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Adverse drug reaction study in tertiary care hospital

Avanthika Sidda*, K.Chandralekha, Dr. Shivkumar Kashinath Shete

Department of Pharmacy Practice, Sree Dattha Institute of Pharmacy, Sheriguda, Ibrahimpatnam, Telangana.

***Corresponding Author: Avanthika Sidda**
Email id: avanthika.sidda@gmail.com

ABSTRACT

The prospective and observational non-interventional study was conducted in Aware Global Hospital. In-patients treated with drugs in the various clinical departments of hospital were reviewed on daily basis. All suspected ADRs will be suitably assessed for causality, severity, preventability and predictability. The results were presented as number and percentage. Among the 1129 cases (males and females), a total of 139 ADRs were detected, an overall incidence of 46.64% adverse drug reactions in inpatients. The prevalence of ADR mostly occurred in the age group between 31-60 years (46%) and in female patients (56.83%). The most frequent adverse drug reaction were due to Antibiotics (46%), Anti-Tubercular drugs (5.75%), Oral-Hypoglycemics (5.04%), NSAIDs (5.03%). Adverse drug reactions were a common occurrence and awareness about them was found to be essential for early detection and prevention. The healthcare system can promote the spontaneous reporting of ADR to Pharmacovigilance centre's for ensuring safe drug use and patient care. Our study suggests that there is a need of intensive ADR monitoring in tertiary care hospital for early detection and prevention to ensure the patient safety.

Keywords: Adverse drug reaction, Causality, Severity, Preventability, Probability.

INTRODUCTION

Definition

The WHO defines an "Adverse drug reaction as "any response to a drug which is noxious and unintended and which occurs or doses normally used in man of prophylaxis diagnosis or therapy of disease or for the modification of physiologic function". [1]

Pharmacovigilance has been defined by the WHO as 'The science and activities relating to the "detection, assessment, understanding and prevention of adverse effects or any other drug-related problems". [2]

Adverse drug reactions (ADRs) are types of adverse drug events (ADEs). ADEs include ADRs, medication errors and other drug-related problems. ADEs are the negative consequences of drug misadventures. Henri Manasse defined drug misadventure as the iatrogenic hazard that is an inherent risk when drug therapy is indicated.

The American Society of Health- System Pharmacists (ASHP) defines significant ADRs as any unexpected, unintended, undesired, or

excessive response to a drug that includes the following. [3,4,5]

- ❖ Requires discontinuing the drug
- ❖ Requires changing the drug therapy
- ❖ Requires modifying the dose
- ❖ Necessitates admission to the hospital
- ❖ Prolongs stay in a health care facility
- ❖ Necessitates supportive treatment
- ❖ Significantly complicates diagnosis
- ❖ Negatively affects prognosis or results in temporary or permanent harm, disability or death.

Consistent with this definition, an allergic reaction (an immunologic hypersensitivity, occurring as the result of unusual sensitivity to a drug) and an idiosyncratic reaction (an abnormal susceptibility to a drug that is peculiar to the individual) are also considered as ADR.

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that increases toxicity, decreases desired therapeutic effect or both.

METHODOLOGY

Study location

The study is carried out at Aware Global Hospital in General Medicine & all Clinical Departments.

Study design

Prospective, Observational and Non-interventional.

Study period

Study period was carried out for 6 months (October 2016 to March 2017**)**

Study setting

Study includes only those patients who experience an adverse reaction to medicine used either during their stay in hospital (IPD) or visiting the outpatient departments (OPD).

PATIENTS SELECTION

Study participants were inpatients in general medicine department according to the inclusion and exclusion criteria.

Inclusion Criteria

- Patients of either sex above 12 years.
- All patients admitted in Aware Global Hospitals.
- All suspected ADRs that conforms to WHO's definition.
- Patients of either sex receiving treatment.
- Any patient who developed ADR during the treatment period.
- Patients willing to Participate.

Exclusion Criteria

- Out Patient Dept. (OPD) patients.
- Day care surgery patients.
- Patients unable to respond to verbal questions.
- Patients who are not willing to participate.
- Pediatric patients (below 12yrs of age).
- Emergency Patients.

ANALYSIS OF ADRS

Types of adverse drug reactions based on Rawlins and Thompson classification

In this classification, the ADRs are categorized into two classes viz type A and type B reactions.

Type A reactions

These include the reactions that are predictable from the drug's known pharmacology and are usually dose dependent. Their incidence and morbidity are generally high while mortality is usually, but not invariably low. Examples are bradycardiawith b adrenoceptor blockers, hemorrhage with anticoagulants, hypoglycaemia with sulphonylureas, etc. Some type A reactions have a long latency, like teratogenicity, chloroquine retinopathy, delayed effects like vaginal adenocarcinoma in daughters of women who received diethylstilbestrol during pregnancy, etc.

