

ORIGINAL ARTICLE**PREVALENCE AND ASSESSMENT OF FACTORS CONTRIBUTING TO ADVERSE DRUG REACTIONS IN WARDS OF A TERTIARY CARE HOSPITAL, INDIA**Demissew Berihun Haile¹, Wubeante Yenets Ayen², Pramila Tiwari³**ABSTRACT**

BACKGROUND: Adverse drug reactions account for the highest proportion among the causes of morbidity and mortality in clinical wards and are posing a considerable challenge. Hence, the objective of this study was to find out the prevalence of adverse drug reactions and the factors which contribute to their prevalence.

METHODS: A prospective patient record review was carried out at a tertiary care hospital in North India from August 2010- May 2011. A total of 1033 subjects admitted to hospital for any kind of treatment were included while patients admitted in the ward because of adverse drug reactions were excluded. The ward where we collected the data includes multispecialty and cardiovascular wards. The causality, severity, and preventability of adverse drug reactions were assessed using Naranjo, modified Hartwig, and Schumock and Thornton criteria, respectively. Kolmogorov-Smyrnov, chi-square and multiple logistic regression tests were used to determine adverse drug reactions ascribed to drugs.

RESULTS: Out of 1033 patients whose records were assessed, 167(16.2%) experienced one or more adverse drug reactions. The metabolic systems, which accounted for 49(24.6%) were most frequently affected by adverse drug reactions, followed by gastrointestinal, 45(22.6%); hematological, 28(14.1%) and cutaneous, 21(10.6%) systems. The drug classes most frequently associated with the reactions were antibiotics 40(20.1%), diuretics 35(17.6%) and anticoagulants 30(15.1%). According to the selected preventability scale, 72(36.2%) adverse drug reactions were classified as probably or definitely preventable. About 165(83%) of the reactions were type A, which represents augmentation of the pharmacological action of a drug. Number of drugs, length of hospitalization and number of diagnosis were identified as significant predisposing factors for ADRs.

CONCLUSION: The result of this study suggested that adverse drug reactions were significant causes of superimposed health problems that occur following hospitalization. The major risk factors associated with ADR include number of drugs, length of hospitalization and number of diagnosis. Based on the findings a rigorous study is recommended to determine the burden and identify the risk factors of adverse drug reactions to target interventions.

KEYWORDS: Adverse drug reactions, Causality assessments, Type A reactions, Predisposing factor

INTRODUCTION

Adverse drug reactions are the most frequently reported causes of morbidity and mortality during hospitalizations (1), affecting up to 20% of all hospitalized patients in many countries and becoming an important challenge in today's

modern medicine in terms of early recognition, proper management and their prevention (2, 3, 4). A meta-analysis made by Lazarou *et al.* (1998) to assess 39 American studies showed that the rate of serious and fatal ADRs were 6.7% and 0.3%, respectively (1).

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The same authors reported that ADRs ranked between the fourth and sixth leading causes of death in the USA. In India, very few studies were conducted 5 to 10 years ago and looked at ADRs as the cause of hospital admissions. A study carried out in a tertiary referral center in Mumbai indicated that ADRs were responsible for 6.9% of total admissions (5). This author reported that deaths due to ADRs accounted for 0.8%. These days, ADR is a known cause of morbidity and mortality after hospitalization in different countries of the world (3, 4, 6).

Despite the relevance of this, there is no available data regarding the characteristics and the incidence of ADRs among hospitalized patients, in India. One study conducted on hospitalized patients by Jose *et al.* (2006) (7) in Karnataka showed that the overall incidence of ADR calculated from the patient population was only 0.15%. The reason for this low incidence was that information on the ADRs was collected only if physicians reported through the spontaneous reporting system. More recent data are thus needed to determine the actual incidence of ADRs after admission to hospital. Therefore, this study aimed at obtaining more recent and accurate data on the prevalence of ADRs among hospitalized patients and ascertaining their contributing factors.

