

# A pharmacovigilance study of monitoring & focusing of adverse drug reactions induced by antiepileptic drugs used in epileptic patients

## Abstract

Epilepsy is a chronic disorder of the brain that affects people worldwide. The standard treatment of epilepsy is optimal use of antiepileptic drug. Efficacy of an antiepileptic drug refers to its effectiveness in preventing or reducing the recurrence of a particular seizure type. For example, physicians may not use sodium valproate in female patients who are planning to have children because of its teratogenic side effects. So, clinicians should give emphasis for patients with these characteristics to counsel on how to minimize or prevent adverse effects from antiepileptic drugs or giving reassurance about it if it is minor. Pharmacovigilance (PV) is the monitoring of drugs and the prevention of the risk of adverse effects resulting from their use, whether this risk is potential or proven. The aim of the PV study to detect and identify the adverse drug reactions (ADRs) induced by the treatment of antiepileptic drugs in epileptic patients. This prospective study was carried out for three months in an out-patient department of neurology of a multispeciality teaching hospital.

**Keywords:** uppsala monitoring centre, epileptic seizure, valproic acid, morbidity, mortality

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## Saurabh Nimesh

Research Scholar, Department of Pharmaceutical Technology,  
Meerut Institute of Engineering and Technology, India

**Correspondence:** Saurabh Nimesh, M. Pharm (Pharmacology),  
Research Scholar, Department of Pharmaceutical Technology,  
Meerut Institute of Engineering and Technology, NH-58 Baghpat  
crossing Bypass, Meerut-250005 (Uttar Pradesh.), India, Tel 91-  
7455923397, Email sk4676549@gmail.com

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**Abbreviations:** WHO, world health organization; ADRs, adverse drug reactions; PV, pharmacovigilance; EEG, electric encephalography; UMC, uppsala monitoring centre; ATC, anatomical therapeutic chemical classification; ICD: international classification of diseases

## Introduction

According to the WHO epilepsy is a chronic noncommunicable disease of the brain that affects more than 50 million peoples with epilepsy worldwide, 80% reside in developing countries.<sup>1</sup> About 10 million persons living with epilepsy are there in India. It is the second leading neurological cause of reduced disability adjusted life years.<sup>2</sup> Epileptic convulsions have negative consequences on the patients psychological and social life such as relationships, education and employment.<sup>3</sup> Uncontrolled seizures are associated with physical and psychosocial morbidity, dependent behaviour, poor quality of life and an increased risk of sudden unexpected death. Drugs acting on the central nervous system such as antiepileptic, antipsychotic, and anxiolytic contribute to ADRs such as extrapyramidal symptoms, insomnia, sedation, and even serious effects such as increasing suicidal tendency and depression.<sup>4</sup> The main stay of treatment in epilepsy is the use of antiepileptic medications. More than 20 Food and Drug Administration approved antiepileptic drugs are available in the current market.<sup>5</sup> The patient may experience ADRs with single or multiple drugs as anticipated or may show up instantly, on continued use, even after cessation of therapy. Although ADRs influence all age groups, yet the most usually influenced ones are geriatrics and paediatrics.<sup>6</sup> The use of drugs in the management of epilepsy is accompanied by adverse events such as idiosyncratic reactions, dose-related neurocognitive effects and complications of long-term use. Studies have showed that the patients in neurology department experience 23.5% of ADRs.<sup>7</sup> Pharmacovigilance is 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> Monitoring of ADRs helps to evaluate the effectiveness and risk of medications, empower safe and rational use of drugs and enhance general patient care and well-being. The cost of ADRs in the community is high, and under-reporting of ADRs by health care professional's is a globally perceived issue.<sup>9-11</sup> There are limited studies in India to report ADRs in children. Under-reporting of ADRs is a major health problem affecting PV programme in India. So, the drug regulators in India are dependent on other countries for data regarding drug safety especially in children.<sup>12</sup> ADR identification and reporting may prevent the occurrence of ADRs and drug-related problems in future. The goal of epilepsy treatment is to achieve adequate seizure control and improve quality of life without adverse events from the medication.<sup>13,14</sup>

