E-ISSN 2250-0944

ISSN 2250-1150
doi: 10.48047/ijprt/15.02.81

PATTERN AND EXTENT OF ADVERSE DRUG REACTIONS (ADRS) WITH ANTIEPILEPTIC DRUGS AEDS

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Received date: 10-July-2025, Accepted date: 21-July-2025, Date of publication: 21-July-2025.

Abstract:

Background: There are additional challenges associated with anti-epileptic medications, such ADRs and compound interactions. The findings of systematic reviews and meta-analyses examining prospective research on medication surveillance in pediatric patients indicate that approximately 10% of hospitalized children would encounter an ADR.
Objective: To investigate the pattern and extent of adverse drug reactions (ADRs) with antiepileptic drugs AEDs**.**
Methods: This Prospective and pharmacovigilance study was conducted on epileptic patients at Tertiary Care Hospital. Duration of study was from August 2022 to October 2023. Ethical clearance was obtained from the Institutional Ethical Committee**.**
Results: Type A ADRs account for 77.1% of the cases, with 135 individuals affected. Type B ADRs, on the other hand, make up 22.9% of the cases, affecting 40 individuals. A significant majority, 80.6% of cases (141 individuals), experienced ADRs appearing more than 30 days after medication initiation. Total of 42.9% (75 individuals) experienced mild ADRs. 46.9% (82 individuals) of the study population reported moderate ADRs. The remaining 10.3% (18 individuals) experienced severe ADRs. The majority of patients (40%) were prescribed 4 drugs, followed closely by those prescribed 5 drugs, accounting for 38.8%.
Conclusion: Type A ADR was more common than type B ADR. Due to the elevated occurrence of ADRs associated with antiepileptic drugs, it is essential to promote the detection and reporting of ADRs among nurses, physicians, and patients alike
Keywords: Pattern and extent, adverse drug reactions (ADRs), Aantiepileptic drugs AEDs.

INTRODUCTION

Approximately 0.5% of children will encounter an ADR annually. The newer AEDs are associated with notable ADRs. Furthermore, the documentation of medication toxicity in clinical trials including AEDs is inadequate.[1]

In a 2014 study, it was determined that as many as 61% of patients who were prescribed conventional AEDs, such as Phenytoin, Carbamazepine, Valproate, and Phenobarbital, may experience unforeseen ADRs such as skin reactions, severe hematological disorders,

abnormalities in the central nervous system (CNS), or liver failure.[2] The majority of these diseases are associated with the toxic metabolic byproducts of AEDs, which are believed to play a role in the initial treatment failure observed in around 40% of patients.[3] The pharmacokinetic profile and therapeutic range of antiepileptic medicines are characterized by clinically significant interactions, both among themselves and with other treatments. The occurrence of interactions mostly accounts for the unanticipated alterations in the patient's clinical condition resulting from the controlled dosage.[4]

Drug interactions can be classified into two categories: pharmacokinetic and pharmacodynamics. The pharmacokinetic interactions that hold the greatest significance are those pertaining to cytochrome P450 isoenzymes in the context of hepatic metabolism.[5]

In developing nations, the financial resources allocated to healthcare and pharmaceuticals are constrained, underscoring the significance of sensible drug prescription practices to maximize the utilization of existing monies. It is important to exercise caution regarding potential medication interactions with conventional AEDs before considering their usage as a supplementary treatment.[6] The inception of drug utilization studies can be traced back to the early 1960s, and its significance has subsequently escalated. This can be attributed to the proliferation of new drugs in the market, the diverse patterns observed in drug prescription and consumption, mounting apprehension regarding delayed adverse effects, and the escalating concerns surrounding drug costs.[7] Drug use studies are used to analyze, intervene, and encourage the intelligent prescription, distribution, and management of medication. Consequently, the final results of DUR include enhanced patient care quality, superior therapeutic outcomes, and cost-effective medication.[8]

This study would make a valuable contribution to the field of pharmacovigilance by systematically monitoring and analyzing adverse drug reactions. This would also enable the identification of potential risks associated with these medications and facilitates the implementation of evidence-based interventions, ultimately leading to improved patient care and management of epilepsy. Therefore, this study was conducted.

MATERIAL AND METHODS

This Prospective and pharmacovigilance study was conducted on epileptic patients at Tertiary Care Hospital. Duration of study was from August 2022 to October 2023. Ethical clearance was obtained from the Institutional Ethical Committee.

Sample size: All the epileptic patients who attended OPD and admitted in wards for treatment during above duration of period.

