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A PROSPECTIVE OBSERVATIONAL STUDY ASSESSMENT OF ADVERSE DRUG REACTIONS DEVELOPED WITH NEWLY PRESCRIBED DRUGS IN PATIENTS WITH CHRONIC DISEASES

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ABSTRACT

Objective: The objective of present research is to identify the adverse drug reactions (ADR), study the pattern of ADRs caused by newly prescribed drugs and asses its prevalence in patients with chronic diseases.

Methods: The study carried out in 500 bedded multispecialty Hospital at general medicine department over a period of three years. The data was collected from patient case sheet, treatment charts, and lab reports and by direct interviewing patients and their care takers.The collected data is analysed for determining causative drug's relationship to ADR, for assess causality of ADR, for ADR severity assessment and for determining preventability of an ADR. Predictability and preventability were also assessed. Data analysed using SAS version 9.1. Chi-square and p values were calculated using Medcalc's calculator.

Results: Among 330 cases, 409 adverse drug reactions were identified, which shows the probability of multiple adverse drug reactions in a single patient.Among various age groups adults (64.24%) show higher prevalence, with male at higher risk than female.Majority of ADRs were identified by doctors or prescribers 208(50.85%).Among 592 patients specific and symptomatic treatment was given for majority

of 191 (46.69%) patients. The casuality assessment indicate that Possible and Probable are statistically significant.Most of ADRs were gastrointestinal 106 (25.91%) reactions, central nervous 72 (17.60%) reactions followed by cardiovascular 43(10.51%) reactions. A definite improvement was predominant in dechalleged patients whereas recurrence of symptoms was significantly observed among rechallenged patients with the respective suspected drug.In 409 ADRs cases majority (47.67%) weredefinitely preventable adverse drug reactions are followed by probably preventable adverse drug reaction.

Conclusion: Adverse drug reactions are more common and preventable. Vigilance by physicians, clinical pharmacists and other healthcare professionals in detecting, diagnosing and reporting can reduce their impact.

Keywords: WHO ART, Chi-Square Value / P-Value, Adverse Drug Reactions, Newly Prescribed Drugs, Chronic Diseases

INTRODUCTION

Any response to a drug which is noxious and unintended and which occurs at doses used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function is called adverse drug reaction (WHO). ADRs refer to the unwanted or dangerous effects that a drug may possess **[1]**. The incidence and severity of ADRs are influenced by patient characteristics such as age, gender, body weight, coexisting diseases, ethnicity, genetic or geographic factors and by drug factors such as the type of drug, dosage, treatment duration, co-ingestion of other drugs, and route of administration **[2]**. The seriousness of ADRs can vary and may results in persistent or significant disability/incapacity, hospitalization, a medically important or life-threatening condition, or even death **[3]**. When a new medicine is released into the market, there is still a substantial amount that is unknown about the safety of the medicinal product. When initiating new medications, the physician must provide appropriate directions (the reason for the medication, how to take it, and potential side effects.) and communicate the critical elements of the medical use in order to improve patient's medication adherence. Furthermore, better patient counsel about medications is associated with better medication adherence **[4-6]**. The newly prescribed drug must meet this Quality-of-life criterion which is generally defined as those that improve patient satisfaction with the quality of life but do little to improve medical outcomes or reduce overall health care costs **[7, 8]**. The probability of prescribing a particular drug varies between physicians. An important explanation for the decreased expenditure is

the shift from old and expensive drug to new and less expensive drug represents genuine welfare improvement. The patients that are studied in the pre-marketing clinical trials of new medicines are usually limited to a small number and are studied for a short period of time. Hence, only the more common ADRs are detected during the clinical trials. Information about rare but serious ADRs, drug interactions, chronic toxicity, and risks in special patient groups (e.g. pediatric groups, geriatric groups, males, females, certain race groups, pregnant women) is often not available or incomplete at the time of marketing **[9,10]**.

MATERIAL AND METHODS

A prospective observational study was conducted in various departments of a tertiary care teaching hospital for a period of three year. Prior to the initiation of study, ethical clearance was obtained from the hospital ethical committee.Objectives of the study include identification of group of people (age, sex, area) at higher risk, type of drugs involved in ADR development due to newly prescribed drugs for chronic diseases, treatment of ADRs, assess the severity of ADRs. Inclusion criterion of this study was an association between chief complaints on admission and the drug newly prescribed patient or patient caretaker being adequately communicable. Hospital admissions attributed to complaints unrelated to newly prescribed drugs for chronic conditions, ADRs caused by drugs prescribed for acute conditions are excluded from the study. Data of the patients (demographic details, past medical history, past medication history, laboratory investigations, suspected drug, drug stopped, drug reinitiated, provisional and conformational diagnosis, results of assessment of ADRs by various scales/criterion, treatment, interviewing patient and patient caretakers) with ADRs, caused by the drug initially prescribed admitted in hospital during the study period were collected and analysed. Case sheets of patients who were initially prescribed with a new drug for chronic case and revisited with complaints related to that drug are assessed for the impact of medication used in the past on the current complaints. Based on the information available, the severity of ADR was assessed (based on various ADR assessment scales- WHO probability scales and Naranjo scale). Data analysis was done by considering the categorical variables, which were represented in number and percentage. Data were analyzed using SAS version 9.1.Chi-square and p values were calculated using Medcalc's calculator **[11-18]**.

