Original Article

Evaluation of Drug Utilization and Analysis of Drug Related Problems of Anti-Epileptic Drugs in Inpatients at Tertiary Care Teaching Hospital

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Received: 09-10-2025; **Revised:** 23-11-2025; **Accepted:** 29-11-2025; **Published online:** 20-12-2025.

ABSTRACT

Aim: This study evaluates drug utilization patterns and analyzes drug-related problems (DRPs) associated with Antiepileptic drugs in inpatients admitted to the Medicine and Pediatric departments of a tertiary care teaching hospital.

Methods: A hospital-based prospective study was conducted from March 25, 2024, to September 25, 2024. Total 100 patients with a history of seizures or newly diagnosed epilepsy, admitted to the Medicine and Pediatric departments of a tertiary care teaching hospital. Drug utilization analysis was stratified by age, gender, type of seizure, and rationality. Suspected adverse drug reactions (ADRs) were reported, and causality was assessed using the Naranjo scale.

Results: AEDs were predominantly prescribed for patients aged 2–11 years, with a higher prevalence of epilepsy among males. Generalized seizures were the most prevalent across the spectrum of seizure types. Levetiracetam was found to be the most frequently prescribed monotherapy and the drug of choice. Sodium valproate, lacosamide, and clobazam were commonly used as adjunct therapies alongside levetiracetam. Levetiracetam represented largest number of DRPs and ADRs, including dizziness, thrombocytopenia, and vomiting. Rationality assessment was performed, with the NICE and IAP guidelines being the most frequently followed.

Conclusion: The preference for newer AEDs, particularly levetiracetam, over conventional drugs was evident. However, its widespread use was tied to a greater occurrence of ADRs. Drug utilization evaluation (DUE) plays a crucial role in ensuring appropriate medication use and monitoring DRPs to enhance patient outcomes.

Keywords: Levetiracetam, Drug Utilization, Antiepileptic drugs, Drug related problems, Generalized seizures.

INTRODUCTION

Epilepsy is an enduring neurological disease marked by spontaneous and unprovoked seizures that occur erratically and impose a significant burden on a patient's life. These seizures result from hypersynchronous electrical discharges in neurons, primarily in the brain's cortex. Affecting approximately 0.5% to 1% of the global population, epilepsy is the commonest disorder of the central nervous system (CNS).[1]

Medications are the primary treatment for epilepsy and with the appropriate selection and administration of antiepileptic drugs (AEDs), 60–90% of epilepsy patients can achieve effective management. Successful seizure control relies on accurate diagnosis, patient adherence, and consideration of drug side effects, all of which are crucial in ensuring treatment compliance.[2] To ensure proper treatment for both epileptic and non-epileptic patients, a Drug Use Evaluation (DUE) is conducted. This is a criteria-based assessment designed to promote the appropriate use of medicines.[3]

Drug related problems (DRPs) are frequently observed in epilepsy patients due to the intricacy of both the disease and AED regimens. The presence of multiple medical conditions and concurrent medications increases the risk of drug interactions and toxicity, which can, in turn, contribute to DRPs.[4] AEDs typically known to have narrow therapeutic index, and their prolonged use heightens the risk of adverse drug reactions (ADRs). Commonly reported ADRs include gastrointestinal disturbances, hematological abnormalities such as anemia and thrombocytopenia, hepatotoxicity, neurological impairment, and bone-related disorders. These challenges may negatively impact seizure control and overall treatment outcomes.[5]

This study also aims to highlight the clinical pharmacy services provided by pharmacists to enhance rational drug therapy by evaluating the current trend in prescription pattern in our country. This assessment considers factors

such as patient age, the use of monotherapy or polytherapy, and the adoption of newer antiepileptic drugs (AEDs). These services can help ensure the appropriate use of medications and improve patient adherence to prescribed treatments.