Inclusion criteria:

- Patients of both gender and all age group receiving antiepileptic treatment.
- Newly diagnosed and old patients receiving treatment for epilepsy.

- Patients attended OPD for follow-up treatment as well as patients admitted in ward for treatment of acute epilepsy.

Exclusion criteria:

- Patients with secondary epilepsy due to head injury, cerebral palsy, stroke, metabolic disorders.
- Patients not willing to participate in the study were excluded from our study.
- Patients diagnosed as pre eclampsia and eclampsia with seizures.
- Patients on herbal therapy for treatment of epilepsy.
- Epileptic patients taking drug treatment for nonepileptic disorder.

Data collection:

- The Dose and Formulation of drug.
- Duration and frequency of drug.
- Details of drug use.
- Drug prescribing indicators.
- Doing casualty assessment of adverse effects.
- Type and severity of adverse effects.

Assessment of core indicators:

- Average number of antiepileptic drugs prescribed per prescription
- Percentage of drugs prescribed by generic name out of total drugs prescribed
- Percentage of drugs prescribed from essential drug list out of total drugs prescribed
- Percentage of drugs prescribed from hospital formulary list out of total drugs prescribed
- Percentage of fixed drug combinations prescribed out of total drugs prescribed
- Percentage of injections prescribed out of total drugs prescribed

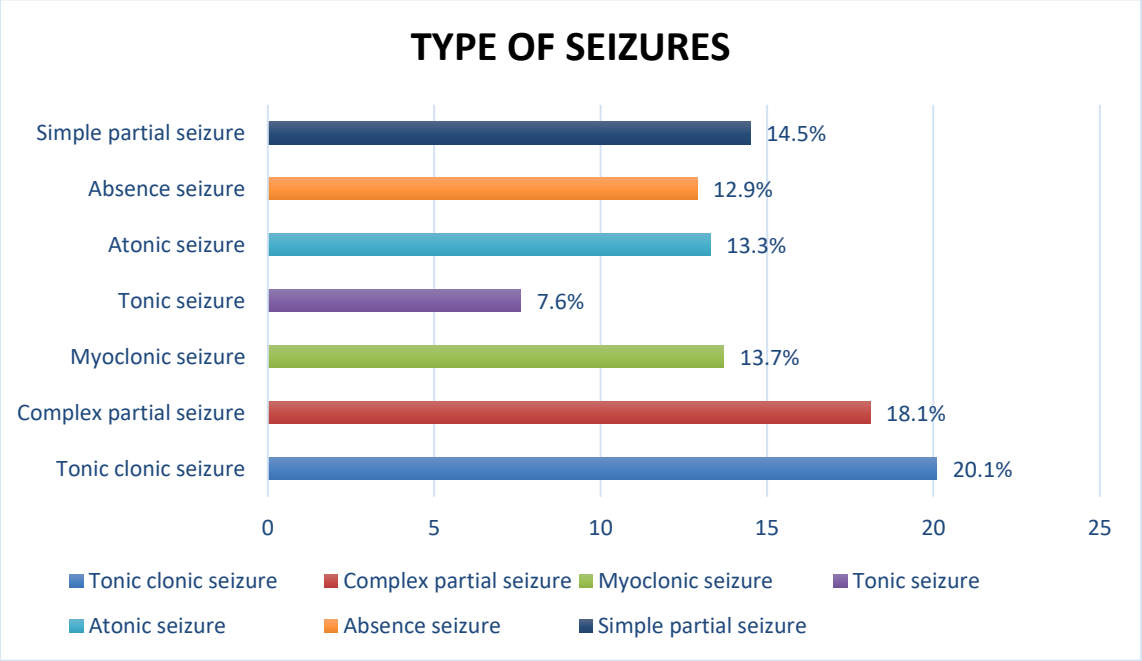
RESULTS

The most represented age groups are 21-30 years and 41-50 years, each comprising 22.0% of the study population. Following closely is the 51-65 age group, which accounts for 23.6%, making it the largest single group. Individuals aged 31-40 make up 14.4% of the population, while those in the 1-14 age group represent 13.2%. The 15-20 age category is less represented, with only 3.6% of the population. Finally, the least represented age group is those over 65 years, making up just 1.2% of the total. Overall, the data indicates a relatively

balanced distribution among the various adult age categories, with a notable drop-off in representation among the youngest and oldest age groups.

Males constitute 50.8% of the total population, while females account for 49.2%. This nearly equal distribution indicates a well-balanced representation of both genders in the study, with a slight predominance of males. The total number of participants is 250, with 127 males and 123 females, reflecting a comprehensive inclusion of both genders in the analysis.