RESULTS

Among 330 cases, 409adverse drug reactions were identified, which shows the probability of multiple adverse drug reactions in a single patient. In 330 patients, 277 (83.93%) patients experienced one ADR followed by 31 (9.39%) patients have two ADRs, 8 (5.45%) patients have three ADRs and 4 (1.21%) patients have four ADRs. Total 409 Adverse drug reactions were reported. Statistically, chi-square value is 24.28 and P value is <0.0001.Hence one ADR is statistically significant.Among age groups adults 212 (64.24%) were predominant over geriatric 89 (26.96%) and children 29 (8.78%) in terms of prevalence, males have a higher risk to develop adverse drug reactions among adults andgeriatrics. In children, both the genders have high risk in developing adverse drug reactions.Most of ADRs were gastrointestinal 106 (25.91%) reactions, central nervous 72 (17.60%) reactions followed by cardiovascular 43(10.51%) reactions. Hence gastrointestinal and central nervous systems were found to be statistically significant through Chi-square value (188.42) and P value is <0.0001. Remaining details were mentioned in the **Table 1 (Figure 1)**.

Categorisation of According to Preferred term (WHO-ART) Vs. Suspected drug was detailed in **Table 2**.

Most of ADRs were identified by doctors or prescribers 208(50.85%) followed by other hospital pharmacist 92 (22.49%) and remaining details were given in **Table 3(Figure 2)**.

Statistically, Chi-square value is 110.54 and P value is <0.0001.In 409 ADRs, suspected drug was withdrawn in 276(67.48%) patients followed by 86 (21.02%) and remaining were detailed in **Table 4 (Figure 3)**.

Statistically, Chi-square value is 67.52 and p value is <0.0001.Among 592 patientsSpecific and symptomatic treatment was given in 191 (46.69%) patients followed by only symptomatic treatment 79 (19.31%) patients. Statistically, Chi-square value is 91.32 and P value is <0.0001 and remaining details were mentioned in the **Table 5 (Figure 4)**.

Among 276 dechallenge patients, drug was reinitiated in 83 (30.07%) and not reinitiated in 193(69.92%) patients. Among 276 dechallenge patients the outcome of ADRs were definite improvement 167(60.50%) patients followed by No improvement in 51 (18.47%) patients. Statistically, Chi-square value is 36.89 and P value is <0.0001. Hence, suspected drug withdraw cases definite improvement was found statistically

significant. Among 83 patients, the rechallenge of ADRs were performed in which, recurrence of symptoms was observed in 58 (69.87%) patients followed by no recurrence of symptoms in 18 (21.68%) patients. Statistically, Chi-square value is 44.68 and P value is <0.0001. Hence, recurrence of symptoms was found statistically significant; details were mentioned in **Table 6 (Figure 5)**.

Among 409 ADRs, causality assessment of ADRs according to WHO probability scale was studied where possible reactions in 170 (41.56%) patients followed by probable reactions in 140 (34.22%) patients. Statistically, Chi-square value is 234.87 and P value is <0.0001. Hence, possible and probable are statistically significant. ADRs were assessed using Naranjo scale where possible reactions 326 (54.69%) were followed by probable 207 (34.73%) and others were detailed in the **Table 7 (Figure 6 & 7)**.

Statistically, Chi-square value is 194.08 and P value is <0.0001. Hence, possible and probable are statistically significant. In 409 ADRs, predictable adverse drug reactions are 176 (43.03%) and not predictable are 233 (56.96%). Therefore, no statistical significance was seen. In 409ADRs, definitely preventable adverse drug reaction are 195 (47.67%) followed by probably preventable adverse drug reaction 187 (45.72%) and others were mentioned in **Table 8 (Figure 8 & 9)**.

Statistically, Chi-square value is 57.42 and P value is <0.0001. Hence, Definitely Preventable and Probably Preventable were found statistically significant.