Type B reactions

These are aberrant or bizarre effects that cannot be predicted on the basis of the drug's pharmacology. These reactions are generally unrelated to dosage and though comparatively rare, they often cause serious illness and death. These reactions are often not observed during conventional pharmacological and toxicological screening programmes and consequently account

for many drug withdrawals from the market. Some examples are: malignant hyperthermia of anaesthesia, anaphylaxis due to penicillin, and many immunological reactions. [6]

CAUSALITY ASSESSMENT [7]

Different scales for assessing causality relationship between suspected drug and reaction was established by using

EXPERT JUDGEMENT/GLOBAL INTROSPECTION

World Health Organization (WHO) - Uppsala Monitoring Centre (UMC) causality assessment criteria

WHO-UMC system has been developed in consultation with the National Centers participating in the programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment considering the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since Pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. This method gives guidance to the general arguments which should be used to select one category over another.

The WHO–UMC causality assessment method includes the following four criteria

- ✓ Time relationships between the drug use and the adverse event.
- ✓ Absence of other competing causes (medications, disease process itself).
- ✓ Response to drug withdrawal or dose reduction (dechallenge).
- ✓ Response to drug re administration (rechallenge).

The level of causal association is groped into six categories which are based on a number of the above criteria being met. Causal category is "certain" when all the four criteria are met. It is "probable" when criteria a, b and c are met. When only criterion is met, the event is categorized as "possible" and it is "unlikely" when criteria a and b are not met. Beside these four categories, ADR can also be categorized into "Unclassified/Conditional" or "Unassessable/ Unclassifiable" in WHO-UMC causality assessment. The term "Unclassified/Conditional" is applied when more data is needed and such data is being sought or is already under examination. Finally, when the information in a report is incomplete or contradictory and cannot be complemented or verified, the verdict is "Unclassifiable". For drug-drug interactions the WHOUMC system can be used by assessing the interacting drug, which influences the kinetics or dynamics of the non-interacting drug (which has usually been taken over a longer period), in the medical context of the patient. Dechallenge is the clinical decision to withdraw/discontinue a drug treatment after possible ADR has occurred. A dechallenge is "positive" or "suggestive" if the reaction abates, partially or completely when the drug is withdrawn and is considered to be "negative" or "against" if the reaction does not abate when the treatment is stopped. Rechallenge is nothing but the deliberate or inadvertent administration of a further dose(s) of the same medicinal product to a person who has previously experienced an adverse event/adverse drug reaction that might be drug related. Failure of the product, when reintroduced, to produce signs and symptoms similar to those observed when the suspect drug was previously introduced implies a negative rechallenge, while recurrence of similar signs and symptoms upon reintroduction of the suspect product implies a positive rechallenge.

Naranjo scale

It is used to assess causality in a variety of clinical situations using the conventional categories and definitions of "definite", "probable", "possible" and "doubtful". It consists of ten questions that are answered as "yes", "no", "unknown (don't know)". The event is assigned to a probability category based on the total score. A total score of ≥ 9 is "definite", "probable" is 5–8, "possible" 1–4 and "doubtful" ≤ 0. This scale is intended to assess the likelihood of an ADR associated with only one drug, not for adverse drug events resulting from interactions between two drugs. The Naranjo scale does not address the main points that are necessary in causality evaluation of potential drug interactions.

SEVERITY ASSESSMENT

The severity of reported reactions was assessed by using **Hartwig&Seigel scale**which arecategorized into mild, moderate and severe

Mild reactions were self-limiting and able to resolve over time without treatment and did not contribute to prolongation of length of stay.

Moderate ADRs were defined as those that required therapeutic intervention and hospitalization prolonged by 1 day but resolved in <24 h or change in drug therapy or specific treatment to prevent a further outcome.

Severe ADRs were those that were life threatening, producing disability and those that prolonged hospital stay or led to hospitalization, required intensive medical care or led to the death of the patient. [8,9]

PREVENTABILITY ASSESSMENT

The preventability of reported ADRs was assessed by **using Modified Shumock and Thornton scale**and was categorized as definitely preventable, probably preventable and not preventable, was shown in annexure-6. When an event was reported, all patients who experienced an ADR were followed from the day of reporting of an ADR until the discharge of patients to gather up-dated information regarding the changes and the progress in the patients' condition and management. [10]

Section A

Answering "yes" to one or more of the following implies that an ADR is

Definitely Preventable

- Was there a history of allergy or previous reactions to the drug?
- Was the drug involved inappropriate for the patient's clinical condition?
- Was the dose, route, or frequency of administration inappropriate for the patient's age, weight, or disease state?
- Was a toxic serum drug concentration (or laboratory monitoring test) documented?
- Was there a known treatment for the ADR?