SUBJECTS AND METHODS

This study was carried out in wards of a tertiary care hospital in northern India from August 2010-May 2011. This hospital is one of the largest private health facilities. The hospital was founded in 2001 and includes multispecialty and super specialty in heart. It has 7 operational theatres, 215 operational beds for inpatients with installed capacity for up to 300 beds. The hospital has standard multispecialty and cardiovascular wards from which the data was collected.

All patients admitted to the wards were included in the study and evaluated for ADRs. Only ADRs that occurred during hospital stay as a result of drugs initiated or continued in the wards were included while patients admitted to the hospital because of ADR were excluded. Intensive care units (ICUs) were excluded as the focus of the study was on ADRs occurring only

among ward patients. Patient files without proper documentation were also excluded from the study. The follow up of the patients was done until patient discharge or transfer from wards to ICUs. All the information was collected from patients' recorded files using a pre-tested data collection form. The definition of ADR used in this study was the one developed by the World Health Organization, i.e. "all the noxious and unintended drug responses which occur at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (8). In identification of ADRs, objective criteria that involve changes in laboratory values and vital signs which are not related to the disease pathology and subjective criteria which include increase in severity of symptoms or appearance of new symptoms were identified as an ADR from patients' record file as well as from the physicians and nurses notes. Additionally, ADRs from patients' charts that were identified by physicians or nurses were also included in the study. For validation, ADRs were discussed and confirmed with the clinical pharmacologist of the hospital after they were identified and assessed for causality, severity and preventability.

The assessment of causality was then performed for all the cases using the Naranjo's algorithm (9). The severity of ADRs was determined by using the modified Hartwig criteria (10) as described in Table 1, while the preventability of ADRs was assessed by using the modified Schumock and Thornton criteria (11). ADRs were also classified as either type A (dose-dependent and predictable from the known pharmacology) or type B (idiosyncratic, no clear dose response relationship, and not predictable from the known pharmacology) according to the system introduced by Rawlins and Thompson (12). Drugs were categorized according to the Anatomical Therapeutic and Chemical (ATC) classification system (13), and ADRs were coded according to the MedDRA terminology (14).

Statistical analysis: The Kolmogorov-Smyrnov test was used to determine the distribution of variables. Approximately, normally distributed variables were summarized using mean and standard error of mean (mean \pm SEM) while

variables without normal distribution were summarized using the median, the lower (Q1) quartile, and upper (Q3) quartile. Chi-square test was applied for comparing categorical variables and multiple logistic regression with 95% confidence interval was calculated to observe relationships of predisposing factors for ADRs. P-value below 0.05 was considered as significant. All the analyses were performed using the statistical software sigma stat version 3.5.

This study was approved by Institutional Ethics Committee and by the Hospital. Patients' written informed consent to participate in the study was obtained after comprehensive explanation of the purpose and procedure of the study. During the data collection, the patients at any risk of complication of adverse reactions were treated at spot after the response was taken. To ensure confidentiality, any attempt to collect information that would expose the identity of respondents was avoided.

RESULTS

The results were based on data collected from the records of 1033 patients (590 males, 443 females) taken from different inpatient wards. Of those patients used in the study, 167 (16.2%) experienced at least one ADR. Among those, 144 patients experienced only one ADR whilst 23 patients had more than one ADR:

