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# Comprehensive Assessment of Adverse Drug Reactions in Antiepileptic Drugs: A Prospective Observational Study in a Tertiary Care Hospital

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**Abstract:**

Throughout the world, millions of people suffer from epilepsy, a neurological condition that is more common in countries that are developing like India. The cornerstone of epilepsy treatment, anti-epileptic medications are linked to a variety of adverse drug reactions because of their intricate pharmacokinetic profiles and limited therapeutic index. This prospective observational study sought to thoroughly examine adverse drug reactions connected to antiemetic drugs at a Tertiary Care hospital. After screening 150 people in total, 100 were eventually added to the research. Pharmacovigilance measures were among the materials and methods used in the data-gathering process. The study showed that the individuals were mostly female and that there were disparities in the frequency of ADR according to age and gender. The two AEDs that were most commonly associated with side effects were phenytoin and carbamazepine. Notable side effects included ataxia, gum hypertrophy, and skin reactions like Stevens-Johnson syndrome. Additional insights into the groups of ADRs were obtained through severity assessment and causation assessment utilizing the WHO and Naranjo scales. The results highlight the significance of frequent follow-up, dose modifications, and attentive monitoring in reducing adverse drug reactions (ADRs) and improving patient compliance and quality of life.

**Keywords:** Epilepsy, anti-epileptic drugs, adverse drug reactions, pharmacovigilance, causality assessment.

## Introduction:

The frequently occurring neurological ailment is epilepsy. Epilepsy is a long-lasting disorder which has distinguished by a tendency for recurrent seizures, which occur in cortical neurons due to the changes in the spread of electrical discharge.[1] Its prevalence rate is higher in developing countries, it affects usually 0.5-1% of people, and in children, its rate is 3%.[5] In most people epilepsy generally occurs in a combination of different types of seizures and with other neurological complications.[2] In India nearly 50 million individuals suffer from epilepsy. This can be effectively treated by using anti-epileptic drugs (AED) in almost 80% of the population.[1] Carbamazepine (CBZ), Valproate (VPA), Phenytoin (PHT), and Phenobarbitone (PB) are frequently used AEDs for epilepsy.[5] Some ADRs are observed in long-term usage of these medications. Adverse drug reaction (ADR) is defined as 'any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function' by World Health Organization (WHO).

In AEDs, ADRs are mostly due to the narrow therapeutic index and complex pharmacokinetic parameters of these drugs, which results in the discontinuation of the medication.[3] Most of the complaints that occur highly are related to the CNS (68%) and cognitive (62%) whereas Mood and behavioral complaints are less frequent (22%).[4] Side effects like lethargies, sleepiness, dizziness, and cognitive impairment; other adverse effects such as weight gain, metabolic acidosis, nephrolithiasis, closed-angle glaucoma, rashes of the skin, hepatocytes malfunctioning, colitis, and motor and behavioral disorders are associated with long-term AED treatment.. One study stated that 11% of total ADRs are accounted for solely by AEDs. The older drugs specifically phenobarbital (PB), phenytoin (PHT), and vigabatrin (VGB) are proven to cause cognitive dysfunction. Lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), gabapentin (GBP), pregabalin (PGB) and lacosamide (LCS) are the latest AE drugs which have comparable effects to that of older medications but have greater acceptability. Some newer AEDs also known to cause specific effects on language and memory such as topiramate (TPM) and zonisamide (ZNS) and another drug that is levetiracetam (LEV) is identified to be producing greater mood effects in patients. The health care cost for the curing of these ADRs is calculated to be very high as US $26.675 (1840.5 ₹) for each patient per year.[4] The cost must be lessened as low as possible to decrease the burden of the patient. So the evaluation of the ADRs at the first level is important to attain good therapeutic outcomes that improves patient compliance.[3] Change of medication and monitoring of ADRs help in decreasing the patient's nonadherence. To reduce the adverse drug effects drugs Pharmacovigilance study is essential in India. The ultimate goal is seizure freedom without adverse effects of medication and improved quality of life.