Table 1: ADRs were distributed according to the WHO ART system codes

Sl. No	System	No. of ADRs	Percentage	Chi-Square Value / P-Value
1	Dermatology	40	09.77	88.42/ < 0.0001
2	Muscular skeletal	31	07.57	
3	Respiratory	33	08.06	
4	Central nervous	72	17.60	
5	Ophthalmic	02	0.48	
6	Otic system	02	0.48	
7	Gastrointestinal	106	25.91	
8	Hepatic system	15	03.66	
9	Endocrine	34	08.31	
10	Cardiovascular	43	10.51	
11	Haematology	04	00.97	
12	Renal system	11	02.68	
13	Others	16	03.91	
	Total	409	99.96	

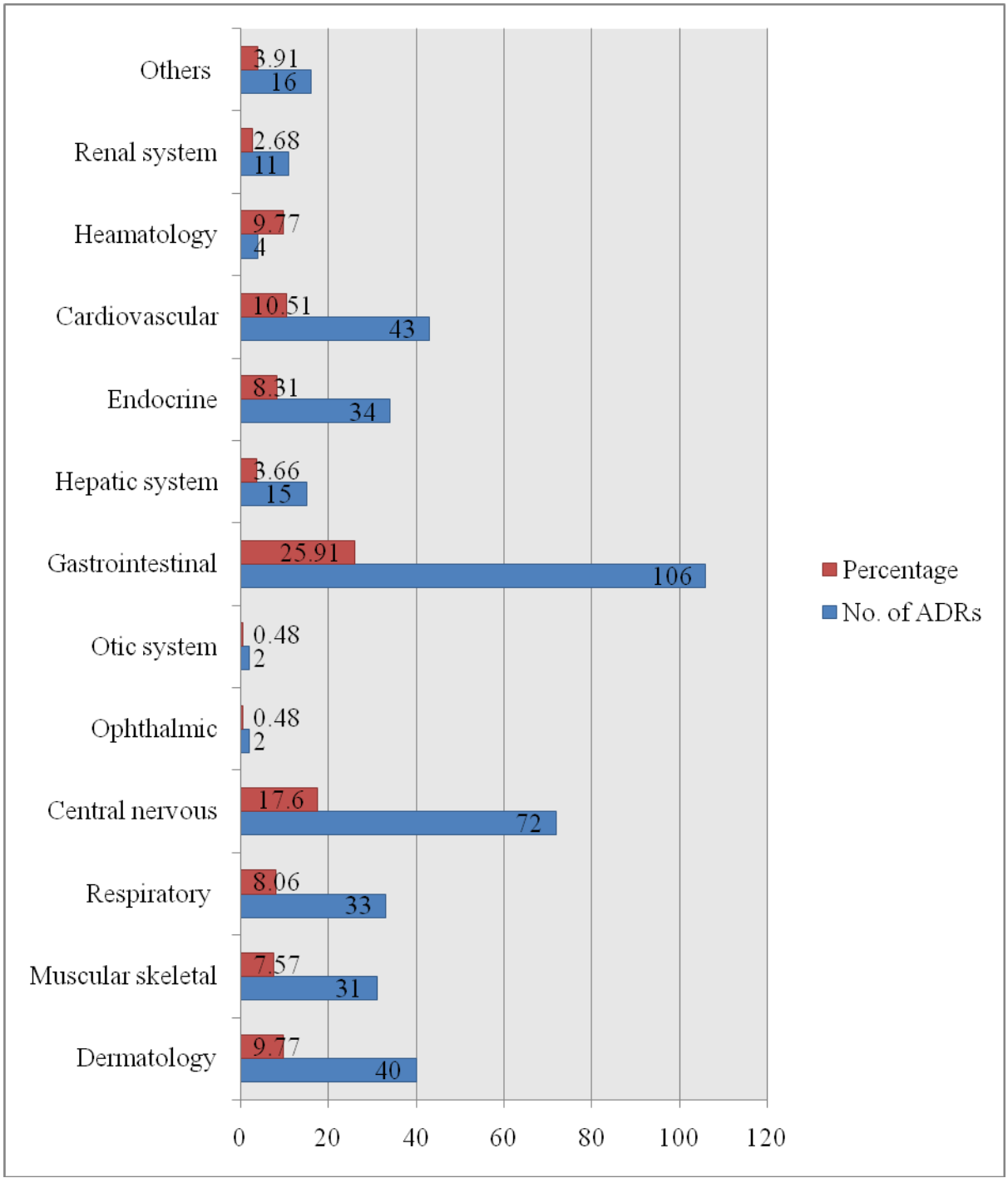

Figure 1: ADRs were distributed according to the WHO ART system codes

Table 2: ADRs were categorized according preferred term (WHO-ART) Vs. Suspected drug

