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Research Article

## Retrospective Analysis of Adverse Drug Reactions at South Indian Tertiary Care Teaching Hospital

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### Abstract

**Background:** Adverse drug reaction (ADR) is an appreciably harmful reaction from an intervention related to the use of the medicinal product, which predicts hazard from future administration and specific treatment, or alteration of the dosage regimen, or withdrawal of the product. This study aimed to analyze ADRs retrospectively to understand their nature at the study site.

**Methods:** Retrospective analysis of the ADRs reported over 6 months was conducted at a South Indian Tertiary Care Teaching Hospital. We analyzed Patient characteristics, Causality, Severity, Dechallenge, Rechallenge, Management, Outcomes, Department, Drug Class, and Organ system involved related adverse events.

**Results:** Out of 116 ADRs females developed 51.72 % of reactions, and ADRs are more common in the adult population (73.2 %), followed by geriatrics (11.2 %). Antibiotics were the most frequently used medication class and also lead to the majority of reactions (16.3%). A total of 55 ADRs were assessed for causality, and 31 (57.4%) reactions were possibly linked to the implicated medications. At the time of reporting, 41 (35.6 %) patients had recovered from the reaction, 37 % of ADRs were non-serious, and no deaths had been reported.

**Conclusions:** The majority of ADRs were minor, and patients were able to recover from them after discontinuing the implicated medicine. We were unable to estimate the severity of the ADRs using this reporting form, and the majority of ADRs lacked a causation assessment, which is not a mandatory condition for reporting any suspected ADR.

**Keywords:** ADRs, Retrospective study, Causality assessment, HCPs, Pharmacovigilance program of India.

## INTRODUCTION

Drugs are primarily used for the diagnosis, prevention, treatment of various diseases. But it is sometimes observed, that these drugs have been proved fatal. This could be due to variable person-to-person responses towards a drug. Even at therapeutic doses, people develop adverse effects.<sup>1</sup> Adverse drug reactions (ADRs) are one of the leading cause of repeated hospitalization and they adversely affects the quality of life.<sup>2</sup>

## EPIDEMIOLOGY:

The frequency of ADRs and other drug-related problems in society is not known. Many studies have been carried in several parts of the world on the incidence in hospitalized patients and of hospital admission that results from ADRs and other drug-related problems.<sup>3</sup> The incidence of ADRs reported by various studies across the world is 6%-20%, whereas, in India, it is up to 3%.<sup>4</sup> There is an increase in the number of ADRs reporting every year. It is estimated that only 6-10% of all ADRs are reported to the regulatory authorities. India is lacking in reporting ADRs and conducting studies on ADRs.<sup>5</sup> It has been estimated that approximately 2.9%-5.6% of all hospital admissions are caused by ADRs and 35% of the

hospitalized patients experienced an ADR during their hospital stay.<sup>5</sup> ADR incidence has been reported in the range of 5.9 to 22.3% of all emergency department admissions in India. It has been reported that deaths due to ADRs contributed to 1.8% of the total deaths in India.<sup>6</sup> Therefore, setting up ADR monitoring centers at a more regional or hospital level and integrating them with a sound network can reveal unusual or rare ADRs prevalent in the Indian population.

## DEFINITIONS:

An **ADR** is an unwanted or harmful reaction experienced by an individual, after using a drug or drugs, under normal conditions, and which is suspected of being related to the drug.<sup>7</sup>

According to the world health organization (WHO), an ADR can be defined as any response of a drug that is noxious and unintended, that occurs at doses used in humans for the prophylaxis, diagnosis or therapy of disease; or for the modification of physiologic function purposely excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors.<sup>3</sup>

According to FDA (USA), "an ADR is any undesired experience associated with the use of a drug, whether or not considered drug-related, and includes any side effect, injury, toxicity or sensitivity reaction or significant failure of expected pharmacological action.<sup>7</sup> American Society of Health-System Pharmacist (ASHP) defines a significant ADR as any unexpected, unintended, undesired, or excessive response to a drug that

- Requires discontinuing the drug (therapeutic or diagnostic)
- Requires changing the drug therapy
- Requires modifying dose (except for minor dosage adjustment)
- Necessitates admission to hospital
- Prolongs stay in a healthcare facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis
- Results in temporary or permanent harm, disability, or death.