Graph 1. Percentage distribution of study population – according to type of seizures



Tonic clonic seizures are the most common, affecting 20.1% of the population. This is followed by complex partial seizures, which are experienced by 18.1% of the participants. Simple partial seizures account for 14.5%, making them the third most prevalent type. Myoclonic seizures are reported by 13.7% of the population, and atonic seizures by 13.3%. Absence seizures are present in 12.9% of the cases. The least common type is tonic seizures, affecting 7.6% of the population. Overall, the data indicates a diverse range of seizure types within the study group, with tonic clonic seizures being the most frequent and tonic seizures the least.

Table.1: Percentage distribution of study population – according to type of ADR

		Frequency	Percentage
Type of ADR	Type A	135	77.1%
	Type B	40	22.9%
	Total	175	100

Type A ADRs account for 77.1% of the cases, with 135 individuals affected. Type B ADRs, on the other hand, make up 22.9% of the cases, affecting 40 individuals. This distribution

indicates that Type A ADRs are significantly more prevalent within the study population compared to Type B ADRs. Type A reactions typically involve predictable responses to medications, often related to pharmacological effects, while Type B reactions are more unpredictable and may be related to immune responses or idiosyncratic reactions.

Table 2: Percentage distribution of study population – according to duration of appearance of ADR

		Frequency	Percentage
Duration of appearance	1-30 days	34	19.4%
	>30 days	141	80.6%
	Total	175	100

A significant majority, 80.6% of cases (141 individuals), experienced ADRs appearing more than 30 days after medication initiation. In contrast, 19.4% of cases (34 individuals) reported ADRs appearing within the first 30 days of starting medication. This distribution suggests that a substantial portion of ADRs in this study population manifests after an extended period of medication use, highlighting the importance of long-term monitoring and surveillance for adverse effects beyond the initial treatment phase.

Table3. Percentage distribution of study population – according to severity

		Frequency	Percentage
Level of severity	Mild	75	42.9%
	Moderate	82	46.9%
	Severe	18	10.3%
	Total	175	100

Mild: A total of 42.9% (75 individuals) experienced mild ADRs. **Moderate**: 46.9% (82 individuals) of the study population reported moderate ADRs. **Severe**: The remaining 10.3% (18 individuals) experienced severe ADRs.

Table 4. Percentage of Level of severity, Type of ADR

Level of severity - type of ADR Cross tabulation						
			Type of ADR		Total	
			Type A	Type B		P value
Level of severity	Mild	Count	61	14	75	0.063
		% within Level of severity	81.3%	18.7%	100.0%	
	Moderate	Count	64	18	82	

		% within Level of severity	78.0%	22.0%	100.0%	
	Severe	Count	10	8	18	
		% within Level of severity	55.6%	44.4%	100.0%	
Total		Count	135	40	175	
		% within Level of severity	77.1%	22.9%	100.0%	

The table shows the distribution of Adverse Drug Reactions (ADRs) categorized by both severity level and type (Type A and Type B). Here's the interpretation:

- Mild ADRs: Among the cases classified as mild, 81.3% (61 out of 75 cases) are Type A reactions, while 18.7% (14 out of 75 cases) are Type B reactions. The p-value of 0.063 suggests a borderline significant association between severity and type of ADR for mild cases.

- Moderate ADRs: For moderate ADRs, 78.0% (64 out of 82 cases) are Type A reactions, and 22.0% (18 out of 82 cases) are Type B reactions. The association between severity and type for moderate cases is not explicitly significant.

- Severe ADRs: In severe cases, 55.6% (10 out of 18 cases) are Type A reactions, while 44.4% (8 out of 18 cases) are Type B reactions. The distribution indicates a less clear association between severity and type for severe cases.

Table 5.Total number of drugs prescribed

Total no. of drugs	Frequency	Percentage
4	100	40%
5	97	38.80%
6	42	16.80%
7	10	4%
8	1	0.4%
Total	250	100%

It shows that the majority of patients (40%) were prescribed 4 drugs, followed closely by those prescribed 5 drugs, accounting for 38.8%. A smaller proportion, 16.8% of patients, was given 6 drugs. Only 4% of patients were prescribed 7 drugs, while a mere 0.4% received 8

drugs. Overall, the data indicates that most patients (nearly 80%) were typically prescribed either 4 or 5 drugs, while prescriptions involving a higher number of drugs were relatively rare.