Newly prescribed Medications	Preferred Term	No. of Patients	Percentage
Linagliptin 48	Hypoglycemia	12	25.00
	Abscess at site of Injection	6	12.5
	Arthralgia	5	10.41
	Weight increased	4	08.33
	Backache	4	08.33
	Headache	3	06.25
	Hyperlipidemia	3	06.25
	Diarrhea	3	06.25
	Cough	3	06.25
	Constipation	2	04.16
	Bullous pemphigoid	2	04.16
	Pancreatitis	1	02.08
Ivabradine 11	Bradyarrhythmia	5	45.45
	Increase heart rate	3	27.27
	Hypertension	2	18.18
	Visual impairment	1	09.09
Simeprevir 61	Nausea	13	21.31
	Hyperbilirubinemia	13	21.31
	Rash	8	13.11
	Myalgia	8	13.11
	Diarrhea	6	09.83
	General weakness and Fatigue	6	09.83
	Pruritus	4	06.55
	Photosensitivity	3	04.91
Saxagliptin 39	Urinary tract infectious disease	10	25.64
	Hypoglycemia	10	25.64
	Upper respiratory infection	8	20.15
	Peripheral edema	4	10.25
	Headache	4	10.25
	Arthralgia	1	02.56
	Pancreatitis	1	02.56
	Renal Impairment	1	02.56
Fosinopril 34	Dizziness	8	23.52
	Cough	6	17.64
	Hypotension	6	17.64
	Myalgia	5	14.70
	Hyperkalemia	3	08.82
	Nausea and vomiting	3	08.82
	Cardiac dysrhythmia	2	05.88
	Lichenoid drug eruption	1	02.94
Riociguat 78	Headache	17	21.79
	Nausea and vomiting	17	21.79
	Dizziness	14	17.94
	Diarrhea	12	15.38
	Hypotension	9	11.53
	Constipation	6	07.69
	Anemia	3	03.84
Alogliptin 31	Headache	9	29.03
	Upper respiratory infection	8	25.80
	Nasopharyngitis	6	19.35
	Hypoglycemia	6	19.35
	ALT/AST level raised	2	06.45
Pimavanserin 33	Nausea	10	30.30
	Peripheral edema	8	24.24
	Constipation	6	18.18
	Confusional state	6	18.18

	Hallucinations	3	09.09
Obeticholicacid 47	Pruritus	12	25.53
	Fatigue	10	21.27
	Arthralgia	7	14.89
	Constipation	6	12.76
	Rash	6	12.76
	Peripheral edema	4	08.51
	Pain in throat	2	04.25
Lixisenatide 27	Nausea and vomiting	9	33.33
	Diarrhea	7	25.92
	Headache	7	25.92
	Dizziness	4	14.81

Table 3: ADRs reported by person

Sl. No.	ADRs reported Person	No. of ADRs	Percentage (%)	Chi-Square Value / P-Value
1	Doctors or Prescriber	208	50.85	110.54/ < 0.0001
2	Hospital Pharmacist	92	22.49	
3	Patients	64	15.64	
4	Nurses	18	4.40	
5	Patient care taker	27	6.60	
Total		409	99.98	

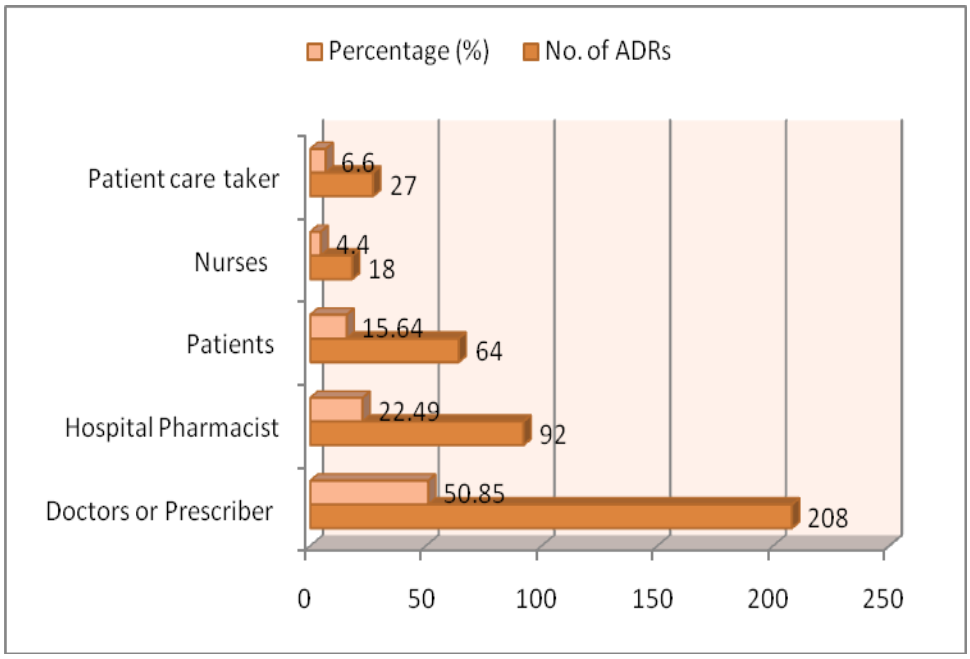

Figure 2: ADRs reported by management of the adverse drug reaction

Table 4: Fate of the suspected drug

Sl. No	Fate of the suspected drug	No. of ADRs	Percentage	Chi-Square Value / P-Value
1	Drug withdrawn	276	67.48	67.52 / < 0.0001
2	Dose altered	86	21.02	
3	No change	47	11.49	
	Total	409	99.99	