### Pharmacovigilance

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems".<sup>8</sup>

Pharmacovigilance has several methods to detect these problems related to the use of medicines. Thus, active pharmacovigilance includes studies of prescription event monitoring or intensive review of potential ADRs in hospital admissions or discharges (electronic medical records databases) among others. On the other hand, passive pharmacovigilance relies mainly on spontaneous reporting. Any suspicion of ADRs encountered in clinical practice should be reported to the pharmacovigilance system, according to the healthcare community. More complicated data mining approaches have recently been developed, particularly in electronic medical records and claim databases.<sup>8</sup>

## METHODS:

### Study design:

A retrospective analysis was conducted at Government General Hospital-Rajiv Gandhi Institute of Medical Sciences (RIMS) on ADRs reported in 6 months period (from July 2019 to December 2019).

### Study inclusion

All of the Adverse Drug Reactions (ADRs) reported by the study site to PvPI from July 2019 to December 2019 were included in this analysis. The ADRs that were not reported and incomplete were excluded. All the reports were reviewed for possible inclusion in this analysis.

### Data Sources

We have collected the data regarding the demographics, reaction, and its description, suspected drugs, concomitant drugs, and details of the ADR treatment and its outcome, and other details necessary for the evaluation.

### Quality assessment

All the filled suspected ADR reporting forms were analyzed for their completeness, credibility, and correctness' according to the IPC-PvPI guidelines.

### Data Evaluation:

Reported ADRs were analyzed to see if there was a trend in terms of patient demographics, nature of the reactions, medication features, management, and reaction outcome. The reactions were evaluated for causality, seriousness, and the presence of predisposing circumstances.

### Patient demographics

We have considered the patient's age, gender, and other relevant information for the evaluation, and data were categorized accordingly.

### Drug characteristics

Drugs that are responsible for ADRs were classified according to the WHO Anatomical Therapeutic Chemical classification system.

### Reaction characteristics:

All the reactions were categorized based on the systems affected with ADRs i.e. System Organ Class (SOC), Causality, seriousness, etc.

### Causality

The extent of the relationship between the suspected drug/s and the reaction was established by the reporters through the WHO Causality assessment scale<sup>9</sup> this information might have been used in the management of the reaction. According to this, ADRs were categorized as certain, possible, probable, and un-assessable. This information was collected and categorized.

### Seriousness

We have collected the information on the seriousness which was assessed by the reporters using the PvPI criteria<sup>9</sup> i.e. Life-threatening required intervention to prevent permanent impairment/damage, Hospitalization/Prolonged hospital stay, Disability, Congenital anomaly, and Death.

### De-challenge and Re-challenge

Information on dechallenge and rechallenge was collected to understand the relation between the reaction and the suspected drug.

### ADR Management and outcome

Treatment given for the management of the reaction and its outcome were assessed. The management strategies were included, no change in the treatment (except observation), reduction of the dose, drug withdrawal, substitution with another drug, and addition of another drug. The outcome of the ADR management was noted as recovered, recovering, and not recovered.

**Statistical Analysis** The data were analyzed by using descriptive statistics like mean, percentage.

## RESULTS

### Demographics:

#### ADRs on Gender and age:

A total of 116 ADR reports were analyzed, of them, 60 (51.7%) were developed by Female patients followed by Males 56 (48.2%).

The frequency of ADRs in different age groups was calculated and found that 85 (73%) ADRs were developed by the Adult

population (19-65 years), detailed findings were depicted in Figure 1.

#### ADRs on departments:

The frequency of ADRs in various clinical departments was calculated and found that 69(59.4%) ADRs were reported from the General medicine department followed by psychiatry and dermatology i.e., 20(17.2%) detailed findings were depicted in **Table 1**.

#### ADRs on Causality:

Out of 116 ADRs, Causality Assessment was done for 55 ADRs, among them 31(57.4%) ADRs were possibly related to the suspected drug followed by probable 20(37%), detailed findings were depicted in **Figure 2**.

#### ADRs on Seriousness:

Among 116 ADRs, 43 (37%) reactions were non-serious, and 43 reactions can be prevented by the intervention (37%), then patients with 22 reactions were hospitalized (18.9%) and 5 were other medically important (4.3%), and 3 were life-threatening (2.5%).

#### De-challenge and Re-challenge of ADRs:

Out of 116 ADRs, de-challenge information is available in 78 reports and re-challenge information is available in 16 reports. In 78 ADRs, the suspected drug was withdrawn and observed the patient and the response was positive in 74 % of reactions.

Re-challenge was performed in 16 ADRs and in 9 patients the reaction was not reappeared.

#### Management of ADRs:

In 58 reactions the suspected drug was withdrawn, in 12 reactions suspected drug was not changed, and in 5 reactions the dose of the suspected drug dose was reduced.

