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ASSESSMENT OF ADVERSE DRUG REACTIONS OF NEWER ANTIEPILEPTIC DRUGS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Epilepsy is one of the most common chronic neurological disorders, affecting around 50 million people worldwide, with most of the burden in low- and middle-income countries. Older antiepileptic drugs are associated with enzyme induction or inhibition, many drug interactions, narrow therapeutic windows and a significant burden of adverse effects. From the 1990s onward, newer or second-generation antiepileptic drugs were introduced. They were developed mainly to improve tolerability and pharmacokinetic predictability, with fewer interactions. Despite these advantages, adverse drug reactions remain an important clinical concern, as they can lead to poor medication adherence, treatment modification, or discontinuation. Evaluating adverse drug reactions alongside drug utilisation patterns can help identify drug-specific safety concerns, irrational prescribing practices, and factors contributing to adverse outcomes. This study aims to assess adverse events associated with newer antiepileptic drugs, its utilization patterns, causality, severity, and preventability. where data remains limited in our population. Assessing adverse events in our local clinical setting will help determine its real-world applicability, optimize treatment decisions, and potentially improve the quality of care for patients with epilepsy.

PRIMARY OBJECTIVES

- To assess adverse events associated with newer antiepileptic drugs in a tertiary care hospital.

SECONDARY OBJECTIVES

- To assess causality of adverse events using WHO-UMC scale.
- To assess severity using Hartwig and Seigel scale and assess preventability using Schmock and Thornton scale.
- To study drug utilization pattern of newer antiepileptics.

Study Design, Study Site, Study Period: A cross-sectional study was conducted at Department of Neurology, Govt. Medical College, Thiruvananthapuram from February 2026 to November 2026. **Method:** A total of 88 patients diagnosed with epilepsy were evaluated. Adverse drug events were assessed, and their causality, severity, and preventability were evaluated alongside the drug utilisation patterns of newer antiepileptic drugs. **Result:** Among the specifically identified adverse drug events, Obesity was the most frequently reported 10(11.4%), followed by dizziness7(8.0%), somnolence 5(5.7%), ataxia and headache each accounted for 2(2.3%) cases. While rash was the least frequently reported adverse drug events 1(1.1%). A statistically significant association was observed between adverse drug event type and age group (Fisher's exact test, p = 0.019). No, statistically significant associations were observed between adverse drug event type and the other assessed parameters. The majority of reported adverse events were mild in severity and possibly related to therapy, with a substantial proportion identified as preventable. Conclusion: This study demonstrated that the majority of reported adverse events were mild in severity and possibly related to therapy, with a substantial proportion identified as preventable, but their occurrence indicates the need for continuous monitoring during therapy. Among the specifically identified adverse drug events, Obesity was the most frequently reported. Majority of patients were classified as others. These findings emphasize the importance of regular adverse drug reaction monitoring, appropriate drug selection. Patient counselling, adherence monitoring, and active pharmacist involvement to promote safe and effective antiepileptic therapy.

KEYWORDS: Adverse drug events (ADE); Adverse drug reaction (ADR); Antiepileptic drugs (AED); Antiseizure medications (ASM); Preventability Assessment; Severity Assessment; Causality Assessment; Drug utilisation Pattern.

INTRODUCTION

Epilepsy is a long-term neurological disorder that affects millions of people worldwide. Its impact is particularly substantial in developing countries, where access to timely diagnosis, appropriate treatment, and continued medical care may be limited.[1,2] Epilepsy is characterised by a persistent tendency to experience epileptic seizures and can also significantly affect an individual's neurological functioning, cognition, psychological and social well-being.[3] It represents an important public health concern in India, where millions of people are affected and many patients continue to face barriers to receiving adequate diagnosis and treatment.[4] Since epilepsy frequently requires prolonged pharmacological management. The selection of antiseizure therapy should consider seizure control alongside medication safety, tolerability and suitability for long-term treatment.