**Methodology:**

The investigation was planned as a prospective observational spontaneous reporting project that was carried out in a tertiary care teaching hospital. After the screening, a total of 150 patients were screened out of them 100 were eventually included after the screening. For data collection, a variety of documents were used, including prescription drugs, case files, ADR documentation forms, patient permission forms, and forms for reporting potential adverse reactions. The criteria for inclusion were individuals who were hospitalized for the treatment of prior adverse medication reactions as well as inpatients and outpatients who were diagnosed with any adverse drug response during their stay. Patients identified with adverse drug reactions (ADRs) as a result of poisoning, exposure to fresh blood or its byproducts, or situations involving abuse or intoxication were excluded based on specific criteria. People who refused to provide permission for their information to be disclosed were also excluded. With informed consent forms and questionnaires produced and approved for use, data collection started after receiving ethical approval. Standard forms for potential adverse medication reactions were used to improve data collection. Pharmacists who independently suspected adverse drug reactions (ADRs) and clinical pharmacists who encouraged other healthcare workers to report ADRs they saw while on duty were the two main approaches used to get data. Analysis and tabulation were performed on the gathered data. The WHO causality evaluation scale and Naranjo's causality assessment scale were two of the tools used to determine causation. To further measure the severity of ADRs, the Modified Hartwig and Siegal severity assessment of ADRs was employed.

**Results:**

A total of 150 ADRs were screened and only 100 ADRs were accepted as represented in **Fig.1**In the study, females exceeded males concerning of gender distribution. Of the fifty-nine females, the largest percentage 14 fell between the ages of 0 and 10, and the lowest 61 to 70. On the other hand, there were more male respondents in the 0–10 age group and fewer in the 11–20 age group.

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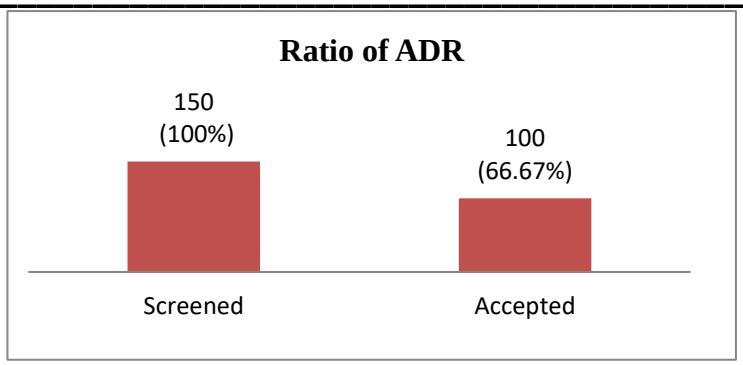


**Figure 1:Ratio of ADR screened and accepted**

In general, the age group of 0 to 10 had the most subjects, while the age group of 61 to 70 had the least number. Regarding social behaviors, the majority of the fifty-nine men and women were abstainers from alcohol and tobacco. On the other hand, only 4 males and 21 females acknowledged using tobacco in any capacity. About drinking and smoking, 1 female and 9 males acknowledged drinking alcohol, while 10 females and 11 males reported smoking. The skin and appendages were the organ systems most impacted by adverse drug reactions (ADRs) in both sexes. The neurological system was the next most impacted system in females after the skin, and then the gastrointestinal, endocrine, musculoskeletal, and hematological systems. The neurological system, musculoskeletal, gastrointestinal, special senses, and hematological systems were the next most impacted systems in males, following the skin. Interestingly, no ADRs affecting the male endocrine system were reported as represented in Table 1

**Table 1:Demographics distribution of Study Population**

| Subgroups | Category | Gender distribution | |
|---|---|---|---|
| | | Female (n=59) | Male (n=41) |
| Age | 0 to 10 | 14 | 10 |
| | 11 to 20 | 6 | 2 |
| | 21 to 30 | 8 | 7 |
| | 31 to 40 | 6 | 7 |
| | 41 to 50 | 13 | 7 |
| | 51 to 60 | 9 | 4 |
| | 61 to 70 | 3 | 4 |
| Social history | Smoker | 10 | 11 |
| | Alcoholic | 1 | 9 |
| | Both Smoker and alcoholic | 1 | 5 |
| | Not a smoker and alcoholic | 26 | 12 |

| | | | |
|---|---|---|---|
| | Tobacco in any form/Pan | 21 | 4 |
| **System affected** | Skin and appendages | 28 | 16 |
| | Gastrointestinal | 5 | 2 |
| | Nervous system | 17 | 16 |
| | Hematological system | 1 | 1 |
| | Endocrine/ metabolic | 4 | 0 |
| | Musculo skeletal | 1 | 5 |
| | Special senses | 3 | 1 |

Most of the ADRs reported by the subjects (53) were Type-A in that 33 were females and 20 was males. The second highest ADR type reported was Type-H which were 1/4 ratio of total ADRs reported. After that 15 ADRs were Type-B and only 7 ADRs were Type-C as represented in Fig:2.