## ATC code of antiepileptic drugs & ICD-10 code of patients suffering from seizure

The dosages of the antiepileptic drugs currently available in India, Anatomical therapeutic chemical classification system divides the drugs into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties.<sup>15</sup> The ATC system is based on the earlier Anatomical Classification System, which is intended as a tool for the pharmaceutical industry to classify pharmaceutical products (as opposed to their active ingredients) (Table 1).<sup>16</sup> International Classification of Diseases is published by the WHO and which uses unique alphanumeric codes to identify known diseases and other health problems.<sup>17</sup> According to WHO, physicians, pharmacist, coders, nurses and other healthcare professionals also use ICD-10 code to assist them in the storage and retrieval of diagnostic information (Table 2). ICD records are also used in the compilation of national mortality and morbidity statistics.<sup>18,19</sup>

**Table 1** ATC code of antiepileptic drugs

Category	Drug name	ATC code
Barbiturate	Phenobarbitone	N03AA02
Hydantoin	Phenytoin, Fosphenytoin	N03AB02, N03AB05
Iminostilbene	Carbamazepine, Oxcarbazepine	N03AF01, N03AF02
Succinimide	Ethosuximide	N03AD01
Aliphatic carboxylic acid	Valproic acid (sodium valproate), Divalproex	N03AG01
Benzodiazepines	Clonazepam, Diazepam, Lorazepam, Clobazam	N03AE01, N05BA01, N05BA06, N05BA09
Phenyltriazine	Lamotrigine	N03AX09
Deoxybarbiturate	Primidone	N03AA03
Cyclic GABA analogues	Gabapentin, Pregabalin	N03AX12, N03AX16
Newer drugs	Vigabatrin, Levetiracetam, Topiramate, Lamotrigine, Oxcarbazepine, Zonisamide, Lacosamide, Rufinamide, Stiripentol	N03AG04, N03AX14, N03AX11, N03AX09, N03AF02, N03AX15, N03AX18, N03AF03, N03AX17

**Table 2** ICD-10 code of seizure

Seizure type	ICD code
Generalized tonic-clonic	G40.309
Simple partial	G40.109
Status epilepticus	G40.A11
Complex partial	G40.209
Diverse seizures	G40.919
Absence seizures	G40.A09

## Materials and methods

This is a prospective, observational, and pharmacovigilance study was conducted among the out-patient Department of Neurology of Dr. Ram Manohar Lohia Hospital, New Delhi over carried out for a period of three months, from January to March 2019. Patients visiting out-patient department at hospital with complaints of convulsions for the first time were assessed and examined by the treating physician for the presenting complaint. To confirm the diagnosis of convulsion Electric encephalography (EEG) was done. Radiological investigations like *Computed tomography* and *Magnetic resonance imaging* were done to rule out organic cause for convulsions. Based on the history and finding of EEG and radiological examination, appropriate antiepileptic drug was prescribed to patients by the physician. Detailed personal, demographic and history about onset, duration and frequency of convulsions was also taken. Parents of each patient were individually counselled regarding benefits and dosing schedule of antiepileptic drugs therapy. They were also informed to observe and report any change in sleeping pattern, change in dietary habits, bladder and bowel habits, skin reactions or any other symptom in their patient after taking antiepileptic drugs therapy. Information about antiepileptic drugs prescribed was recorded which included- pharmaceutical company, batch number, manufacturing date, expiry

date and dose prescribed. Patients receiving antiepileptic drugs were evaluated for ADR, every one week through detailed interview of parents on the basis of preformed questionnaire. Significant ADRs were also brought to the notice of treating physician. Final decision regarding continuation of the drug, decreasing the dose of drug, withholding the drug or whether to change the drug was left to the treating physician. Causality assessment of ADRs was done according to WHO-UMC scale.<sup>16</sup> Preventability assessment of ADRs was done by Schumock and Thornton scale.<sup>17</sup> Severity assessment of ADRs was done according to Hartwig's and Siegel scale method.<sup>18</sup>

## Statistical analysis

For the percentages and standard deviation were calculated by using Microsoft Excel 2019.

## Ethical clearance

The patient's data were recorded and privacy of identity was maintained. The pharmacovigilance study starts with the clearance/permission of Head of Department of Neurology and Medical Superintendent of Dr. Ram Manohar Lohia Hospital, New Delhi: file number is (RML/2016/4072).