Table 6.Other drugs prescribed during course of treatment

Other drugs prescribed	Frequency	Percentage
Antacid	230	92%
Antibiotic	50	20%
Multivitamins	210	84%
IV fluids	200	80%
Corticosteroids	20	8%
Oral Hypoglycemic drugs	75	30%
Antihypertensives	55	22%

Antacids (92%), multivitamins (84%), and IV fluids (80%) were the most frequently prescribed medications, suggesting common gastrointestinal management, nutritional supplementation, and fluid maintenance in the cohort. Oral hypoglycemics (30%) and antihypertensives (22%) were prescribed to manage chronic conditions like diabetes and hypertension in a notable portion of patients. Antibiotics (20%) and corticosteroids (8%) were used more selectively, likely for specific infections or inflammatory conditions. Overall, the prescription pattern highlights a focus on addressing nutritional, fluid, and chronic disease needs in this patient population.

DISCUSSION

In our present study the most represented age groups are 51-65 years (23.6%), followed by 21-30 years and 41-50 years, each at 22.0%. Individuals aged 31-40 comprise 14.4%, while the 1-14 age group accounts for 13.2%. The 15-20 and 65+ age groups are less represented at 3.6% and 1.2%, respectively. Epilepsy shows a bimodal distribution, with a significant increase in cases during childhood and a second peak in the elderly.[9]

In the current study, the proportion of males is 50.8% and females constitute 49.2% of the total sample size of 250 participants. This suggests a somewhat balanced gender distribution, with a small male predominance observed, with 127 males and 123 females. The study conducted by **Murthy et al.** demonstrated a higher incidence of epilepsy in males compared to females.[8]

Within the scope of our current investigation, it was observed that tonic clonic seizures had the highest prevalence rate at 20.1%, followed by complex partial seizures at 18.1% and

simple partial seizures at 14.5%. Myoclonic seizures (13.7%), atonic seizures (13.3%), and absence seizures (12.9%) exhibit lower prevalence rates, with tonic seizures being the least frequent (7.6%). In the study conducted by **Sharvani et al.**[10], most patients experienced generalized tonic-clonic seizures, followed by atypical, typical, status epilepticus, febrile, partial seizures, alcohol-induced seizures, and hot water-triggered convulsions.

Based on our study findings, it was determined that 77.1% of the population exhibited type A ADR, whereas 22.9% displayed type B ADR. The predominant ADRs seen were of type A, which were associated with drug dosage, whereas just 4 cases (2%) were classified as type B, characterized by idiosyncrasy. The findings of our investigation align with those of **Kaushik et al.**[11]

Adverse drug reactions (ADRs) are classified based on their characteristics and underlying mechanisms:[12]

Type A (Augmented): Dose-dependent reactions predictable from the drug's known effects, like insulin-induced hypoglycemia. Managed by adjusting dosage.

Type A ADRs are more common than Type B due to their predictable, dose-dependent nature linked to the drug's mechanism, such as insulin-induced hypoglycemia or benzodiazepine-induced drowsiness.[13]

Type B reactions are rare and unpredictable, often due to immune responses or idiosyncratic traits, unlike Type A reactions, which are common, predictable, and dose-dependent.[14]

ADRs of Type A are frequently observed and predominantly impact the organs and systems that are directly engaged in the primary mechanism of action of the drug.[15] Medications can cause predictable, dose-dependent Type A ADRs, such as gastrointestinal issues from NSAIDs, cardiovascular effects from antihypertensives, CNS effects from sedatives, and liver or kidney toxicity from statins and antibiotics.[16]

The majority of patients in our study had moderate adverse drug reactions (46.9%), with mild ADRs accounting for 42.9%. Out of the mild ADRs, 61 were Type A and 14 were Type B. For moderate ADRs, 64 were Type A and 18 were Type B.The study conducted by **Hernandez et al.**[17] revealed that a majority of the drugs identified in the analysis had minor adverse drug reactions (ADRs) when assessed in terms of severity.

In the study, 80.6% of ADRs appeared after 30 days of medication initiation, while 19.4% occurred within the first 30 days. This highlights the need for long-term monitoring of adverse effects.ADRs range from mild (e.g., nausea) to moderate (e.g., hypersensitivity) requiring medical attention, to severe (e.g., anaphylaxis) that demand urgent care and typically necessitate stopping the medication.[12]

CONCLUSION

Type A ADR was more common than type B ADR. Due to the elevated occurrence of ADRs associated with antiepileptic drugs, it is essential to promote the detection and reporting of ADRs among nurses, physicians, and patients alike

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