#### ADRs on Outcomes:

Based on our study results 41 patients (35.6%) were recovered, followed by 34 (29.5%) who were at recovering stage at the time of reporting.

#### ADRs on System Organ:

A total of 125 reactions were experienced by the study patients, and were distributed according to their System Organ Class (SOC) and found that 26.4% were related to the Gastrointestinal system which includes constipation, vomiting, etc., followed by the Cutaneous system (21.6%) and Central nervous system reactions (15.2%) like itching and tremors respectively.

#### ADRs on Drug Class:

We have distributed the ADRs according to the suspected drug therapeutic classification. A total of 114 reactions were developed with a single drug and 2 were with drug combinations. Among all classes, Antibiotics are involved in 16.3% of ADRs followed by Antipsychotics (14.6%) and Anti Hypertensives (8.6%).

In this study mostly observed reaction was Constipation <sup>12</sup> followed by Rashes <sup>10</sup> and. Ceftriaxone (Antibiotics) and Olanzapine (Antipsychotic) were involved in the majority of ADRs. The ADRs experienced due to usage of Ceftriaxone were Vomiting, Nausea, Scaly patches, Itching, Rash. And Dry mouth, Tremors, Constipation, Weight gain were experienced by patients due to the usage of Olanzapine.

## DISCUSSION

Based on today's scenario, ADRs are the major cause of mortality and morbidity in hospitals. Understanding their incidence and nature is essential in improving the medication use and minimizing the negative consequence of medications. With this retrospective study we tried to assess the nature of ADRs at the study site and we have considered the 116 ADR reports reported to the IPC PvPI. All the ADRs were analyzed based on demographics of the patients, causative drugs' characteristics, organ systems involved, clinical departments, seriousness, outcome and management.

We have found that the occurrence of ADRs was almost similar in both genders i.e., Females (51.72%) and Males (48.28%), only around 3% higher in Females. Studies conducted in north Indian states i.e., Uttarakhand and Haryana by Rangeel Singh Raina et al<sup>10</sup> and Manmeet Kaur et al<sup>11</sup> have observed 6.8% and 14% more ADRs in female patients. Generally, Females experience more ADRs to treatment with therapeutic drugs than males which may be due to different pharmacokinetic and pharmacodynamic parameters as well as genetic/metabolic and hormonal differences.<sup>12</sup>

The Average age of the study patients was 40.77 ( $\pm 19.72$ ). In the present study the occurrence of ADRs is significantly more (73.2%) in adults than pediatrics, adolescents and geriatrics as this population frequently visits the hospitals and usage of drugs was more often in them. Studies conducted by Hemavathy G et al<sup>13</sup>, Kaksha J Patel et al<sup>14</sup>, and Manodeep Sen et al<sup>15</sup> have also reported that adults were affected with more ADRs.

Majority of the ADRs i.e 59.4% were reported from the department of General Medicine where the rate of consultation is more than other departments. Our results were comparable with the studies conducted by Sangeetha Raja et al<sup>16</sup> and Ankitha L et al<sup>17</sup> have reported that majority of ADRs i.e 37.5% and 61.3% were reported in General Medicine department respectively.

Reporters have assessed the causality using WHO-UMC Causality Assessment Scale to confirm whether the reaction is because of drug alone or other factors also involved. We found that majority of ADRs were possibly (57.4%) related to the suspected drugs. Anuj Kumar et al<sup>18</sup>, and Hemavathy G et al<sup>13</sup> have concluded the similar results that majority of ADRs were possible i.e. 52.73% and 71.09% respectively.

We have assessed the outcomes of the reactions available at the time of documentation of the reports, a considerable number of patients were (35%) not recovered from the reactions. Majority of the patients have shown recovery from the reaction, where 35.6% were recovered and 29.5% were at recovering stage. With this study we observed the lack of follow-up of patients as majority of the patients' recovery status was not monitored or patients might have discharged or referred to other centers. But, follow-up of patients is utmost important to understand the nature of the ADR. Studies conducted by Manodeep Sen et al <sup>15</sup> (88.33%) and Rangeel Singh Raina et al<sup>10</sup> (71.81%) have concluded similar results.

The seriousness of the reaction is directly related to the cost burden which is necessary for risk assessment and also an important parameter to be considered in ADR management. We found that majority (37%) of the ADRs were non-serious and 37% were serious which requires intervention to prevent impairment or prolonged hospitalization. Studies conducted by Ankitha L et al<sup>17</sup> reported that majority of ADRs were serious which requires intervention to prevention i.e 36.4% Manodeep Sen et al<sup>15</sup> reported most of the ADRs were non-serious i.e 83%.