## Observations

The socio-demographic profile of total 30 epileptic patients enrolled in the study. Among these reports age below 8 to 14 years was 9(30%) of total report, 15 to 21 years was 16(53.3%), and 5(16%) of ADRs reported more than 22years (Figure 1). There were more male 17(56.6%) patients as compared to female 13(43.3%) (Figure 2). Majority of the patients were from rural area 9(30%) followed by urban area 21(70%) (Figure 3). Total 30 ADRs were reported in 30 patients, most commonly seen ADR were rashes 6(20%), abdominal pain 5(16.6%), sedation 3(10%), tremors 4(13.3%), weight gain 7(23.3%), and loss of appetite 5(16.6%) were commonly found adds in majority of patients (Figure 4). The ADRs experienced by the epileptic patient were non-serious and for the management of those

ADR an add-on drug therapy was done and there was some withdraw the suspected drug. The total ADRs in epileptic patient were 30 and these ADR was managed by add-on therapy/no drug change were 20(66.6%), drug permanently withdrawn 5(16.6%), dose reduced 3(10%) and frequency of dose schedule reduced 2(6.7%) (Figure 5). The outcomes of 30 ADRs, which were classified as recovered are 25(83.3%), followed by recovering 5(16.6%), not recovered 0(0%) and unknown 0(0%) (Figure 6).

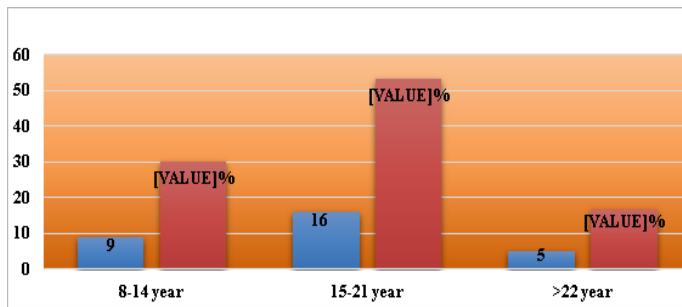


Figure 1 Age.

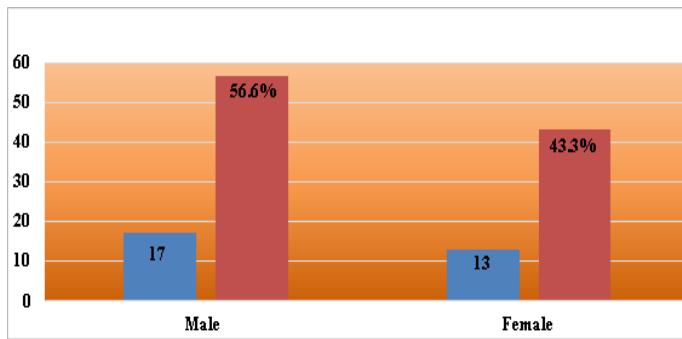


Figure 2 Sex.

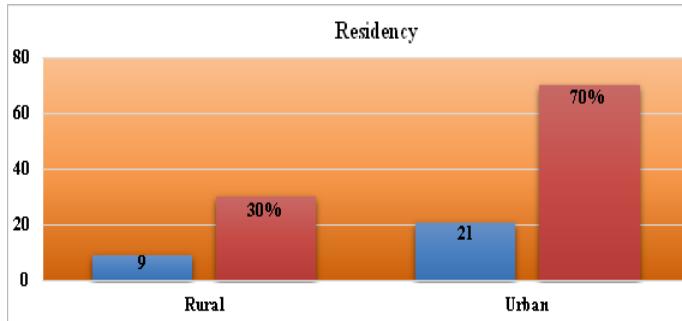


Figure 3 Residency.

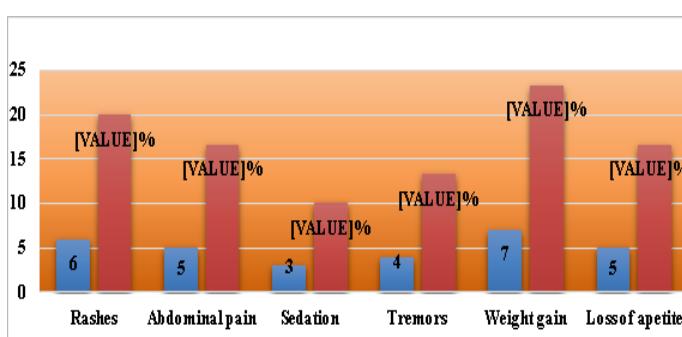


Figure 4 Types of ADRs.