METHODOLOGY

This prospective study, spanning six months (25 March 2024 to 25 September 2024), aimed to assess the drug utilization patterns and rationality of antiepileptic drug (AED) prescriptions among 100 inpatients admitted to the General Medicine and Pediatric departments of a tertiary care teaching hospital in India. Following approval from the Institutional Ethics Committee, the study recruited patients of all ages and both sexes undergoing treatment in the aforementioned departments, provided they were receiving AEDs as part of their treatment regimen. Conversely, patients receiving outpatient treatment and pregnant women were excluded from the study. Patients meeting the study's eligibility criteria were enrolled, and relevant data were collected daily from their case files. To evaluate the rationality of AED prescriptions, the study employed standard clinical guidelines from reputable sources, including:

- International League Against Epilepsy (ILAE) guidelines
- Indian Pediatric Association guidelines (IPA) - National guidelines
- National Institute for Health and Care Excellence (NICE) clinical guidelines - International guidelines

Data analysis was performed using statistical methods such as percentage and proportion to draw conclusions and determine significant difference.

RESULTS

Socio-demographic details of subjects

Total 100 patients admitted in the hospital were subjected for review. The study's findings indicated a notable male preponderance in the utilization of antiepileptic drugs (AEDs), with the majority of prescriptions being issued to children within 2-11 year age group, and characterized by a higher incidence of generalized seizures (49%) followed by seizures due to secondary causes.

Characteristics of seizure with respect to its type of onset and etiology.

Out of 86 patients 6 (6.97%) were categorized under established followed by recurrent 42 (48.83%) and new onset cases were 37 (43.03%). According to etiological basis 62 (72.09%) were of primary and 24 (27.90%) of secondary causes.

AED utilization pattern

During the study period a total of 100 patients were studied, where in epileptic patients were mostly treated with monotherapy which constitute 65 (65%) followed by two drug therapy 30 (30%) and three drug therapy 3(3%).

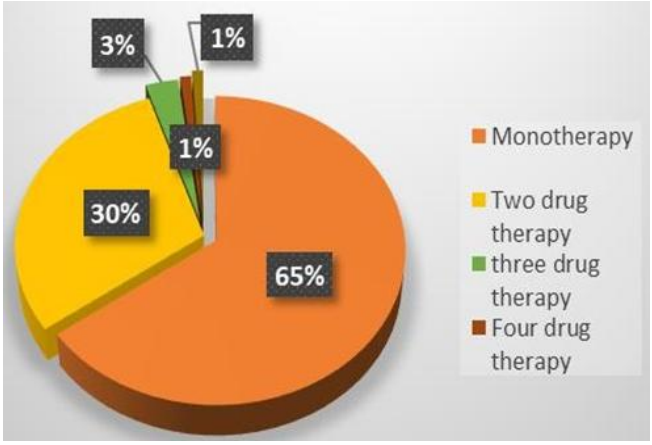

Figure 1: Pattern of antiepileptic drug (AED) utilization among patients. Monotherapy was prescribed in 65% of cases, two-drug therapy in 30%, three-drug therapy in 3%, four-drug therapy in 1%, and five-drug therapy in 1%.

AED usage as monotherapy:

Out of 100 patients, 65 patients used monotherapy. In this study, levetiracetam 52 (36.6%) was the most frequently prescribed AED, followed by clobazam and brivaracetam 4 (2.81%) each, sodium valproate and lacosamide each accounting 2 (1.40%) and oxcarbazepine 1 (0.7%) was used as monotherapy. Here, levetiracetam was the highly used AED as monotherapy.

AED usage as combination

A total of 30 prescriptions were observed with two AED combinations. The most commonly prescribed AED combination therapy was combination of sodium valproate with levetiracetam and combination of levetiracetam and lacosamide both accounts 16.66% each, levetiracetam and clobazam with 13.33%, combinations of brivaracetam and lacosamide and phenytoin and levetiracetam both accounts 10% each.