Conventional antiseizure medications including phenobarbital, phenytoin, carbamazepine and valproate remain important in epilepsy management but may be limited by pharmacokinetic variability, drug interactions, dose-related toxicity and other adverse effects.[5] Beginning in the late twentieth century, several newer antiseizure medications became available for clinical use. These agents include lamotrigine, levetiracetam, topiramate, oxcarbazepine, zonisamide, lacosamide, perampanel and brivaracetam became available.[6] Despite the availability of additional treatment options, a substantial proportion of people with epilepsy do not maintaining long-term seizure control, despite appropriate medication. These patients may require combinations of antiseizure medications, increasing treatment complexity and the potential for adverse effects and drug–drug interactions.[7,8]

An adverse drug reaction is harmful and unintended response to a medicinal product when it is used at doses normally recommended for therapeutic purposes.[9] Adverse drug reactions may adversely influence patient's clinical outcomes by contributing to illness, additional healthcare requirements, longer hospital admissions, increased treatment expenditure in serious cases like death.[10,11] A side effect is an unintended or secondary effect of a medicine that occurs at therapeutic doses, in addition to its intended therapeutic effect. It may be beneficial, neutral, or harmful, although the term is commonly used to describe unwanted effects.[75] In patients receiving long-term antiseizure treatment, medication-related adverse effects may interfere with daily functioning, reduce adherence to prescribed regimens and lead clinicians to modify or discontinue therapy. Such effect may eventually affect patient's quality of life and treatment outcomes.[5,12] The adverse-effect profile of antiseizure medications varies considerably. Some reactions involve neurological effects, such as reduced coordination, somnolence, dizziness and alterations in cognitive function or behaviour. Other effects may involve the skin, electrolyte balance, metabolic function, body weight or vision depending on the medication used. Individual antiseizure medications have different safety considerations. Lamotrigine requires attention to skin reactions, topiramate may affect cognition and metabolic function with irritability, mood disturbances and other behavioural symptoms.[5,12]

The assessment of adverse drug events involves several complementary components, including identification, causality assessment, severity assessment, and preventability assessment. Causality assessment evaluates the likelihood that a suspected reaction is related to a particular medication. This assessment is essential because the occurrence of an adverse event during therapy does not automatically establish a causal relationship with the medication; the patient's underlying illness, other medications, comorbid conditions, or alternative explanations may contribute to the observed symptoms. The World Health Organization–Uppsala Monitoring Centre (WHO–UMC) system provides a structured approach to evaluating the relationship between a suspected drug and an adverse reaction. Depending on the available clinical information, cases may be classified as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable.[14] Appropriate documentation of the onset of symptoms, treatment history, de-challenge information, alternative causes, and relevant laboratory findings supports a more reliable assessment. However, causality categories indicate the strength of the available evidence and do not always establish definitive proof of a causal relationship.

Severity assessment is another important component of adverse drug event monitoring because it helps determine the clinical consequences of a reaction and the level of intervention required. In pharmacovigilance, the terms *severity* and *seriousness* have different meanings. Severity describes the intensity or clinical level of a reaction, whereas seriousness is generally determined by regulatory outcomes such as death, a life-threatening event, hospitalisation or its prolongation, persistent or significant disability, congenital anomaly, or another medically important event. The Hartwig and Siegel severity assessment scale is commonly used to classify adverse drug events into mild, moderate, and severe categories according to the treatment required and the impact on patient management.[15] Mild reactions may require minimal intervention, while moderate reactions may necessitate changes in therapy or additional treatment. Severe reactions may require intensive medical intervention, hospitalisation, or result in significant clinical consequences. Applying a standardised severity scale facilitates consistent documentation and comparison of suspected adverse drug events.

Preventability assessment determines whether an adverse drug reaction may have been prevented through proper prescribing, dispensing, medication administration,

clinical monitoring, and patient education. The Schumock and Thornton criteria provide a structured method for examining whether the occurrence of a reaction may be associated with factors such as unsuitable drug selection, dosing errors, preventable drug interactions, insufficient monitoring, or non-adherence to recommended safety precautions.[16] Reactions are commonly categorised as definitely preventable, probably preventable, or not preventable, depending on the version and scoring method used. This assessment is particularly useful in clinical pharmacy practice because it can identify opportunities to improve medication safety. Nevertheless, a reaction should not be labelled preventable solely because it occurred; each case must be evaluated against the applicable criteria and the clinical information available.