If answers are all negative to above, then proceed to Section B

Section B:

Answering "yes" to one or more of the following implies that an ADR is **Probably Preventable.**

- Was required therapeutic drug monitoring or other necessary laboratory tests not performed?
- Was a drug interaction involved in the ADR?
- Was poor compliance involved in the ADR?
- Were Preventive measures not prescribed or administered to the patient?

If answers are all negative to the above, then proceed to section C

Section C

ADR is **'Not Preventable**

PREDICTABILITY ASSESSMENT

The predictability of the reported ADRs was assessed by using developed criterion for determining predictability of an ADR and wascategorized as predictable or not predictable based on the incidence rate of reported adverse drug reaction.

Criteria for determining predictability of ADRs

Patients who have had the drug on previous occasion**.**

- If the drug was previously well-tolerated at the same dose and ROA, the ADR is **'not predictable'**.
- If there was a history of allergy or previous reactions to the drug, the ADR is **'predictable'.**

Patients who have never had the drug previously.

- Incidence of the ADR reported in product information or other literature determines its predictability.
- Incidence more than 1% is **predictable.**
- Incidence less than 1% is **not predictable.**

RESULTS AND STATISTICAL ANALYSIS

Table 6.1 shows details of the encountered ADR are reported by spontaneous method. Out of 139 reported, 77 were reported by Pharmacist, 34 were reported by Doctor, 16 by Nurse and 12 by Patient.

Table 6.1: Detection of Adr By Spontaneous Method

ADR reported by spontaneous method	No. of ADR (n=139)	PERCENTAGE %
DOCTOR REPORT	34	24%
PHARMACIST REPORT	77	55%
NURSE REPORT	16	12%
PATIENT	12	9%

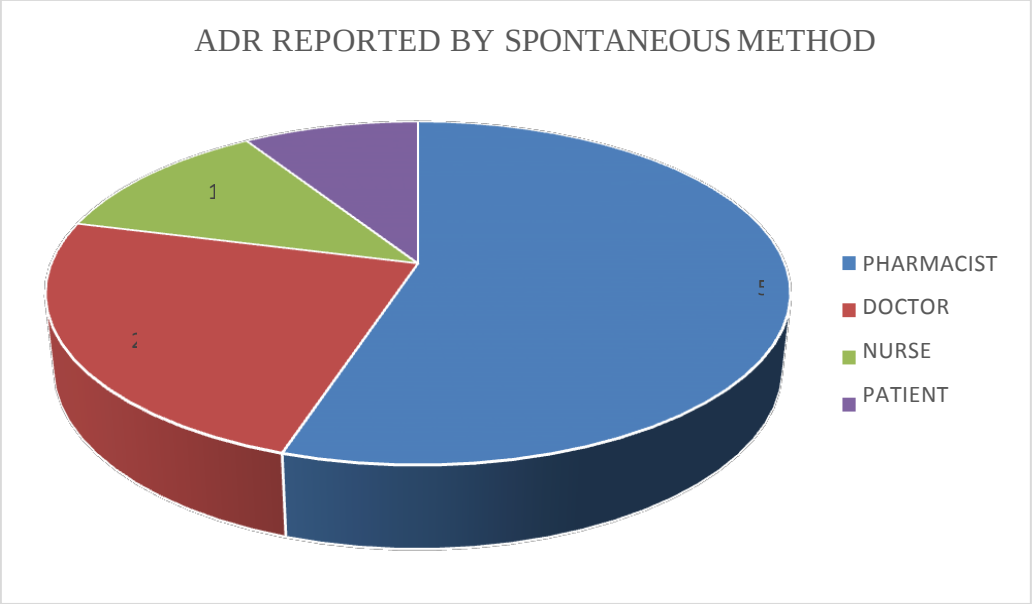

Figure 6.1: Detection Of Adr By Spontaneous Method

Table 6.2shows age distribution of the patients who had encountered ADRs at the study site. The data revealed that maximum number of patients(64) who had encountered ADRs during the study period were in the age group31-60years.