All the identified ADRs are needed to be managed appropriately. In this study, in 77.3% of ADRs the suspected drug was withdrawn, in 16% ADRs the suspected drug dose was not changed and in 6.66% ADRs the dose was reduced.

We have categorized all the reported ADRs according to the SOC and found that majority of the reactions i.e. 26.4% were related to the GI System and 21.6% were Cutaneous reactions. In this study Majority of the patients had experienced Constipation<sup>12</sup> followed by Rashes<sup>10</sup> V J Ambika Abhishake et al<sup>19</sup> had concluded that majority of ADRs were from Gastro Intestinal System (39%). However Ankitha L et al<sup>17</sup> reported different results documenting Skin and Appendages constituted the most common system affected (59%).

With the analysis of drug class involved in the ADRs we found the majority of the ADRs (16.3%) were due to the Antibiotic therapy either for prophylactic or curative therapy followed by Anti-psychotics (14.6%). Ceftriaxone is most commonly involved drug among all the antibiotics and other drugs. The ADRs experienced due to usage of Ceftriaxone were Vomiting, Nausea, Scaly patches, Itching, Rash. This may be the reason that the usage of antibiotics was more in the study centre. Patients have developed Dry mouth, Tremors, Constipation, Weight gain with the usage of Olanzapine. Similar trend has been reported in other studies conducted by Dinesh K Badyal et al<sup>20</sup> (47%), Anuj Kumar et al<sup>18</sup> (56.5%).

## CONCLUSION

The reporting system is operational at the study site and ADRs are being reported using a standard form. Patients recovering from the reactions following the withdrawal of the suspected drug, and the majority of ADRs were mild. We could not assess severity with this reporting form, and many ADRs did not have a causality assessment because reporting any suspected adverse reaction is not mandatory.

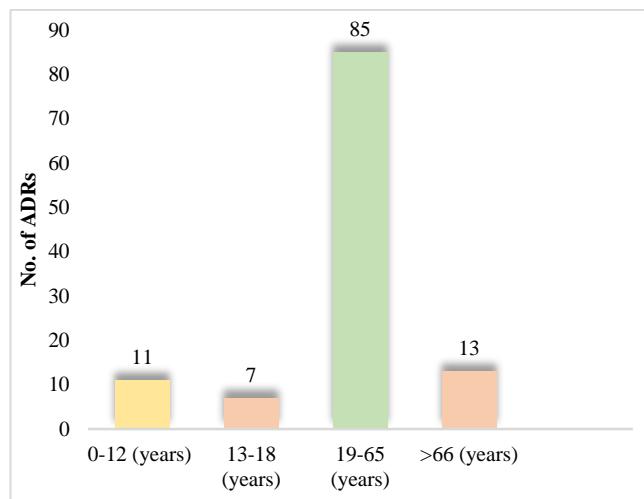


Figure 1: Distribution of ADRs based on Age

Table 1: Frequency of ADRs in various clinical departments

S.N.	Department	No. of ADRs n=116	Percentage
1.	Dermatology	20	17.2
2.	General medicine	69	59.4
3.	Psychiatry	20	17.2
4.	Cardiology	06	5.1
5.	Orthopedics	01	0.8

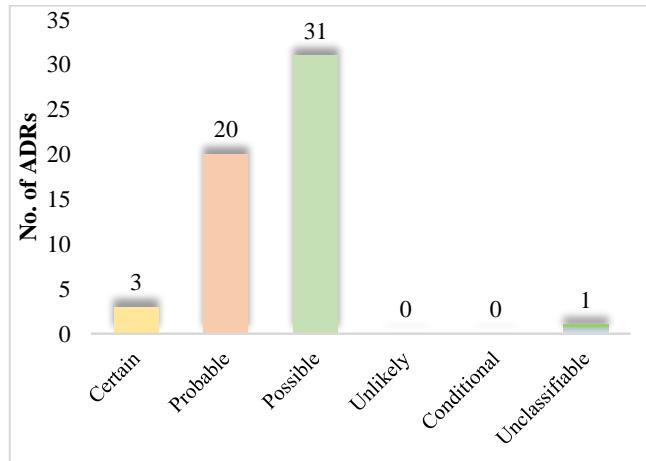


Figure 2: Distribution of ADRs based on Causality

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## CONFLICT OF INTEREST:

None

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