encountered simultaneously or successively, totaling up to 199 ADRs. The highest number of ADR observed in a single patient was four. About 9% of ADRs were caused by a combination of two or more drugs leading to the same ADR. No statistically significant difference was observed in the incidence of ADRs in both males and females ($X^2 = 1.38, p = 0.24$), and the incidence of ADRs among different age groups was also not statistically significant ($X^2 = 3.18, p = 0.2$). More patients admitted to the cardiovascular ward experienced ADRs (n = 54, 21.8%) than those who were in the multispecialty ward (n = 113, 14.4%) ($X^2 = 7.037, p < 0.05$). From multivariate analysis, the only significant indicators for the occurrence of ADRs observed in this study were the number of drugs [OR: 1.1 (1.06-1.14), $p < 0.001$], length of hospitalization [OR: 1.1 (1.04-1.14), $p < 0.001$], and number of diagnosis [OR: 1.22 (1.06-1.4), $p < 0.05$]. The median length of hospitalization was 7 days (Q1–Q3 = 5-8 days, range = 2–37 days). The median age of patients was 61 years (Q1-Q3 = 49-68.3 years, range = 1-98 years). The top ten diagnoses of patients admitted included: hypertension 318 (13.6%), osteoarthritis 215 (9.2%), coronary artery disease 193 (8.2%), type-2 diabetes mellitus 177 (7.6%), hypothyroidism 56 (2.4%), cancer 48 (2%), fracture 38 (1.6%), urinary tract infection 30 (1.3%), dengue fever 27 (1.2%) and sepsis 26 (1.1%).

Table 1: The modified Hartwig's severity classification

Level	Description	Grade
1	An ADR occurred but no change in treatment with suspected drug	Mild
2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in length of stay	Mild
3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment. No increase in length of stay	Moderate
4	Any Level 3 ADR which increases length of stay by at least one day or the ADR was the reason for admission	Moderate
5	Any level 4 ADR which requires intensive medical care	Severe
6	The ADR caused permanent harm to the patient	Severe
7a	The ADR was indirectly linked to death of patient	Severe
7b	The ADR was directly linked to death of patient	Severe

The nature of the ADRs and the drugs mostly involved are presented in Table 2. Metabolic ADRs were the most frequent, 49 (24.6%), followed by gastrointestinal ADRs, i.e. 45 (22.6%), hematological ADRs, 28 (14.1%), and cutaneous ADRs making 21 (10.6%). The most prevalent metabolic ADR was hypokalemia, 34 (69.4%), mainly due to diuretics, 25 (73.5%).

None of the ADRs identified were new (unlabelled). The drugs associated with the 143

(72%) identified ADRs were clustered in a few therapeutic classes. Cardiovascular agents were responsible for 53 (26.6%) of all ADRs followed by antibiotics, 40 (20.1%), anticoagulants, 30 (15.1%), and opioids, 21 (10.6%). All the other classes accounted for 30% of the ADRs. The summary of classes of drugs responsible for ADRs is presented in Figure 1.