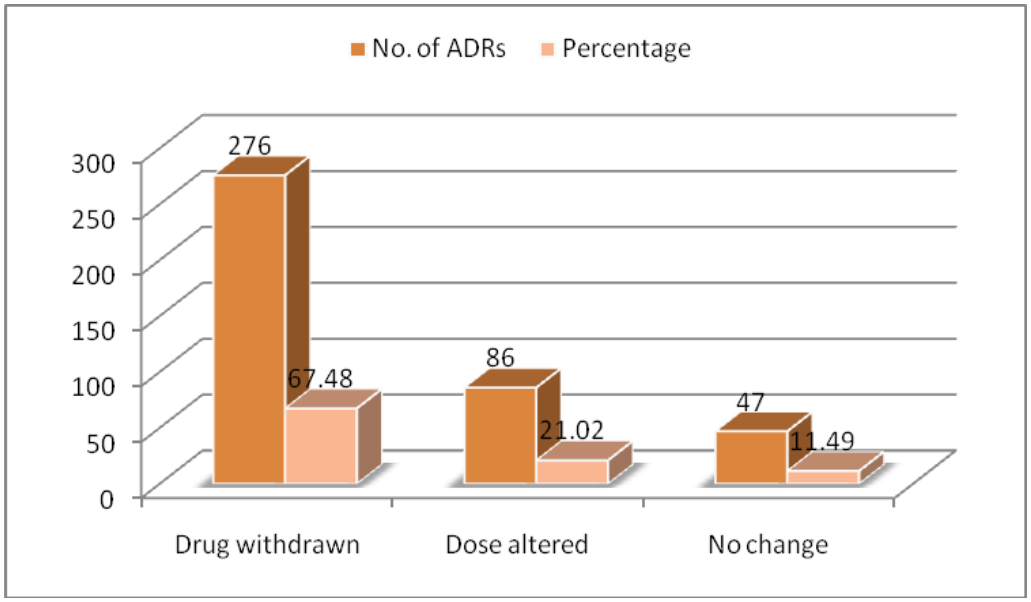

Figure 3: Fate of the suspected drug

Table 5: Treatment for ADRs

Sl. No	Treatment given	No. of ADRs	Percentage	Chi-Square Value / P-Value
1	Specific + Symptomatic	191	46.69	91.32/ <0.0001
2	Symptomatic	79	19.31	
3	Specific	71	17.35	
4	Nil	68	16.62	
	Total	409	99.99	

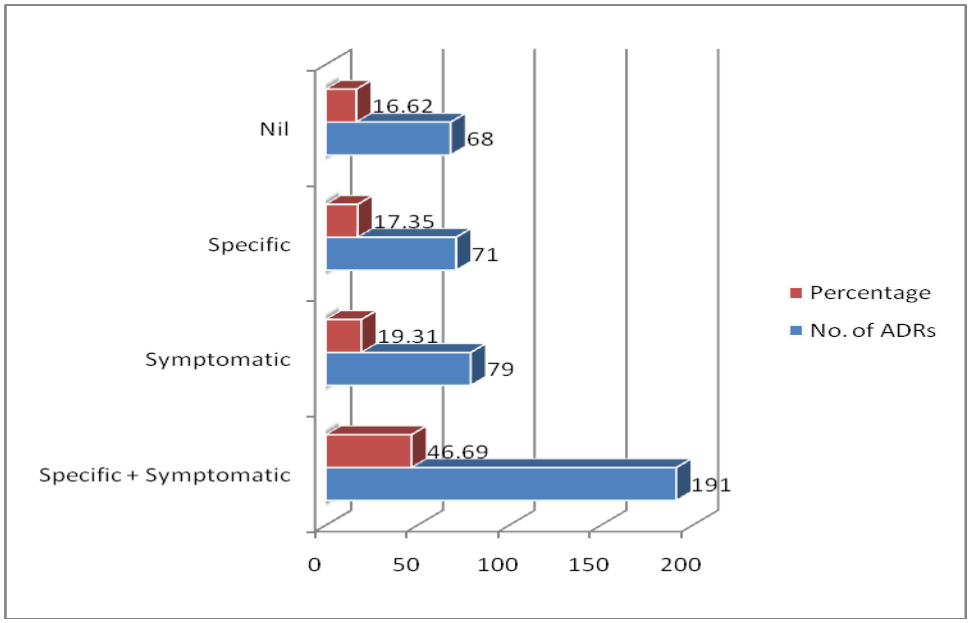

Figure 4: Treatment for ADRs

Table 6: Dechallenge and rechallenge information

Sl. No.	Group	adverse drug reactions	Frequency	Percentage (%)	outcomes	Frequency	percentage
1.	Dechallenge	Yes	276	67.48	Definite improvement	167	60.50
					No improvement	51	18.47
					Unknown	58	21.01
					Chi-Square Value / P-Value	36.89/<0.0001	
		No	133	32.51			
2.	Rechallenge	Yes	83	30.07	Recurrence of symptoms	58	69.87
					No recurrence of symptoms	18	21.68
					Unknown	07	08.43
					Chi-Square Value / P-Value	44.68/<0.0001	
		No	193	69.92			