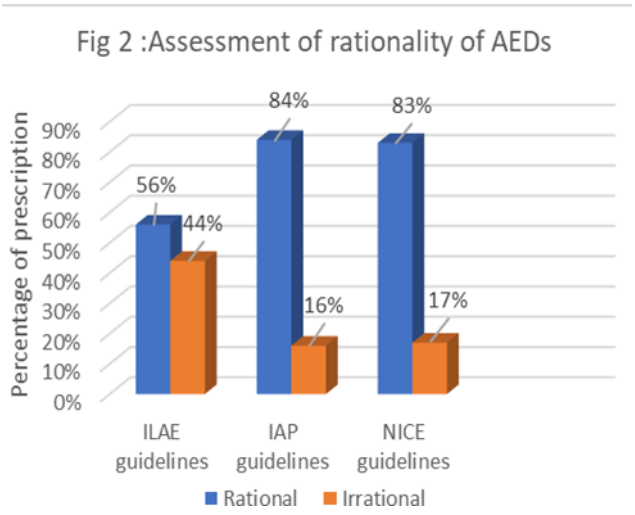

Figure 2: Assessment of rationality of antiepileptic drug (AED) prescriptions as per ILAE, IAP, and NICE guidelines. According to ILAE guidelines, 56% of prescriptions were rational and 44% irrational. As per IAP and NICE guidelines,

rational prescriptions were 84% and 83%, respectively, while irrational prescriptions accounted for 16% and 17%.

Assessment of rationality of AEDs

A total of 142 AEDs out of 100 prescriptions, 102 drugs were analyzed for rationality assessment. In which only 97 drugs were selected for rationality assessment as per the global standard ILAE (International League Against Epilepsy) guidelines {> 18 years) of which 54 (56%) were found to be rational and 43 (44%) were irrational. IAP (Indian Association of Pediatrics) guidelines (<18 years) were used for assessing 50 drugs, in which 42 (84%) were found to be rational and 8 (16%) were irrational. Similarly, by NICE (National Institute for Health and Care Excellence) guidelines of United Kingdom 100 drugs were subjected for rationality review, only 83 (83%) were found rational and 17 (17%) were irrational.

Table 1: Sociodemographic details of the patients

According to gender classification		
Gender	**No of patients**	**Percentage**
Male	67	67%
Female	33	33%
According to age categorization		
Age groups	**No of patients**	**Percentage %**
Newborn infants (0 to 27 days)	0	0%
Infants & Toddlers (28 days to 23 months	14	14%
Children (2 to 11 years)	22	22%
Adolescents (12 to 18 years)	7	7%
Young adult (18 - 30 years)	17	17%
Adults (31 - 45 years)	19	19%
Older adults (46 - 60 years)	7	7%
Elderly adults (60 - 75 years)	13	13%
Very elderly adults (> 75years)	1	1%
According to type of seizures		
Type of seizures	**No of patients**	**Percentage**
Generalized seizures	**49**	**49%**
a) Tonic seizures	2	2%
b) Clonic seizures	1	1%
c) Absence seizure	3	3%
d) Atonic seizure	1	1%
e) Tonic – clonic seizures	40	40%
f) Myoclonic seizures	1	1%
g) Unknown Seizure	1	1%
Partial seizures	**12**	**12%**
a) Simple partial seizure	5	5%
b) Complex partial seizure	3	3%
c) Partial seizure with secondary generalized	4	4%
Seizures due to secondary causes	**25**	**25%**
a) Diseases	23	23%
b) Toxicity	2	2%
Others (prophylactic treatment)	14	14%

Table 2: Drug related problems of AEDs

S.No	Types of DRPs	No of DRPs	Incidence
1	Untreated indication	3(7.14%)	0.34%
2	Improper drug selection	5(11.90%)	
3	Adverse drug reaction	22(52.38%)	
4	Drug interaction	3(7.14%)	
5	Sub therapeutic range	3(7.14%)	
6	Overdose	5(11.90%)	
7	Drug Duplication	1(2.38%)	

Table 3: Causality assessment of ADRs

S.No	Name of the drug	Reaction	Assessment scales		
			NARANJO	WHO	HARTWING
1	Levetiracetam	Dizziness	Probable	Probable	Moderate
2	Levetiracetam	Dizziness	Probable	Probable	Moderate
3	Levetiracetam	Vomiting	Probable	Probable	Moderate
4	Levetiracetam	Cough	Probable	Probable	Moderate
5	Levetiracetam	Thrombocytopenia	Probable	Certain	Severe
6	Levetiracetam	Thrombocytopenia	Probable	Certain	Moderate
7	Sodium valproate	Thrombocytopenia	Probable	Probable	Moderate
8	Sodium valproate	Thrombocytopenia	Probable	Probable	Moderate
9	Sodium valproate	Dizziness	Probable	Probable	Moderate
10	Sodium valproate	Erythema multiforme	Probable	Possible	Moderate
11	Sodium valproate	Hepatitis	Probable	Probable	Moderate
12	Oxcarbazepine	Hepatitis	Probable	Certain	Moderate
13	Oxcarbazepine	Hepatitis	Probable	Probable	Moderate
14	Oxcarbazepine	Vomiting	Probable	Probable	Moderate
15	Phenytoin	Hypocalcaemia	Probable	Possible	Moderate
16	Phenytoin	Nephrotoxicity	Probable	Probable	Severe
17	Phenytoin	Megaloblastic anaemia	Probable	Probable	Moderate
18	Clobazam	Cough	Probable	Probable	Moderate
19	Clobazam	Fever	Probable	Certain	Mild
20	Lacosamide	Dizziness	Probable	Probable	Moderate
21	Lacosamide	Dizziness	Probable	Probable	Moderate