Table 6.2: Patient Demographics: Age

AGE	No.of ADR's (n=139)	PERCENTAGE %
13-17	10	7%
18-30	29	21%
31-60	64	46%
Above 61	36	26%

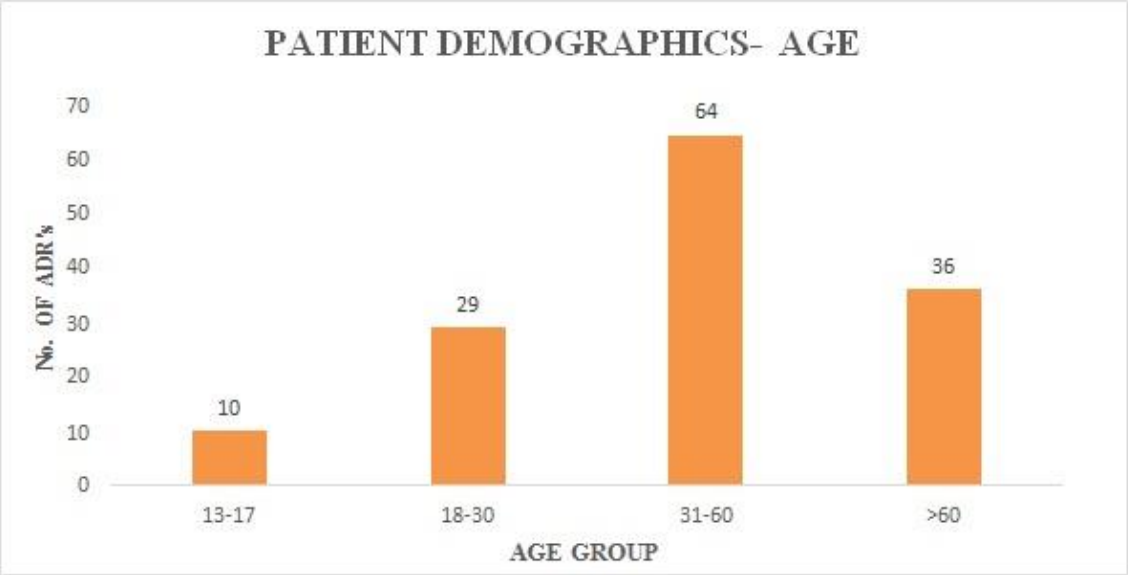

Figure 6.2: Patient Demographics: Age

Table 6.3shows the gender distribution of patients who had encountered ADR's during the study period at the study site. Study reveals Female were more affected by ADR's as compared to male patients.

Table 6.3: Gender Distribution Of Patients

GENDER	No of ADR's (n=139)	PERCENTAGE %
MALE	60	43%
FEMALE	79	57%

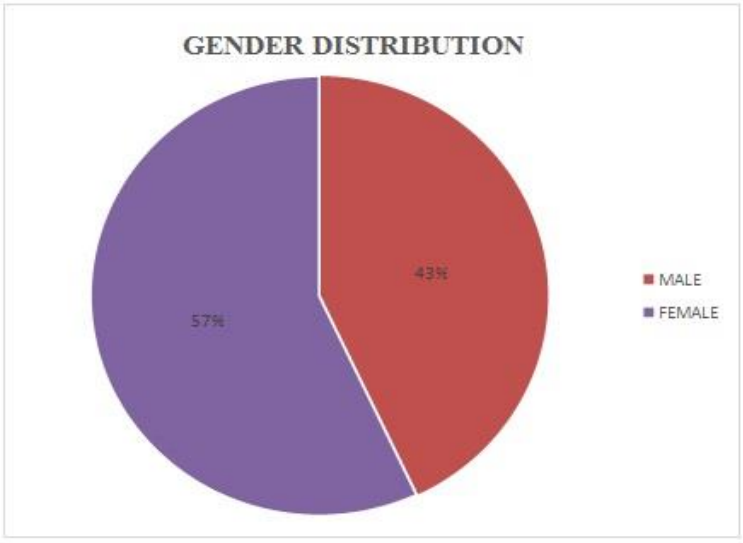

Figure 6.3: Gender Distribution of Patients

Table 6.4 shows the classification of ADR's encountered into Type A and Type B based on Thompson's and Rawlins Classification. It was observed that the most of the reported ADR's were Type A.