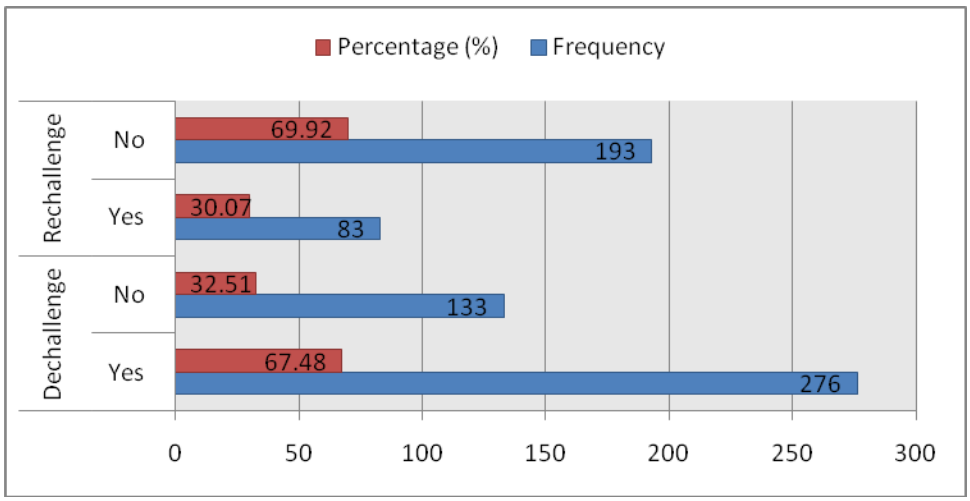

Figure 5: Dechallenge and rechallenge information

Table 7: Causality assessment adverse drug reactions according WHO probability and Naronjo's scale

ADR assessment scale	Category	No. of ADRs	Percentage	Chi-Square Value / P-Value
WHO probability scale	Certain	12	02.93	234.87/ <0.0001
	Probable	170	41.56	
	Possible	140	34.22	
	Unassessable / Unclassifiable	65	15.89	
	Unlikely	17	04.15	
	Conditional/Unclassified	05	01.22	
	Total	409	99.98	
Naronjo's scale	Definite	11	02.68	194.08/ <0.0001
	Probable	203	49.63	
	Possible	174	42.54	
	Unlikely	21	05.13	
	Total	409	99.98	