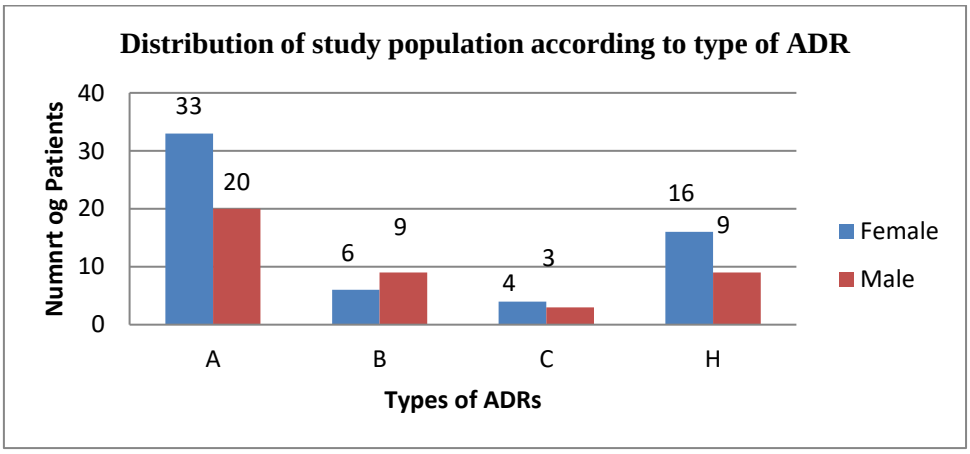


**Figure 2: Distribution of study population according to type of ADR**

From Table 2, a total of 100 ADRs 59 ADRs were reported due to Phenytoin, and among them highest of 11 ADRs were Gum hyperplasia, Ataxia(7), Sedation(2), diplopia(1), drowsiness(1), gastric pain(1), fixed drug eruption (5), hirsutism (2), hyperglycemia (2), hypersensitivity(3),Nausea and vomiting(2), Nystagmus (1), Phenytoin toxicity(2), exfoliative dermatitis(4), bullous (2) and maculopapular rashes(5).Whereas Carbamazepine was second highest drug that caused ADRs which was 22 of total ADRs reported, ADRs like SJS(10), Erythroderma (4), Blurred vision (4), Ataxia(3). Sodium valproate accounted for 6 ADRs which were Tremor (2), Ecchymosis (2), and Headache (2). Clobazam and Pregabalin distribute an equal number of ADRs which was 3 and due to Valproate, 4 ADRs were reported. 2 and 1 ARDs were reported due to Topiramate and Clozapine respectively. From Table 3; causality assessment was done using the WHO causality assessment scale out of 59 ADRs reported by females 45 fell under the probable category, 10 under possible ADRs, 2 of each were certain and unlikely and no ADR came under the unclassifiable category. Where as in 41 males 30 were under probable, 10 possible, 1 certain, and no ADR under unlikely, unclassifiable type. Naranjo's causality assessment scale, a total of 59 ADRs were reported by females among them 27 were probable, 18 were possible, 4 were definite type and no ADR was under the unlikely category. However, in 41 males, the highest of 37 reported were probable, 12 possible, 2 definite type, and no ADR under the unlikely category. Severity assessment was done by using the Hartwig and Siegal severity assessment scale, a total of 59 ADRs were reported by females among them 28 were moderate, 18 were mild and 13 were severe. In males highest of 27 were moderate, 8 were mild and 6 were severe.