Table 6.4: Classification Of Adrs

TYPES	No. of ADR (n=139)	PERCENTAGE %
TYPE A	101	73%
TYPE B	38	27%

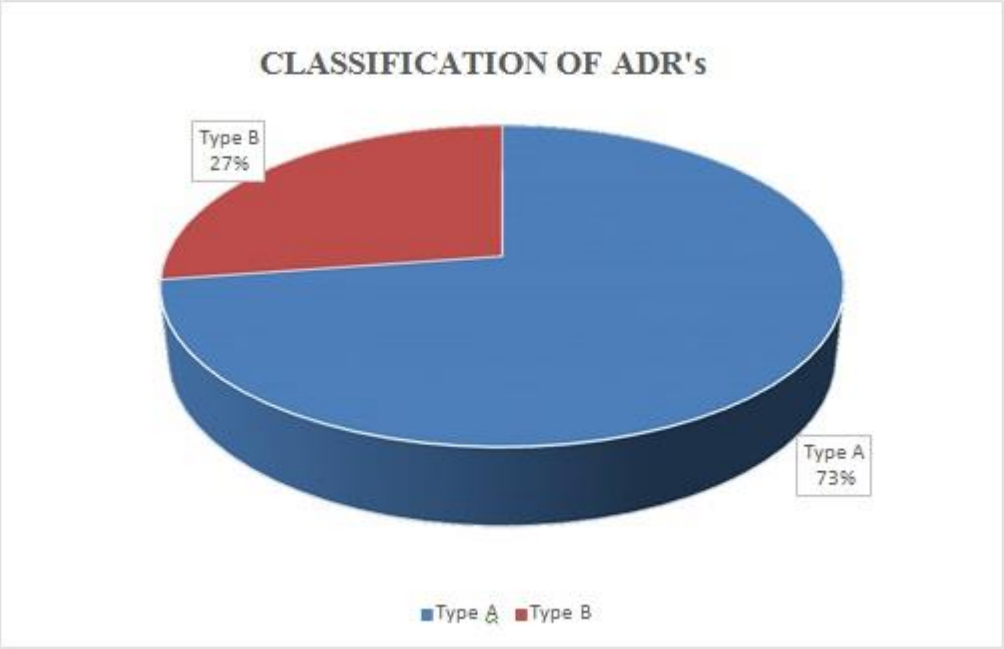

Figure 6.4: Classification of Adrs

Table 6.5 shows the Causality assessment of ADR based on Naranjo's Causality assessment scale.The result showed that most of the encountered ADR were possible.

Table 6.5: Adr Profile: Causality Of Adrs

PROBABILITY	No. of ADR (n=139)	PERCENTAGE %
DEFINITE	1	1%
PROBABLE	63	45.3%
POSSIBLE	72	51.7%
DOUBTFUL	3	2%

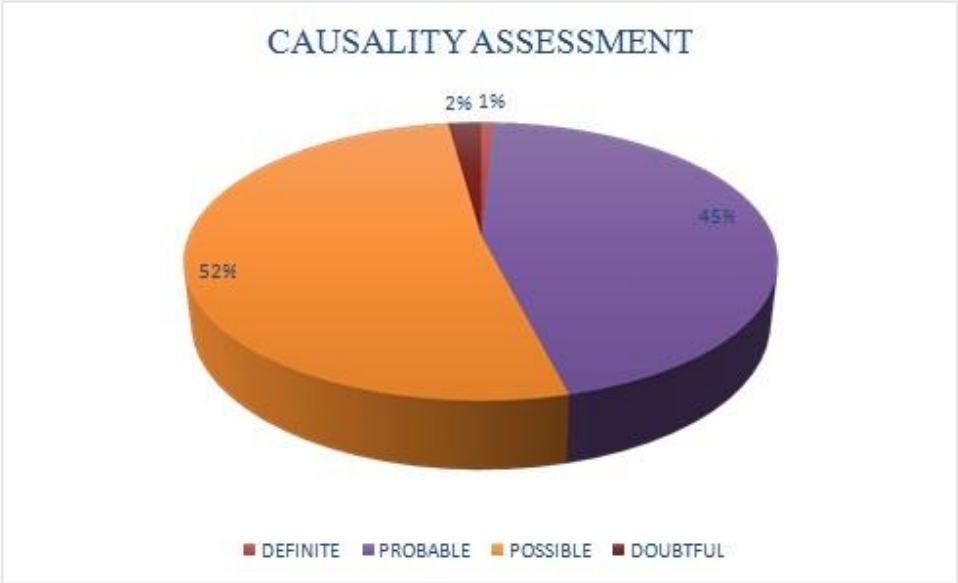

Figure 6.5: Adr Profile: Causality of Adrs

Table 6.6 shows the severity of ADR's encountered during the study period determined by using the Hartwig and Siegel Assessment Scale. The results of the assessment revealed that most of the ADRs were moderate in severity followed by mild and severe cases.