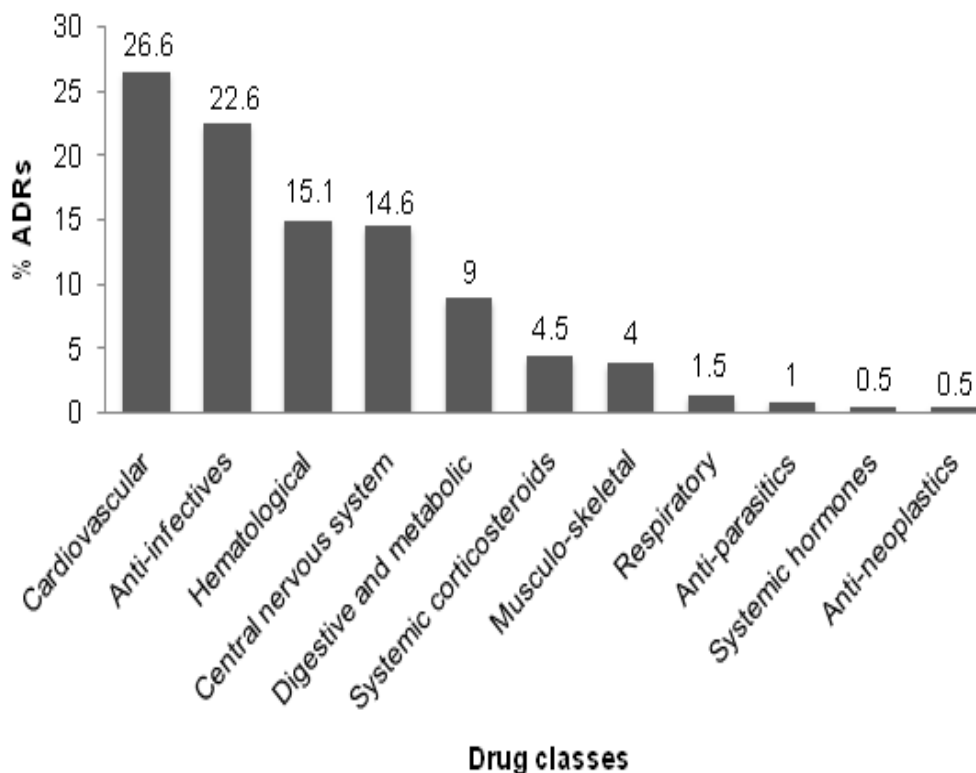


Figure 1. ATC based classification of drugs involved in ADR

Using the Naranjo algorithm for causality assessment, 143 (71.9%) ADRs were identified as probable, 52 (26.1%) as possible, and 4 (2%) as definite due to re-challenge or due to the fact that the patient's ADR history to the same drug or cross reactivity. By using the modified Schumock and Thornton's criteria, 14 (7%) of the reactions were classified as definitely preventable, 58 (29.2%) were probably preventable while 127 (63.8%) were recognized to be not preventable at all.

Using modified Hartwig's classification it was found out that out of 199 ADRs, 95 (47.7%) were identified as mild, 89 (44.7%) as moderate

and 15 (7.5%) as severe. A greater proportion of ADRs, 160 (80.4%), required some intervention (ranging from stopping the causative drug to initiation of other treatments like oral vancomycin or metronidazole for the treatment of antibiotic related diarrhea) but did not increase the length of stay (i.e. level 2 and 3) (Table 1). However, from analysis of records, 19 (9.5%) reactions were observed to have had an impact on the length of stay and were thus classified at level 4 (Table 1).

Table 2: Description of systems affected, drugs involved, and ADRs of Ward patients in the Tertiary Care Hospital in the Northern India from August 2010-May 2011

System	Drug (number)	ADR (number)
Metabolic	Diuretics (30)	Hypokalemia (25), hyponatremia (5)
	Systemic corticosteroids (6)	Hypokalemia (4), hyperglycemia (2)
	Antidiabetes (6)	Hypoglycemia (5), hypokalemia
	Salbutamol (2)/calcium gluconate/fluconazole	hypokalemia (4)
	ARBs (2)/ACEi	Hyperkalemia (3)
Gastrointestinal	Opioids (15)	Vomiting (8), nausea (5), constipation (2)
	Antibiotics (10)/anti-parasitics (2)/ Pyrazinamide (2)	Diarrhea (4), clostridium difficile infection (4), vomiting (3), constipation, anorexia, dryness of mouth
	Laxatives (8)	Diarrhea (8)
	Aspirin (3)	GI bleeding (3)
	NSAIDs (5)	Gastritis (4), epigastric pain
Hematological	Anticoagulants (17)	Thrombocytopenia (14), increased INR (3)
	Antibiotics (9)	Thrombocytopenia (5), pancytopenia (3), anemia
	NSAID/anti-neoplastics	Leukepenia, pancytopenia
Cutaneous	Antibiotics (14)	Rash (13), swelling around the eye
	NSAID/paracetamol/ondansetron/allopurinol	Rash (4)
	NSAID/acenocoumarol/warfarin	Angioedema, facial puffiness, ecchymosis
CNS	Anti-psychotics (6)	Drowsiness (4), extrapyramidal symptoms, sedation
	Opioids (5)	Restlessness (3), drowsiness, psychosis
	Systemic corticosteroids (2)	Delirium (2)
	Aspirin + enoxaparin/Salbutamol/metoclopramide	Intracranial bleeding, tremors, extrapyramidal symptoms
Cardiovascular	B-blockers (5)	Hypotension (3), bradycardia (2)
	Ca ⁺² channel blockers + β - blockers (3)/diuretics	Hypotension (8)
	(2)/ACEi + diuretic/Ca ⁺² channel blocker + diuretic/ARB + diuretic	
	Amiodarone/hyoscine/terlipressin	Bradycardia (3)
Renal	Anticoagulants (9)	Haematuria (9)
	Antibiotics (6)	Increased serum creatinine (3), acute interstitial nephritis, urinary retention, worsening of renal function
		Dry cough (2)
Respiratory	ACEi (2)	Apnea, respiratory depression, bronchospasm
Endocrine	Polymyxin B/tramadol/metoprolol	Hypothyroidism (2)
Sensory	Amikacin/nitroglycerin	Visual impairment, tingling sense
Hepatic	Isoniazid	Increased liver enzymes
Muscular	Prednisolone	Osteoporosis

