs occurred due to errors in prescription, faulty dispensation or administration of drugs.

### Causality assessment

Causality assessment was done for individual cases using both Naranjo Algorithm - ADR Probability Scale and WHO-UMC causality assessment system. The details of the causality assessment are given in Table 3.

### Statistics

All ADRs due to errors in drug intake as defined in the protocol were analyzed. Results were expressed as percentage and Chi-square test was applied for categorical data to find the level of significance.  $p \leq 0.05$  was considered significant.

## DISCUSSION

We found from our study that around 30% of the ADRs reported in the tertiary care hospital were due to errors

**Table 2: Drugs implicated in ADRs due to errors in drug intake.**

Drug	Number of ADRs (%)	ADR's observed
Metformin	6 (21)	Hyperglycemia, headache, dizziness, tingling, sweating, foot ulcer
Insulin	6 (21)	Hyperglycemia, headache, dizziness, sweating, blurring of vision, fatigue
Glimepiride	2 (7)	Hyperglycemia, burning micturition
Glibenclamide	1 (3)	Hyperglycemia
Amlodipine	4 (14)	High BP, giddiness, headache, blurred vision
Atenolol	2 (7)	High BP, giddiness, headache
Levothyroxine	3 (10)	Ankle edema, drowsiness, weight gain
Tramadol	1 (3)	Hallucination
Amoxicillin	2 (7)	Diarrhea
Aspirin	1 (3)	Stroke
Salbutamol	1 (3)	Wheezing
Total	29	

Values expressed as percentage, ADR: Adverse drug reactions, BP: Blood pressure

**Table 3: Causality assessment by Naranjo Algorithm - ADR probability scale and WHO-UMC causality assessment system.**

AE's	Total number (29)	Naranjo scale (%)		WHO assessment system (%)	
		Possible	Probable	Probable	Certain
ADR	25	1 (4)	24 (96)	25 (100)	0
SAE's	4	1 (25)	3 (75)	3 (75)	1 (25)

Values are expressed as percentage. ADR: Adverse drug reaction, SAE: Serious adverse reaction, AE's: Adverse events

in drug intake and common reason was found to be self-discontinuation and missed doses. 4 out of 29 ADRs reported were SAEs, i.e., around 14%. The majority were old people more than 45 years of age, literate and from upper socioeconomic class as per Kuppaswamy classification<sup>11</sup> (Table 1).

Although, patients belonged to the upper class, the annual income was found to be less than 1 lakh in 23% of patients. This discrepancy reflects the fact that many subjects were female who were housewives and were earning lesser than their other family members. Earnings from the other family members have contributed to the higher total family income and hence the higher level in socioeconomic class.

Most of the adverse effects involved the central nervous system. These side effects were mainly attributed to error in drug intake of commonly used long term drugs like anti-diabetic and anti-hypertensives. Error in intake of metformin and insulin drugs were primarily attributed to the hyperglycemia and other associated ADRs. This could be because of frequent prescription of metformin and insulin among all the anti-diabetic medications due to its safety compared to other drugs.<sup>12</sup> The second common group implicated in ADR due to error in drug intake was anti-hypertensive group. In a similar study for evaluation of outpatient ADR, the major therapeutic class implicated in ADRs were anti-diabetic drugs and anti-

hypertensives and the organ system most common involved was endocrinal and cardiovascular systems.<sup>13</sup> Our study similarly implicates the same group of drugs but the system involved were found to be the central nervous system (CNS) and the musculoskeletal system. This difference in the system involvement may be due to the fact that we have restricted our study to assess only ADRs due to error drug intake and not due to other causes. Long-term study with more number of ADRs may be more confirmatory.

In another study of ADR solely due to self-medication, it was observed that CNS was the major system that was involved, but were implicated due to frequent consumption of drugs related to psycholeptic and analgesics.<sup>3</sup>

CNS was the system that was involved in 3 of the four SAE's. The drugs that were implicated were tramadol for hallucination, amlodipine for intermittent claudication, pontine hemorrhage and metformin for foot ulcer. All these were because of sudden stoppage of the drugs.

Causality assessment of the ADRs was done by both the Naranjo Algorithm - ADR Probability Scale and WHO-UMC causality assessment system methods. Most of the ADRs were probably related by both methods (Table 3). The majority of these ADRs were because of self-discontinuation. On having to take the medication for a prolonged period of time, compliance might reduce over time and the patient may decide to stop the medication if his disease or the event is under control. Taking self-decisions with regard to drug intake could prove dangerous and could incur huge unnecessary costs to the patients.

The average direct cost incurred to ADRs due to error in drug intake was Rs. 5773 for non SAE's and Rs. 11,400 for SAE's. There are not many studies showing the cost expenditure due to ADRs in India. In one western study average hospital charge per ADR patient was found to be 9491 USD.<sup>13</sup> However, this varies with each country. In

India still this is very high considering the fact that 75% of the population earns less than 2 USD per day.<sup>14</sup> In our study, majority of the patients up to 86% were medically insured. Only patients with 4 SAE's admitted were able to reimburse all the charges under medical insurance. The others could not reimburse as the outpatient charges were not covered under policy. Hence, there is a compelling need to educate about this preventable medical expense.

## CONCLUSION

- The study showed that nearly 30% of the ADRs were due to errors in drug intake and the major contributing factor is self-modification either by discontinuation or missed doses. Major drugs that are implicated in these ADRs were that metformin and insulins among anti-diabetic drugs and amlodipine and atenolol among anti-hypertensives. These two groups contributed to 18 (62%) of the total 29 ADRs.
- Organ system commonly involved was CNS and that was followed by musculoskeletal system.
- The average direct cost incurred in the management of these ADRs was Rs. 5773 for non-SAE's and Rs. 11,400 for SAE's.

Proper education about the importance of compliance and damaging consequences of self-modification of drugs in patients who are on long-term treatment for chronic disorders like diabetes and hypertension will be an effective strategy to prevent many of these ADRs. The study has given new information on the common preventable errors to avoid ADRs and has laid the basis to carry the research forward by continuing the study in larger number of ADRs for longer term.

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