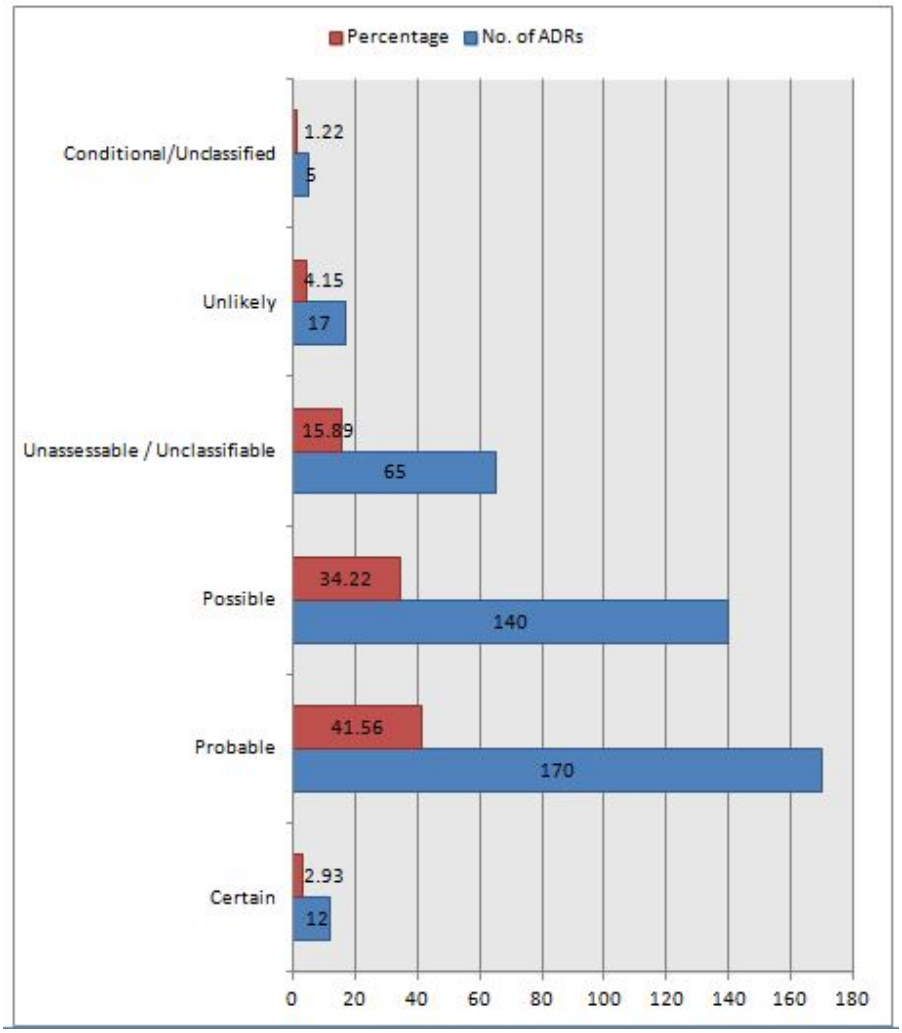

Figure 6: Causality assessment adverse drug reactions according WHO probability scale

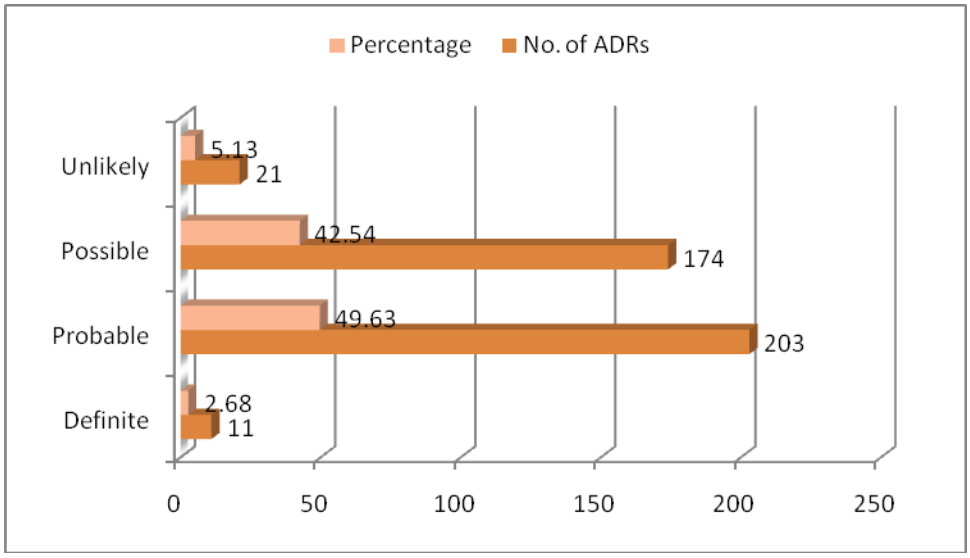

Figure 7: Causality assessment adverse drug reactions according Naronjo's scale

Table 8: Assessment adverse drug reactions predictability and preventability

	Category	No. of ADRs	Percentage	Chi-Square Value / P-Value
Predictability	Predictable	176	43.03	2.72/>0.06
	Not Predictable	233	56.96	
	Total	409	99.99	
Preventability	Definitely Preventable	195	47.67	57.42/<0.0001
	Probably Preventable	187	45.72	
	Not Preventable	27	06.60	
	Total	409	99.98	