CNS, central nervous system; NSAIDs, non-steroidal anti-inflammatory drugs; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; GI, gastrointestinal; INR, international normalized ratio; Numbers in the parenthesis indicate frequency and single frequency wasn't indicated

None of the ADRs resulted in death or permanent damage. However, 15 ADRs, for example acute delirium due to methyl prednisolone, acute interstitial nephritis due to amoxicillin, severe hypotension due to antihypertensive drugs, and respiratory depression due to tramadol were considered as severe that led to admission to intensive care units. Type A reactions accounted for 165 (82.9%) of the ADRs while 34 (17.1%) were type B reactions.

DISCUSSION

The overall prevalence of ADRs in this study was found to be 16.2%, which is consistent with the range of results from recent prospective studies in hospitalized patients which used a similar methodology as the present study (1, 4, 6). However, the figure in this study is higher than 3.7% and 6.9% incidences which were observed in a prospective study by Ramesh *et al.* (2003) (15) and Patel *et al.* (2007) (5), carried out in a tertiary referral center in South India and Mumbai, respectively. The findings of the study conducted by Jose *et al.* (2006) (7) in Karnataka, India showed a prevalence of 0.15% only. This is because this study used spontaneous reporting system as the only method for detecting ADRs. In the present study, ADRs were identified by prospective manner using patient chart as source of information (medical and nursing notes, laboratory diagnosis data) combined with spontaneous reporting. The most frequently encountered ADRs in this study were found to be metabolic ADRs (Table 2). Diuretics were the most prevalent drugs responsible for metabolic ADRs during hospitalization affecting, especially the elderly patients with a high degree of utilization of these drugs. This finding is consistent with the results of another study which included a population of elderly people (2, 16).

In contrast with the results of other studies which detected gastrointestinal ADRs up to a proportion of 31.3% (17) and 17.9% (2), in the present study gastrointestinal ADRs were the second most frequently manifested cases accounting for 22.6% of all ADRs. The majority of these ADRs were moderate symptoms like diarrhea and vomiting. There were only three cases of GI bleeding induced by aspirin. NSAIDs

were responsible for ADRs like gastritis and epigastric pain.

In our present study, hematological and cutaneous reactions were the third and fourth most frequently manifested ADRs accounting for 14.1% and 10.6% of all ADRs, respectively. This observation is consistent with the study conducted in India by Jose *et al.* (2006) (7) who reported cutaneous reactions as the most frequent ones. A study conducted in a teaching hospital in Taiwan also reported cutaneous and hematological reactions as the most frequently manifested ADRs (18).