Table 6.6: Adr Profile: Severity Of Adrs

SEVERITY	No. of ADR (n= 139)	PERCENTAGE %
MILD	33	24%
MODERATE	96	69%
SEVERE	10	7%

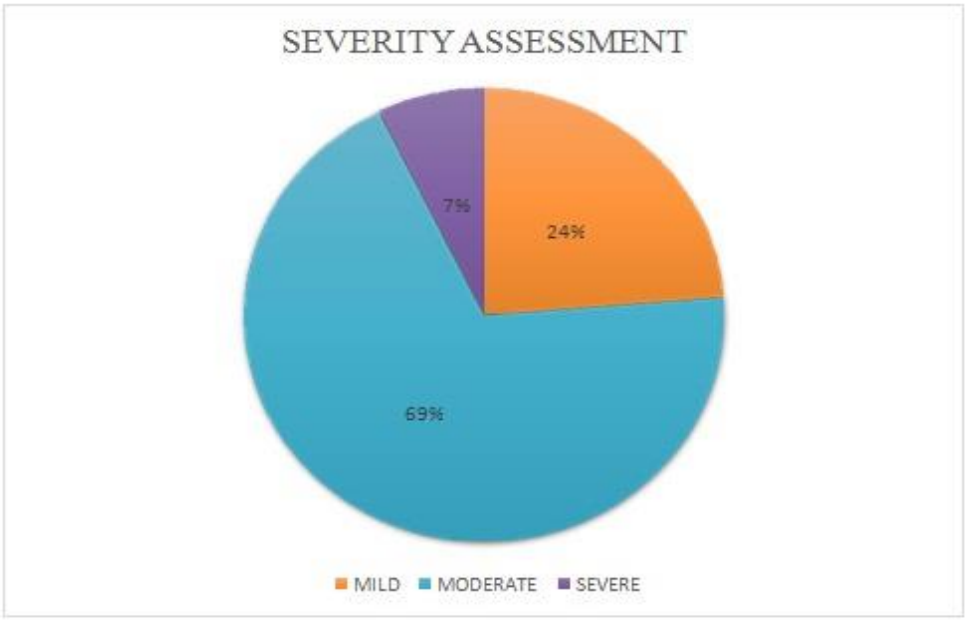

Figure 6.6: Adr Profile: Severity of Adrs

Table 6.7 shows the preventability of the ADR's was assessed by using Modified Shumock and Thornton Criteria. The results were revealed that 5% are definitely preventable, 71% probably preventable and 24% were not preventable.

Table 6.7: Adr Profile: Preventability of Adrs

PREVENTABILITY SCALE	No. of ADR's (n=139)	PERCENTAGE %
DEFINITELY PREVENTABLE	7	5%
PROBABLY PREVENTABLE	99	71%
NOT PREVENTABLE	33	24%

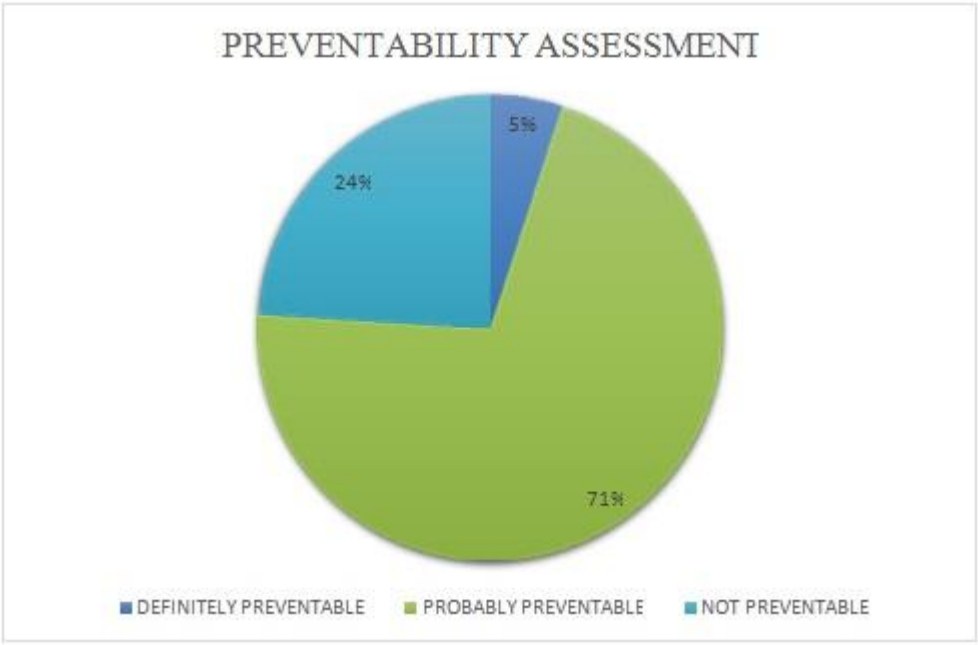

Figure 6.7: Adr Profile: Preventability of Adrs

Table 6.8 shows the various organ systems affected by ADR's encountered during the study period. The most organ systems affected by ADR's were Dermatological, CNS, Haematological, Respiratory, Gastro-Intestinal Tract, Nephrology, ENT, Hepatology, Cardiology, Endocrinology.