The safety monitoring of antiseizure medications is supported by pharmacovigilance, which involves the detection, assessment, understanding, and prevention of adverse effects and other medicine-related problems. Monitoring may include direct patient interviews, review of medical records, examination of laboratory results, medication reconciliation, assessment of concomitant drugs, and documentation of suspected reactions during routine clinical visits, patients should receive information about frequently occurring adverse effects and symptoms that warrant immediate medical evaluation. The nature and extent of monitoring should be guided by the prescribed medication and the patient's clinical status and may involve assessment of mood and behaviour, body weight, serum electrolytes, renal or hepatic function, metabolic parameters, and electrocardiographic findings. Monitoring should be individualised according to the drug's known risks and the patient's comorbidities rather than applying every investigation to every patient.[8,11–13]

Although clinical trials are important for evaluating drug safety, they may not identify all adverse effects that occur after medicines are used in everyday clinical practice. Restrictions in participants selection, follow-up duration and sample size can limit the detection of uncommon reactions and long-term safety concerns.[9] India's pharmacovigilance programme facilitates the detection, recording, and assessment of suspected adverse drug reactions to promote safer medication use. Nevertheless, incomplete reporting of suspected reactions remains an important challenge for pharmacovigilance activities.[13]

Post-marketing surveillance is particularly important because pre-marketing clinical trials may not identify all uncommon, delayed, or long-term adverse reactions. The number and characteristics of participants in clinical trial may be differed from those of patients in routine clinical practice, where comorbidities and concomitant medication use are common. Spontaneous reporting systems, observational studies, electronic medical records, and pharmacovigilance databases can be providing more information about suspected adverse reactions after a medicine has entered clinical use. Healthcare professionals, including clinical pharmacists, play a significant part in recognising suspected reactions, documenting relevant clinical information, counselling patients, and reporting appropriate cases. Although spontaneous reports may help detect possible medication-related safety concerns; however, they are generally insufficient on their own to determine reaction incidence or establish a definitive causal relationship.[7]

Despite these additions, about one-third of patients still have drug-resistant epilepsy, and the proportion achieving seizure freedom has changed little.[10,11] Such patients often need polytherapy, which raises the likelihood of medication-related adverse effects and drug–drug interactions.

Newer antiseizure medications were introduced into clinical practice from the 1990s onwards, with the aim of improving seizure management, enhancing tolerability, reducing drug interactions, and providing more favourable pharmacokinetic characteristics than conventional agents. It includes levetiracetam, lamotrigine, oxcarbazepine, topiramate, lacosamide, and other second-generation antiepileptic drugs prescribed during the study period. Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures and requires long-term pharmacological treatment. Antiseizure medications are fundamental to epilepsy treatment, helping to control seizures and improve patients' overall quality of life.

Despite the therapeutic benefits of newer antiseizure medications, unwanted drug-related effects remain a concern because they may affect adherence, require changes in treatment, or interfere with daily activities.[20] Differences in prescribing practices, dose selection, treatment duration, and concomitant use of medication may be influencing the safety of treatment. Evaluating adverse events alongside medication-utilisation patterns can therefore provide useful clinical information about their use in routine practice.

Treating epilepsy frequently demands extended or chronic administration of antiseizure medications, thereby elevating the likelihood of adverse drug events. Conventional antiepileptic drugs, despite their efficacy, often present with. Dose-related toxicity, drug interaction, and poor tolerability.[30-33] To overcome these limitations, newer antiepileptic drugs such as levetiracetam lamotrigine, oxcarbazepine, topiramate, and lacosamide have seen rising utilization in routine medical practice.

The findings of clinical trials in controlled manner may not fully represent the experiences of patients treated in routine hospital settings. Real-world populations can differ in their comorbidities, concomitant medicines, treatment histories, and individual responses. These factors support the necessity for real-world investigations

that examine medication use and suspected adverse reactions under everyday clinical conditions.[39]

Where patients often have comorbidities, receive multiple medications, and require individualized therapy. In addition, prescribing patterns such as monotherapy versus polytherapy, dosing variations, and 13 concomitant drug use may significantly influence the occurrence and severity of adverse drug reactions.

Drug-utilisation studies examine how medicines are prescribed and used in clinical practice. They can identify prescribing trends, describe dose and frequency patterns, and highlight opportunities to improve the appropriateness of medication use. When combined with adverse-event monitoring, such studies can contribute to a more comprehensive assessment of treatment safety.

Evaluating adverse drug reactions alongside drug utilisation patterns can help identify drug-specific safety concerns, irrational prescribing practices, and factors contributing to adverse outcomes. Such information is essential for promoting rational prescribing, improving patient safety, and strengthening pharmacovigilance systems.[41-45]

Therefore, this study aims to generate real-world data on adverse drug reactions and drug utilisation of newer antiepileptic drugs in a tertiary care hospital.[47]

STUDY DESIGN
Cross sectional study.