Recent studies conducted on hospitalized patients reported antibiotics, diuretics, and anti-diabetics as drugs most frequently linked to ADRs. NSAIDs and opioids have been implicated, particularly in studies involving surgical patients with diuretics being prevalent as causative factors in elderly patients (19). Studies that were conducted in India showed anti-neoplastics 89 (21.8%) (7) and antibiotics 55 (33.5%) (20); as the drug classes to cause most of the ADRs. Similar to results obtained by other investigators, the result of our study showed a high percentage of ADRs in patients taking antibiotics, accounted for 20.1% of all ADRs. Similarly, a research carried out in Spain by Carrasco-Garrido *et al.* (2010) (21) revealed that 22.1% of ADRs were associated with antibiotics. In Italy, Trifiro *et al.* (2005) (22) studied the incidences of ADRs and ADR related hospital admissions from emergency visits and found that antibiotics were associated with 12.9% of ADRs. Diuretics and anticoagulant drugs were the next most common drugs responsible for ADRs, accounting for 16.1% and 15.1%, respectively.

The findings of this study were in accordance with recent studies in which there was a high prevalence of older patients with cardiovascular disease (23, 24). Furosemide 23 (11.6%) and tramadol 21 (10.6%) were the individual drugs to cause the majority of the ADRs. A previous unpublished thesis study conducted in 2010 by Immaculich Rani in the same setting indicated that cardiovascular agents, 89 (24.7%), followed by antibiotics, 66 (18.3%), and anti-coagulants, 51 (14.2%), were the chief groups of drugs in causing ADRs while furosemide and tramadol as the individual drugs to cause most of the ADRs. Common use of these

two drugs in the study hospital could be a good reason for these observed ADRs. Antibiotics were also among the most frequently prescribed drug classes in the hospital. Therefore, this excessive use of antibiotics was also responsible for an increased risk of ADRs.

According to the result of our study, type A reactions accounted for 82.9% of the ADRs while 17.1% ADRs were of type B. This was in agreement with the definition of type A reactions that are more common and predictable and type B reactions that are rare and uncommon. Moreover, our results were consistent with the reports of studies carried out in Karnataka, India and Liverpool, UK. In those reports, type A ADRs were found to be 72.5% (7) and 94.1% (6), respectively. The largest frequency of ADRs was very common in the females and has been described in various reports (19, 25). Wiffen *et al.* (2002) in their review identified gender to be a risk factor for development of ADR (26). Edwards *et al.* (2000) also reported that women were more susceptible to ADRs than men possibly by an association of factors such as greater concentration of adipose tissue and hormonal determinants that can affect metabolism, leading to the development of ADR (27).

In contrast, no significant difference was seen in the incidence of ADRs observed in male and female in the present study. Though the difference was not statistically significant in pediatric and adult population, relatively the highest percentage of ADRs was observed in elderly patients. Those groups of population also took more medications as compared to others to manage a number of co-morbidities associated with increase in age (28). Our findings were also in agreement with several studies. For instance, in a study conducted in Karnataka, India (7), the incidence of ADRs among elderly patients was significantly higher than among patients of other age groups. Similarly, a prospective study carried out in Punjab also showed that elderly patients had a higher incidence of ADRs (29). Studies conducted in England (30) also supported our observations. A retrospective study conducted in Australia also showed that elderly patients had a significantly higher incidence of ADR as compared to other age groups (31).