Table 6.8 Organ-Systems Affected By Adrs

ORGAN SYSTEMS	No. of ADR'S (n=139)	PERCENTAGE (%)
ENT	7	5%
Dermatological	58	42%
CNS	22	16%
Respiratory system	11	8%
Haematological system	15	11%
CVS	3	2%
Gastrointestinal system	8	6%
Hepatological system	5	3%
Endocrinology	3	2%
Nephrological system	7	5%
Total	**139**	**100%**

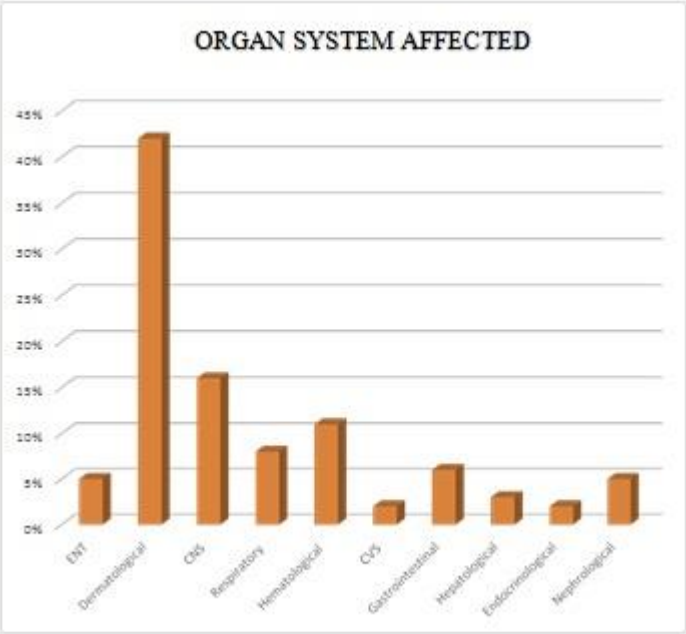

Figure 6.8: Organ-Systems Affected By Adrs

Table 6.9 shows the detail result of drug classes implicated in ADR onset. Out of 139 ADR reported, Antibiotics caused the maximum no. of ADRs followed by other class of drugs.

Table 6.9: Therapeutic Drug Classes Implicated In Adrs

DRUGS	No. of ADR's (n=139)	PERCENTAGE %
Antibiotics	64	46%
Anti-Epileptic	7	5%
Anti-Hypertensive	4	3%
Anti-Cancer	7	5%
Anti-Viral	5	4%
Anti-Psychotics	3	2%
Anti-Histamine	2	1%
Anti-Tubercular	8	6%
Anti-Leprotic	1	1%
Anti-Malarial	2	1%
Anti-Anaemic	5	4%
Anti-Coagulants	7	5%
Antidote	2	1%
Bronchodilator	2	1%
Diuretics	5	4%
Oral Hypoglycaemias	7	5%
NSAIDs	7	5%
Proton Pump inhibitors	1	1%
Total	**139**	**100%**

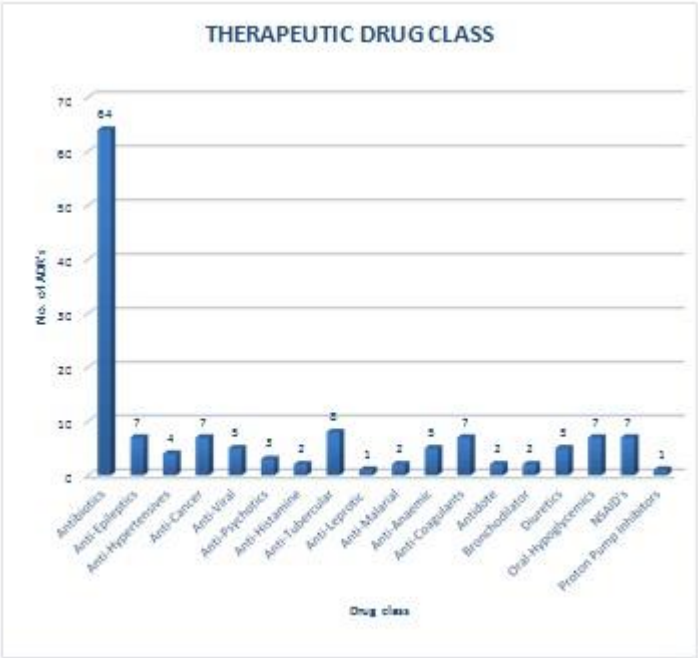

Figure 6.9: Therapeutic Drug Classes Implicated In Adrs

Table 6.10 shows the outcome of management of reported ADR's suggested that 62% were recovered cases, 31% were recovering, 6% were continuing and 1% were fatal.