STUDY SETTING
This research was carried out within the Department of Neurology and the College of Pharmaceutical Sciences at Government Medical College, Thiruvananthapuram.

SAMPLE SIZE CALCULATION
The required sample size was determined using reference data from an investigation by Girgis et al. (2024) entitled "Seriousness and outcomes of reported adverse drug reactions in old and new antiseizure medications: a pharmacovigilance study using EudraVigilance database".

Sample size was calculated using the formulae:

Sample size n = (Z1-α/2) 2× (P x Q) / d2

P-Proportion of adverse drug reaction=65 %

Q- (100-65) =35 %

Z1-α/2= 1.96 for a 95% confidence level

d=10 Percentage points

n= (1.96)2× (35×65)/100 =87.3

A cumulative total of 88 patients evaluating newer antiseizure agents at a tertiary healthcare facility were enrolled in the study.

STUDY POPULATION
Adults (≥18 years) receiving newer antiepileptic drugs in the Department of Neurology, Government Medical College, Thiruvananthapuram.

INCLUSION CRITERIA
- Adult patients (age ≥18 years)
- Patient prescribed with newer antiepileptic drugs for a duration of at least one month were included in the study.
- Patient willing to provide written informed consent.

EXCLUSION CRITERIA
- Patients with incomplete medical records.
- Patient with severe hepatic and renal impairments

STUDY PERIOD
The study was carried out over a period of 9 months after obtaining approval from the Institutional Ethics Committee at Government Medical College, Thiruvananthapuram.

STUDY VARIABLES
EXPOSURE VARIABLES
- Patient demographics: Age, gender, diagnosis, disease duration.
- Use of newer antiepileptic drugs (AEDs).
- Comorbid conditions.

OUTCOME VARIABLES
- Occurrence of adverse events.
- Type of adverse events.
- Severity of adverse events.
- Causality Assessment of adverse events.
- Drug use pattern of newer antiepileptic drugs.

DATA COLLECTION TOOL
- Semi-structured data collection proforma.
- WHO-UMC Causality Assessment scale [37] (2013).
- Hartwig and Siegel Severity Assessment Scale [14] (1992).
- Schumock and Thornton Preventability Scale [15] (1992).

STUDY PROCEDURE
- Patients diagnosed with epilepsy who had been receiving newer antiepileptic drugs for a minimum duration of one month were identified during routine clinical visits.
- Eligible patients were enrolled after screening against predefined inclusion and exclusion criteria and the acquisition of signed informed consent.
- Suspected adverse drug reactions were identified through patient interviews and a review of medical records.
- Each reported adverse events were documented and assessed for causality using the WHO-UMC scale, and preventability using the Schumock and Thornton scale.

- Data was coded, entered, and analysed to determine the prevalence and pattern of adverse event associated with newer antiepileptic drug.

DATAANALYSIS

- Information was compiled and recorded using Microsoft Excel software.
- Statistical analysis was performed by using SPSS version 27.
- Data was presented as frequency tables, bar graphs and Pie chart.
- Causality assessment outcomes were expressed as frequencies and percentages by using WHO-UMC scale.
- Severity of adverse events was presented as mild, moderate, or severe by using Hartwig and Siegel scale.
- Preventability was categorized as preventable or non-preventable by using Schumock and Thornton scale.
- Drug utilization data including type of newer antiepileptic drug, dose, frequencies and duration was summarized using frequencies and percentages.

ETHICAL CONSIDERATION

- Research activities commenced solely subsequent to securing clearance from the Human Ethics Committee at Government Medical College, Thiruvananthapuram.
- Written consent was secured prior to initiating any data gathering processes.
- All collected information was maintained with strict confidentiality and utilized exclusively for research objectives.
- Participants incurred no extra monetary costs as part of the study.

RESULTS AND DISCUSSION

1. DISTRIBUTION OF PATIENTS BASED ON AGE

Table 1: Distribution of patients based on Age.

Age in years	Frequency	Percentage
18-30	14	15.9%
31-40	8	9.1%
41-50	16	18.2%
51-60	22	25.0%
>60	28	31.8%
Total	88	100%

- The average age of the study participants was 49.88 ± 14.56 years.
- Participant ages spanned from 18 to 86 years old.
- In the present study, participants had a mean age of 49.88 ± 14.56 years, with individuals older than 60 years constituting the largest demographic share (31.8%).
- Participants aged 51–60 years accounted for a further 25.0% of the sample.
- These findings indicate that a substantial segment of the study population consisted of middle-aged and elderly patient receiving long-term antiseizure treatment.
- Physiological shifts linked to aging such as alterations in liver and kidney function, body composition, and central nervous system drug sensitivity—can impact overall medication tolerability.