**Table 2: Suspected ADR and causative anti-epileptics (N=100)**

| Drug name | Reactions | ATC code | Female | Percentage | Male | Percentage | Total | Percentage |
|---|---|---|---|---|---|---|---|---|
| **Phenytoin** | Ataxia(7), Sedation(2), diplopia(1),drowsiness(1), gastric pain(1), fixed drug eruption (5)gum,hyperplasia(11), hirtuism (2), hyperglycemia (2), hypersensitivity(3), Nausea and vomiting(2), Nystagmus (1), Phenytoin toxicity(2), exfoliative dermatitis(4), bollous(2), maculopapular rashes(5) | N03AB02 | 34 | 34% | 25 | 25% | 59 | 59% |
| **Carbamazepine** | SJS(10), Erythroderma (4)Blurred vision (4), Ataxia(3). | N03AF01 | 17 | 17% | 5 | 5% | 22 | 22% |
| **Sodium valproate** | Tremor(2), Ecchymosis(2), Headache(2) | | 1 | 1% | 5 | 5% | 6 | 6% |
| **Clobazam** | Ataxia(1), Sedation(2) | N05BA09 | 1 | 1% | 2 | 2% | 3 | 3% |
| **Pregabalin** | Angioedema (1), Dizziness(2) | N03AX16 | 3 | 3% | 0 | 0% | 3 | 3% |
| **Valproic acid** | Nystagmus(2), Alopecia(2) | N03AG01 | 2 | 2% | 2 | 2% | 4 | 4% |
| **Topiramate** | Muscle twitching (2) | N03AX11 | 0 | 0% | 2 | 2% | 2 | 2% |
| **Clozapine** | Hypersalivation (1) | N05AH02 | 1 | 1% | 0 | 0% | 1 | 1% |

**Table 3: Assessment of ADR with assessment scales.**

| Assessment | Category | Female (n=59) | Male (n=41) |
|---|---|---|---|
| **WHO causality assessment** | Certain | 2 | 1 |
| | Possible | 10 | 10 |

| | | | |
|---|---|---|---|
| | Probable | 45 | 30 |
| | Unlikely | 2 | 0 |
| | Unclassifiable | 0 | 0 |
| **Naranjo's causality assessment** | Definite | 4 | 2 |
| | Probable | 27 | 37 |
| | Possible | 18 | 12 |
| | Unlikely | 0 | 0 |
| **Modified Hartwig and Siegal severity assessment (severity)** | Mild | 18 | 8 |
| | Moderate | 28 | 27 |
| | Severe | 13 | 6 |

**Discussion:**

In this study 100 patients (100%) experienced ADRs due to various anti-convulsants; among them, phenytoin (59%) and carbamazepine (22%) were the most common drugs. Phenytoin-induced skin rashes and SJS and carbamazepine-induced SJS were observed in the current study, these results consist of a study by Mockenhaupt et al.[6] One more study also explained that the highest incidence (74.41%) was observed with phenytoin followed by carbamazepine (20.58%). Wu FL et al.[7] reported that phenytoin is the commonest cause in 32% of patients; carbamazepine and phenytoin were the causative AEDs for SJS/TEN (67.8%) and DRESS (43.6%) respectively in the study by Perucca et al.[8]

Phenytoin was the drug most frequently associated with ADR occurrence followed by carbamazepine in studies done by Ding WY et al. and Palanisamy S et al.[9,10] Gum hypertrophy was the commonly observed ADR due to Phenytoin followed by ataxia (n=11), SJS-TEN (10), fixed-dose eruptions (5), Maculopapular rash (5), Hypersensitivity (3), hirsutism (2), hyperglycemia (2), ecchymosis (2), diplopia (1), nystagmus (3) tremors (2) were observed for various anti-convulsants like phenytoin, carbamazepine, pregabalin, clobazam, clozapine, valproic acid, sodium valproate and topiramate. Three patients were reported with topiramate-induced muscle twitching. Carbamazepine was found to elicit the highest incidence of SJS-TEN per user. Valproic acid often used as an alternative to phenytoin was found to have equal risk.

**Conclusion:**

We studied the adverse drug reactions that occur due to antiepileptic agents. AEDs have a restricted therapeutic index, which makes them risky even though they are successful in 80% of cases. ADRs that often occur include tremors, ecchymosis, nystagmus, hypersensitivity, ataxia, maculopapular rash, and gum hypertrophy. To reduce ADRs, improve patient compliance, and improve quality of life, close observation is required for dose modifications or medication discontinuation.

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**Declarations**

**Funding:** None

**Conflicts of interests:** None

**Competing interests:** We declare no competing interests.

**Availability of data and material:** The datasets generated and/or analyzed during the current

study are available from the corresponding author upon reasonable request.

**Ethics approval:** Ethical approval was obtained from the Institute Ethics Committee of Vivekanandha Medical Care Hospital, File Ref. No: IEC/APR/2012/03 reviewed and discussed to conduct the study.

**Consent to participate:** An informed consent was obtained from the individuals who wanted to participate in this study.

**Consent for publication:** Not applicable.

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