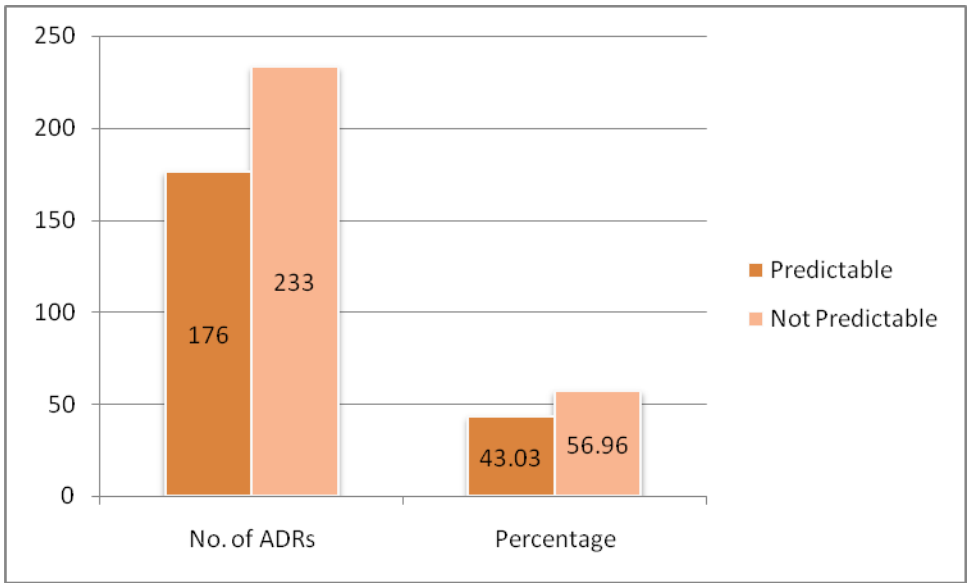

Figure 8: Assessment adverse drug reactions Predictability

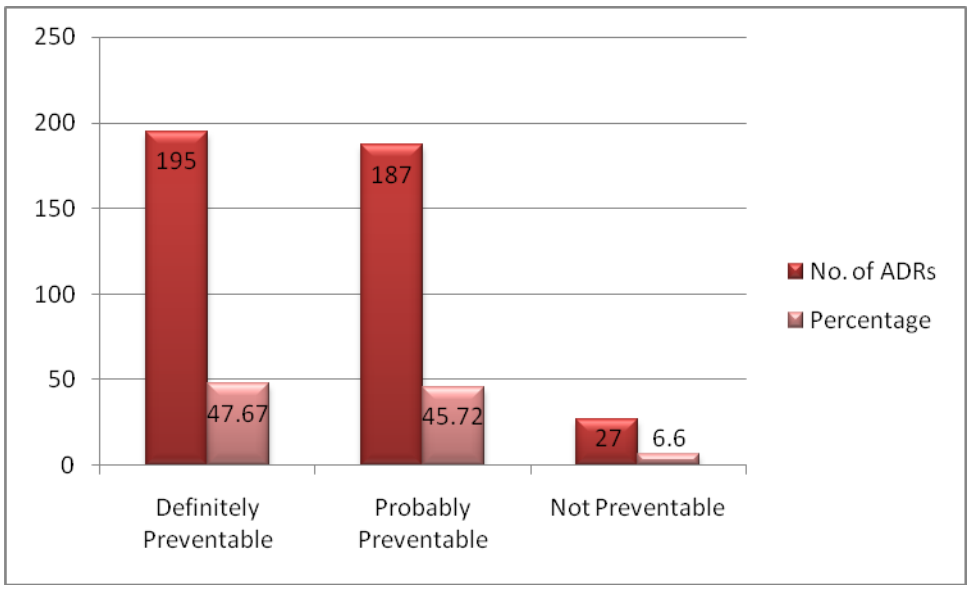

Figure 9: Assessment adverse drug reactions preventability

DISCUSSION

In this study, multiple adverse reactions are found in single patients. Among the 330 patients, adults 64.24% were predominant over geriatric 26.96% and children 08.78% in terms of prevalence, while males have higher risk to develop adverse drug reactions among adults and geriatrics, and in Children both the genders have high risk in developing adverse drug reactions and showing 1.68 times higher risk for males to develop adverse drug reactions. Among the 330patients documented predominance of adverse drug reactions was observed in patients belonging to urban area 60.00%, showing 1.5 times higher risk for adverse drug reactions in individuals of urban area compared to rural area. Among all the individuals regardless of sex, the distribution of drug related problems is significant in rural areas. Among 330patients, the higher prevalence of current medical diagnosis was observed in patients having a current medical diagnosis of metabolic disease and renal disease. Most of ADRs were experienced by dermatology reactions and gastrointestinal.Most of ADRs were identified by doctors or prescribers 50.85% followed by other hospital pharmacist. In 409 ADRs suspected drug was withdrawn in 67.48% patients followed by 21.02% patients dose were altered and no change in prescription in 11.49 patients. Among 409 ADRs, specific and symptomatic treatment was given in 46.69% patients followed by only symptomatic treatment was given in 19.31% patients. Dechallenge done in 67.48% patients and the suspected drug was continued in 32.51% patients. In 276 dechallenge patients 30.07% reinitiated the drug and 69.92% patients not reinitiated. Among 83 patients the rechallenge of ADRs outcome was as follows, recurrence of symptoms was observed in 69.87% patients followed by no recurrence of symptoms in 21.68% patients and unknown patients are 08.43%.Among 409 adverse drug reactions, causality assessment of ADRs according to WHO probability scale and Naranjo scale. In 409ADRs not-Predictable adverse drug reactions are 56.96% and not predictable are 43.03%. In 409 ADRs Definitely Preventable adverse drug reactions are 47.67% followed by probably preventable adverse drug reaction are 45.72% and not preventable are 06.60%. The ADR report analysis was used to compare content from patients-versus HCPs-submitted reports in terms of ADR seriousness, ADR classification by system organ class, and the medication involved based on the anatomical therapeutic class system (ATC). Only ADRs which are classified as ‘serious’ were analysed because

identifying serious ADRs are the primary focus of spontaneous reporting systems and are of particular public health interest.

Adverse drug reactions are the significant problems contributing to morbidity, mortality and results in considerable financial burden. Adverse drug reactions are more common and few of them are preventable with little care.Vigilance by physicians, clinical pharmacists and other healthcare professionals in detecting, diagnosing and reporting can reduce their impact. Adverse drug reactions can be prevented by taking measures which reduce the burden and thereby improve the benefit: harm ratio of drugs.

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