Table 6.10: Outcome of Management Of Adrs

OUTCOME OF ADR	No. of ADR'S (n=139)	PERCENTAGE %
RECOVERED	86	62%
RECOVERING	43	31%
CONTINUING	8	6%
FATAL	2	1%

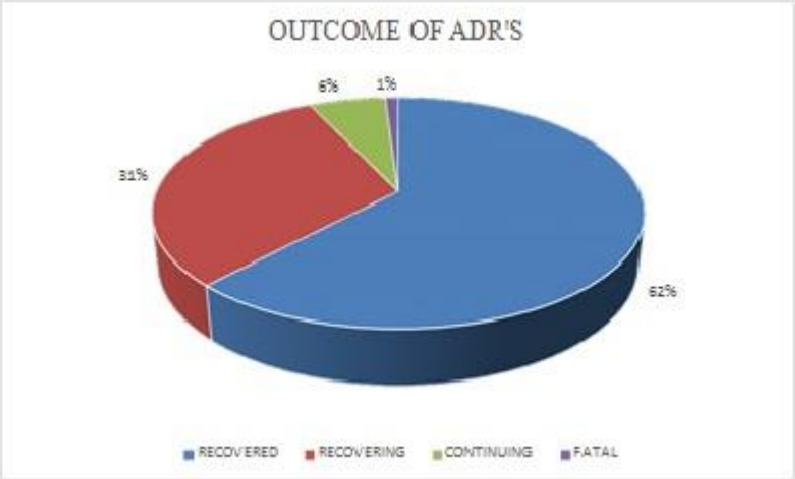

Figure 6.10: Outcome of Management of Adrs

Table 6.11 shows that out of 139 reported ADR's, 64% cases were reported to be non-serious ADR's while 36% were serious ADR's.

Table 6.11: Significant Adrs

TYPES	No. of ADR's(n=139)	Percentage (%)
NON-SERIOUS ADR's	89	64%
SERIOUS ADR's	50	36%

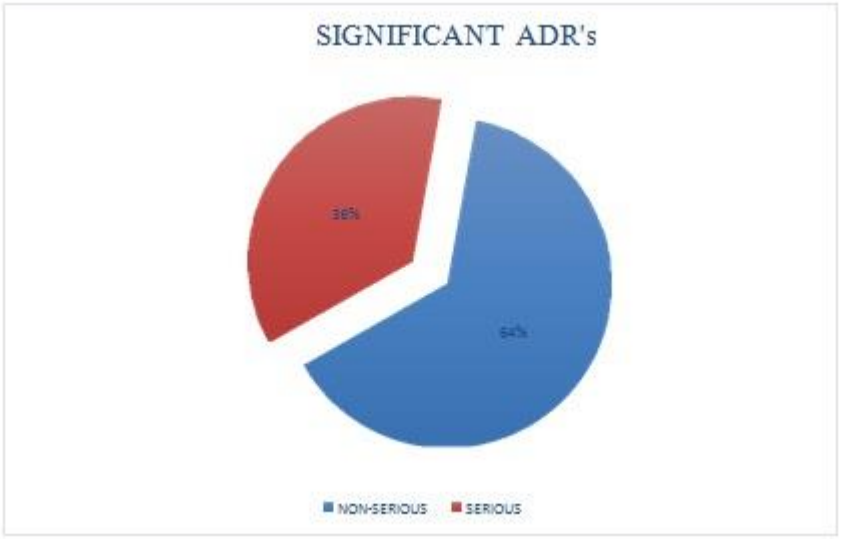

Figure 6.11: Significant Adrs

CONCLUSION

- ADR monitoring and reporting in hospitals is an important program to identify and quantify the risks associated with use of drugs. This information may be useful in identifying and preventing suspected ADR's while generally enhancing the knowledge of prescribers to deal with ADRs more effectively.
- Early detection of ADRs helps to modify the doses or the drug regimen to minimize toxic effects. Similar studies can be used as reference for iatrogenic ADRs and assessment of prevention of expected adverse drug reactions.
- Under reporting of ADRs in the present study revealed that, more awareness and importance about suspected drug events & Pharmacovigilance have to be provided among the healthcare professionals through ADR bulletins and by conducting seminars and workshops.
- ADR reporting and monitoring in a tertiary care hospital should be continuous and ongoing process to keep a record of newly marketed drugs and medicinal products. This helps in providing baseline data regarding the safety of those drugs.
- Serious ADRs account for prolonged hospitalization, increased morbidity and also economic burden. Hence ADR monitoring is considered has an important activity, as it justifies the benefit versus risk ratio of drugs.
- Hence, it can be concluded from the study that more intensive implementation of ADR monitoring and reporting should be performed so as to provide optimum patient care and to obtain therapeutic outcome.

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