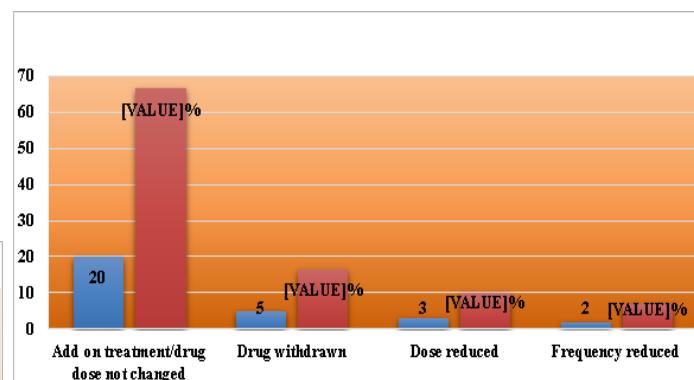


Figure 5 Management of ADRs.

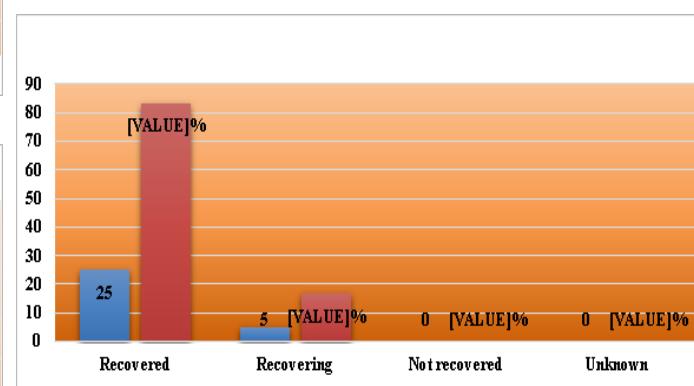


Figure 6 Outcomes of ADRs.

Causality of each ADR was assessed using WHO-UMC scale method. Assessment showed that out of 30 ADRs, possible ADRs were possible 26(86.6%), followed by probable/likely 3(10%) ADRs, were as certain 1(3.3%) and unlikely was 0 (Figure 7).<sup>20</sup> All the identified ADRs were analysed for its preventability assessment using Schumock and Thornton scale method, which showed that definitely preventable ADRs 27(90%), probably preventable were 3(10%) while remaining were not preventable ADRs were 0 describe (Figure 8).<sup>21</sup> The severity assessment of illness based on Hartwig and Siegel scale method. There were 28(93.3%) mild cases, 2(6.6%) moderate cases and 0 case in severe category (Figure 9).<sup>22</sup>

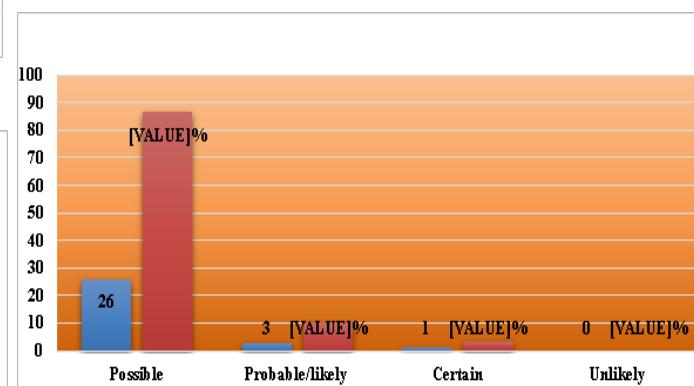
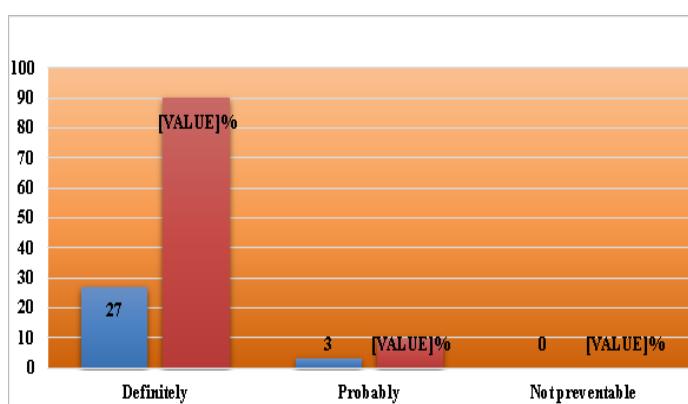
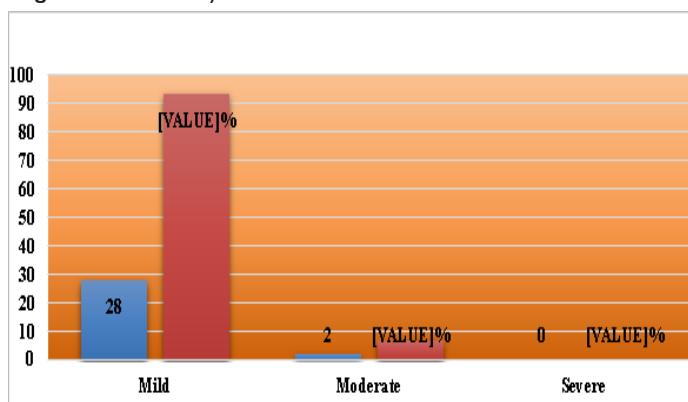