A significant association was observed between the length of hospitalization of a patient and the prevalence of ADRs in the present study ($p < 0.001$). Patients with longer stay in the hospital had more severe conditions, many co-morbid conditions and used a higher dose of different drugs. Therefore, patients with longer hospital stay were more prone to develop ADRs. There was also a definite association between ADRs and increased length of stay found out by several studies. A study conducted by Davies *et al.* (2006) in Royals Liverpool Hospital also indicated an increase in the incidence of ADRs with increased length of hospital stay (6). Similar study conducted in south India also reported that an increase in the incidence of ADRs as the length of stay of the patient increased (7). The number of diagnosis was found to be a significant predisposing factor for ADRs in the present study multiplying the risk by 1.2 with each additional diagnosis. Patients with more co-morbid conditions are always at a higher risk of developing ADRs. As found out in the present study, the majority of the patients admitted to the target hospital had hypertension and diabetes mellitus as co-morbidities. Those diseases could be attributed to impairment of renal function which was an important factor for increasing risk of ADRs, and also using a higher number of drugs to treat the multiple diseases could result in ADRs. The result of our study was also in a complete agreement with two studies conducted by Jose *et al.* (2006) (7) and Hardmeier *et al.* (2004) (32), which identified number of diagnosis as one of the most predisposing risk factors for having ADRs.

Many studies have shown that patients taking more medications suffer from ADRs (17, 24). Likewise, the present study also revealed number of drugs as a significant risk factor for ADRs with each additional medication multiplying the risk of an ADR episode by 1.1 (95% CI 1.06, 1.14). The possible reasons for this fact could be the prescription of multiple drugs which increase the risk of drug-drug interactions and additive or overlapping effects of multiple medications. Since the hospital selected for this study was a cardiac with multi-specialties, the majority of the patients admitted were with a number of co-morbidities which could result in

polypharmacy that lead to the occurrence of ADRs. A study conducted by Davies *et al.* (2006) in Royal Liverpool University Hospital also reported a similar finding to this study with a hazard ratio of 1.14 (95% CI 1.09, 1.20) (6).

In this study, cardiovascular ward had a higher incidence of ADRs than multispecialty ward ($p < 0.05$), which was similar to the previous unpublished thesis study conducted by Immaculich Rani in the same setting in 2010. This was because the majority of patients admitted to this ward were hypertensive and cardiac patients with other concomitant morbidities such as diabetes, anemia, dyslipidemia and so forth which could lead to polypharmacy and multiple organ failure, increasing the chance of the occurrence of ADRs. Moreover, patients who were admitted to the cardiovascular ward were older than those who were in multispecialty ward.

As described in previous sections, ADRs can be classified into definitely preventable, probably preventable and non-preventable. A review by Kanjanarat *et al.* (2003) (33) on preventable ADRs in hospitals revealed a preventability rate of 35.2%, while the present study indicated a preventability rate of 36.2% that was almost comparable with the former.

In conclusion, the present study showed that ADRs represented a significant part of overall medical events. In this study, antibiotics, diuretics, and anticoagulant agents accounted for more than 50% ADRs. That was a signal for a need for intervention and increased prevention level in ADR related health problems. It is important to note that better knowledge of preventable ADRs could help to design preventive strategies to protect patients from being affected by these reactions unnecessarily. Preventing the preventable ADRs (36.2% of the reactions) can result in a considerable health resource savings and at the same time can help improve the quality of health care provision. Therefore, we recommend further studies by health care professionals to accurately quantify the burden and to identify the risk factors of ADRs in hospitalized patients and to plan focused preventive strategies to minimize these drug-induced harms and improve the quality of patient care.

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REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200-05.
2. Farcas A, Sinpetrean A, Mogosan C, et al. Adverse drug reactions detected by stimulated spontaneous reporting in an internal medicine department in Romania. *Eur J Intern Med*. 2010; 21:453-57.
3. Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Begaud B. Adverse drug reactions in a department of systemic disease-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol*. 2000; 55:181-86.
4. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a pilot study. *J Clin Pharm Ther*. 2006; 31:335-41.
5. Patel KJ, Kedia MS, Bajpai D, Mehta SS, Kshirsagar NA, Gogtay NJ. Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: a prospective study. *BMC Clin Pharmacol*. 2007;7(8):1-5.
6. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS one*. 2009; 4(2):e4439.
7. Jose J, Padma GM. Pattern of adverse drug reactions notified by spontaneous reporting in an Indian tertiary care teaching hospital. *Pharmacol Res*. 2006; 54:226-33.