Drug related problems (DRPs) of AEDs.

Adverse drug reactions (ADR):

At the end of the follow up period, a total of 22 ADRs were reported from epileptic patients. The most common drug implicated for ADRs was Levetiracetam 27.27% followed by Sodium Valproate 22.72%, Oxcarbazepine and phenytoin accounts 13.63% each, ADR by Clobazam and Lacosamide accounts 9.09% each and Brivaracetam with 0.04%.

Causality: Upon causality assessment, majority of the reports were rated as probable (95.45%) followed by possible (4.55%) according to Naranjo scale. According to WHO 68.18% are probable, followed by 18.18% are certain and 13.63% are possible. Mild and moderate reactions accounted for 9.09% and 81.81% respectively and only 9.09% of the reactions were deemed to be severe as per Hartwig scale.

Overdosage: 5 patients were found with overdosage, mostly with levetiracetam.

Sub therapeutic dose: 3 patients received a low dose of AED according to the standard dose recommendation in the literature.

Drug duplication: Levetiracetam drug duplication was found in 1 patient.

Improper drug selection: 5 patients received improperly selected drugs according to the standard guidelines. The most common drugs for improper selection were lorazepam and lacosamide.

Drug interactions: A total of 3 patients were reported with drug - drug interactions most commonly with lorazepam. All 3 were major drug interactions. These patients are monitored and followed up for the period of hospital stay.

Among 12,306 cases reviewed in both general medicine and pediatrics, the incidence of DRPs associated with antiepileptic drugs was found to be 0.37%.

DISCUSSION

The study population consisted of 67% males and 33% females; this proportion suggests higher prevalence of epilepsy among males. This gender disparity is similar with findings from a nationwide retrospective cohort study by Goyal et al., which analyzed electronic medical records across India and found 62% patients were male and 38% patients were female.[6] The reason for the male predominance could be that men are more likely to have road accidents, head injuries, occupational hazards and alcohol abuse.

We observed two distinct peaks in epilepsy prevalence in our study, where the first peak was in 2-11 years of age (22%) followed by among adults 31-45 years (19%) age group. This bimodal distribution is similar to study conducted by Singh et al., where a significant peak was observed before 10 years of age followed by young adults. This early childhood peak might be due to perinatal factors

like hypoxia and infections and other complications including Global Developmental Delay, whereas in adults, due to head injury, and lifestyle changes such as irregular sleep, substance abuse and in older adults stroke, brain tumors, neurodegenerative disorders.[7]

There was a higher prevalence of generalized seizures (49%) among our study subjects, followed by partial seizures (12%). These findings are consistent with study conducted by Sivakumaran et al., where out of 100 patients, generalized tonic-clonic seizures were observed in 49% cases while focal seizure accounted for 23%.[8] This could be due to genetic and developmental disorders or other structural changes, brain injury, brain tumors, stroke, infections.

Monotherapy was practiced in 65% of our patients and multiple drug therapies in some patients (35%), this result aligns with findings from Faheem Nazir et al., where 80.25% of their patients received monotherapy.[9] In both studies, monotherapy was preferred for epilepsy management due to its reduced risk of side effects, drug–drug interactions, better patient compliance and easy monitoring.