Figure 7 Causality assessment.



**Figure 8** Preventability assessment.



**Figure 9** Severity assessment.

## Results and discussion

Epilepsy remains one of the most commonly prevalent disease in society affecting 0.5 to 1% of population in India. The present study was envisaged to study pattern of epileptic cases, treatment given and assess the ADRs to antiepileptic drugs prescribed to epileptic patients attending out-patient to department of neurology of a multispeciality teaching hospital. It was observed in this study total 30 ADRs were reported, this study was conducted in department of neurology of Dr. Ram Manohar Lohia Hospital, New Delhi that is a 984 bedded central government multispeciality teaching hospital in urban area. In this observational study we found the age of patients ranged from 8 to >22 years. That there were more male 56.6% patients as compared to female 43.3%. There were adverse events in all the 30 cases on antiepileptic drugs, but these were successfully managed by immediate measures taken. Symptomatic addition of adjuvant drugs for adverse symptoms could relieve the adverse symptoms. This helped in ensuring compliance with antiepileptic drugs. Some antiepileptic drug had to be withdrawn as adverse effects could be managed with dose reduction or adjuvant treatment. Total 30 ADRs were reported in 30 patients who experienced the ADR of out-patient to department of neurology.

The majority of cases of the ADRs were related to the central nervous system such as sedation it happened in 10% mostly due to the antiepileptic drug like Benzodiazepines class (Clonazepam, Diazepam, Lorazepam, Clobazam) followed by gastrointestinal

reactions such as abdominal pain 16.6%, skin reaction such as rash 20%, tremors 13.3%, weight gain 23.3% and loss of appetite 16.6%. The ADR experienced by the epileptic patient were non-serious and all were managed by the add-on drug therapy. On the basis of the risk benefit ratio of the drug therapy for the treatment of antiepileptic drug withdrawn of the suspected drug was required. However, the management of the ADRs occurrence in epileptic patient were done with add-on therapy 66.6%, then followed by drug permanently withdrawn 16.6%, dose reduced 10%, frequency of dose schedule reduced 6.7% cases. The Causality of each ADR was assessed by using WHO-UMC causality assessment scale. On the basis of scale nearly 3.3% of the ADR were classified as certain, 10% probable, 86.6% possible and 0% of the ADR were unlikely. The severity assessment of each ADR was assessed by the modified Hartwig and Siegel scale. As per this assessment highest number of ADR i.e. 93.3% of the ADR comes on the level 1-2 and classified mild ADR, 6.6% of the ADRs were on level 3 i.e. moderate ADR and there was no any ADR were come on the level 4 and above i.e. severe ADR. For the preventability assessment of each ADR Schumock and Thornton scale were used, which showed that 90% of the ADRs were definitely preventable, 10% of ADRs were probably preventable and no any ADR were come under the not preventable class.

## Conclusion

Despite the novel discoveries and recent advances in the treatment and control of epilepsy, traditional drugs like Sodium valproate, phenytoin, and carbamazepine still remain as the most sought choice in the management of seizures in epileptic patients. Potential antiepileptic drug side effects and their occurrence in population not only affect the physician's choice but also determine the acceptance of the drug by the patient. Serious ADRs causes' mortality, morbidity, increases the economic burden and loss of productive time of the patient and the family. The main aim of the treatment of epilepsy is to make the patient completely seizure free, or to reduce seizure frequency and severity if the patient's seizures cannot be completely suppressed. This information may be useful to identify and to minimize the preventable ADRs. So, now the time has come to aware the general public too for the reporting the ADRs to nearest hospital or ADR monitoring centre or to the healthcare professionals. They may directly report the ADR through government. Toll-free number 18001803024, ADR application, email and other method like social media.

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## Conflicts of interest

Author declares that there is no conflict of interest regarding the publication of this paper.

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