8. WHO. International drug monitoring: the role of national centers. *Tech Rep Ser WHO*. 1972; no 498.
9. Naranjo CA, Busto U, Sellars EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-45.
10. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49:2229-32.
11. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm*. 1992;27(6):538.
12. Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions. V- Clinical factors influencing susceptibility. *Ann Int Medicine*. 1966;65:629-39.
13. WHO. International monitoring of adverse reactions to drugs: adverse reaction terminology. WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden, 1992.
14. Wood KL, on behalf of the MedDRA Working Party. The medical dictionary for drug regulatory affairs (MedDRA). *Pharmacoepidemiol Drug Saf*. 1994;3:7-13.
15. Ramesh M, Pandit J, Parthasarathi G. Adverse drug reactions in a South Indian hospital - their severity and cost involved. *Pharmacoepidemiol Drug Saf*. 2003;12:687-92.
16. Passarelli MCG, Jacob-Filno W, Figueiras A. Adverse drug reactions in an elderly hospitalized population. Inappropriate prescription is a leading cause. *Drug Aging*. 2005;22(9):767-77.
17. Camargo AL, Cardoso Ferreira MB, Heineck I. Adverse drug reactions: a cohort study in internal medicine units at a university hospital. *Eur J Clin Pharmacol*. 2006;62:143-49.
18. Chan ALF, Haw Yu Lee, Chi-Hou Ho, Thau-Ming Chain, Shun Jin Lin. Cost evaluation of adverse drug reactions in hospitalized patients in Taiwan: a prospective, descriptive, observational study. *Curr Ther Res*. 2008;69(2):118-29.
19. Leach S, Roy SS. Adverse drug reactions: an investigation on an acute geriatric ward. *Age Ageing*. 1986;15:241-46.
20. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol*. 2008;65(2):210-16.
21. Carrasco-Garrido P, Ana de Andrés L, Hernández Barrera V, Ángel de Miguel G, Jiménez-García R. Trends of adverse drug reactions related hospitalizations in Spain (2001-2006). *BMC Health Serv Res*. 2010;10:287.
22. Trifirò G, Calogero G, Ippolito FM, et al. Adverse drug events in emergency department population: a prospective Italian study. *Pharmacoepidemiol Drug Saf*. 2005;14(5):333-40.
23. Alexopoulou A, Dourakis SP, Mantzoukis D, et al. Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. *Eur J Intern Med*. 2008;19:505-10.
24. Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the elderly (GIFA). *J Am Geriatr Soc*. 2002;50:1962-68.
25. Fattinger K, Roos M, Veregeres P. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol*. 2000;49:158-67.
26. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients: a systematic review of the prospective and retrospective studies. *Bandolier Extra*. 2002:1-16
27. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255-59.
28. Nobili A, Licata G, Salerno F, et al. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *Eur J Clin Pharmacol*. 2011;67:507-19.
29. Saha L, Pandhi P, Malhotra S, Sharma N. Adverse Drug Event (ADE) related Medical

-
- Emergency Department visits and hospital admissions: a prospective study from a North Indian Referral Hospital. *J Clin Diag Res.* 2008;2:600-04.
30. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Adverse drug reactions. *BMJ.* 1998;316(7140):1295-98.
31. Zhang M, Holman C, Price SD, Sanfilippo FM, Preen DB, Bulsara MK. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *BMJ.* 2009;338:2752.
32. Hardmeier B, Braunschweig S, Cavallaro M, et al. Adverse drug events caused by medication errors in medical inpatients. *Swiss Med Wkly.* 2004;134(45).
33. Kanjanarat P, Winterstein AG, Johns TE, Hatton RC, Gonzalez-Rothi R, Segal R. Nature of preventable adverse drug events in hospitals: a literature review. *Am J Health Syst Pharm.* 2003;60 (17):1750-59.