Our study found that levetiracetam was the most commonly prescribed AED as monotherapy as well as polytherapy. Similarly, RK Sori et al, reported that 42.48% of their epileptic patients were managed by levetiracetam monotherapy.[10] This finding highlights levetiracetam's efficacy and tolerability in clinical practice. The preference for levetiracetam as monotherapy as well as in polytherapy may be attributed to its broad-spectrum activity, favorable pharmacokinetic profile, and minimal drug interactions.

In addition to levetiracetam being the choice of drug in our hospital today, this trend contrasts with a similar study conducted in the same hospital by Kulkarni et al., where phenytoin and sodium valproate were the most commonly used drugs in management of seizures.[11] This shift in prescribing trend indicates the levetiracetam has become recognized as an optimal drug for seizure management due to its distinct advantages.

In 30 patients, seizures were managed with dual therapy. The most commonly prescribed AED combination therapies that consist of add-on therapy were combinations of levetiracetam with sodium valproate and levetiracetam with lacosamide each accounting 16.66%. Common use of levetiracetam and sodium valproate as dual therapy as seen in the study by Gupta et al., can be attributed to their complementary mechanism of action.[12]

A total of 22 adverse drug reactions (ADRs) were observed in epileptic patients. The most commonly reported ADRs with levetiracetam (27.27%), were dizziness, thrombocytopenia, vomiting, and cough. These findings are consistent with a study conducted by Sahaya et al., which highlights thrombocytopenia as a clinically relevant but rare adverse effect of levetiracetam, due to its not well-established causal relationship.[13]

Sodium valproate (22.72%) was the second most common drug associated with ADRs in our study, including thrombocytopenia, dizziness, and erythema multiforme. These results align with a prospective study by Esfahani et al., where the majority of patients experienced weight gain (53%), followed by dizziness (1%), rash (0.5%), and thrombocytopenia (1%). Although weight gain is a commonly reported side effect of sodium valproate, it was not observed in our study. However, due to this side effect, sodium valproate is generally avoided in pediatric patients, women with menstrual irregularities, and individuals where weight gain may be of clinical concern.[14]

We conducted the rationality assessment as per ILAE, NICE and IAP guidelines. According to ILAE guidelines, 54 (56%) prescriptions were rational and 43 (44%) were found to be irrational. As per IAP guidelines in which 42 (84%) were found to be rational and 8 (16%) were irrational. Similarly, by NICE guidelines, only 83 (83%) of prescriptions were found rational and the rest 17 (17%) were irrational. As per our study, IAP and NICE guidelines were mostly followed. This indicates that most of the pediatricians in India followed the IAP guideline over other international guidelines.

Study limitations

This study was conducted at a single tertiary care teaching hospital, which may restrict the applicability of the results to other healthcare environments with different patient characteristics, prescribing practices, or resource availability. The modest sample size and limited study duration may have reduced the likelihood of identifying rare drug-related problems and restricted the observation of long-term prescribing trends. Furthermore, the study's scope was confined to assessing drug-related problems and evaluating antiepileptic drug utilization patterns; it did not investigate clinical outcomes such as seizure control, post-treatment sequelae, or the effects on patients' quality of life.

CONCLUSION

Our study on antiepileptic drug (AED) usage in a South Indian tertiary care teaching hospital found that monotherapy was the predominant treatment approach, with levetiracetam being the drug of choice. The combination of levetiracetam and sodium valproate was also frequently used. Levetiracetam was the most commonly prescribed drug in our study and accounted for the highest number of adverse drug reactions (ADRs).Our hospital has increasingly adopted newer antiepileptic drugs like levetiracetam for epilepsy management due to their cost- effectiveness, broad-spectrum activity, and improved safety profile compared to conventional drugs. Although levetiracetam had the highest number of ADRs, it remains relatively safe, as the overall incidence of ADRs was low despite its widespread use. The most common ADRs associated with levetiracetam were dizziness, thrombocytopenia, and vomiting. This study highlights the importance of prudent AED prescribing and monitoring

practices and role of pharmacist to optimize patient outcomes and minimize drug-related problems. These includes conducting thorough medication review and identify potential drug interactions, monitoring of AED serum levels to minimize toxicity, management of AED related adverse reactions, providing patient counseling on AED adherence, dosage and potential side effects.

DATA AVAILABITLITY STATEMENT

The data supporting the findings of this study are not publicly available due to patient privacy, but may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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