AGE

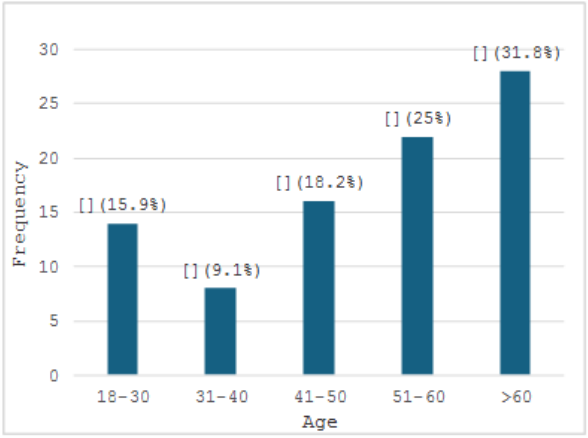


Figure 1: Distribution of patients based on Age group.

- These findings can be compared with a Swedish multicentre observational study published in *Seizure* in December 2023, which included 406 adults with epilepsy.
- The median age was 41 years among participants reporting side effects and 47 years among those who did not, with a statistically significant difference ($p = 0.015$).
- The investigators also identified age and the number of antiseizure medicines as factors associated with side effects, although the predictive performance of their models was limited.
- A Swedish study by Zelano J, et al. in 2023 demonstrates that side effects may be occur across adult age groups and that age alone is not sufficient to predict individual tolerability.[67]

2. DISTRIBUTION OF PATIENTS BASED ON GENDER

Table 2: Distribution of patients based on Gender.

Gender	Frequency	Percentage
Male	47	53.4%
Female	41	46.6%
Total	88	100%

- Males accounted for 53.4% of the participants, while females represented 46.6%.
- Although the proportion of males was marginally higher, this difference describes the composition of the study sample rather than a sex-specific risk of developing adverse events.

- **GENDER**

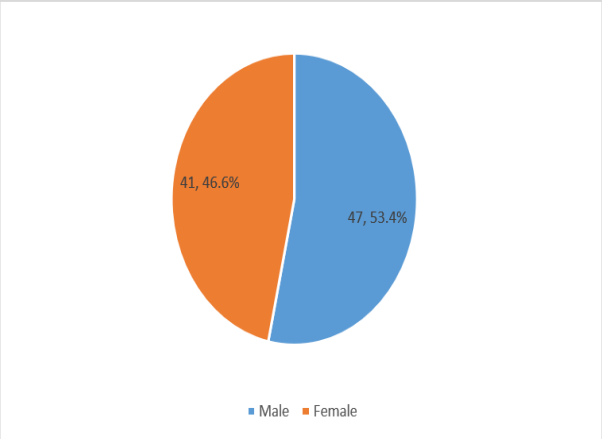


Figure 2: Distribution of patients based on Gender.

- In a 2023 observational study of 486 adults with epilepsy, females constituted 58.2% and males 41.8% of the study population.
- Such differences in demographic composition may reflect variations in recruitment and population characteristics and do not necessarily indicate differences in adverse events susceptibility
- A systematic review published by Giuliano et al. in 2024 identified some sex-related differences in antiseizure medication adverse effects, although findings varied across medicines and outcomes.[68]

3. ADVERSE DRUG EVENTS OF NEWER ANTIEPILEPTIC DRUGS

Table 3: Adverse drug events of newer antiepileptic drugs.

Adverse drug reactions	Frequency	Percentage
Somnolence	5	5.7%
Dizziness	7	8.0%
Ataxia	2	2.3%
Fatigue	5	5.7%
Headache	2	2.3%
Obesity	10	11.4%
Rash	1	1.1%
Others	56	63.6%
Total	88	100.0%

- The largest category of reported adverse effects was classified as “others” (63.6%), followed by obesity or weight-related problems (11.4%), dizziness (8.0%), somnolence (5.7%) and fatigue (5.7%).
- Ataxia, headache and rash were reported less frequently. The high proportion assigned to “others” indicates that the adverse-effect profile was heterogeneous; however, this category is too broad to identify the predominant individual reactions within it.

ADVERSE DRUG EVENTS

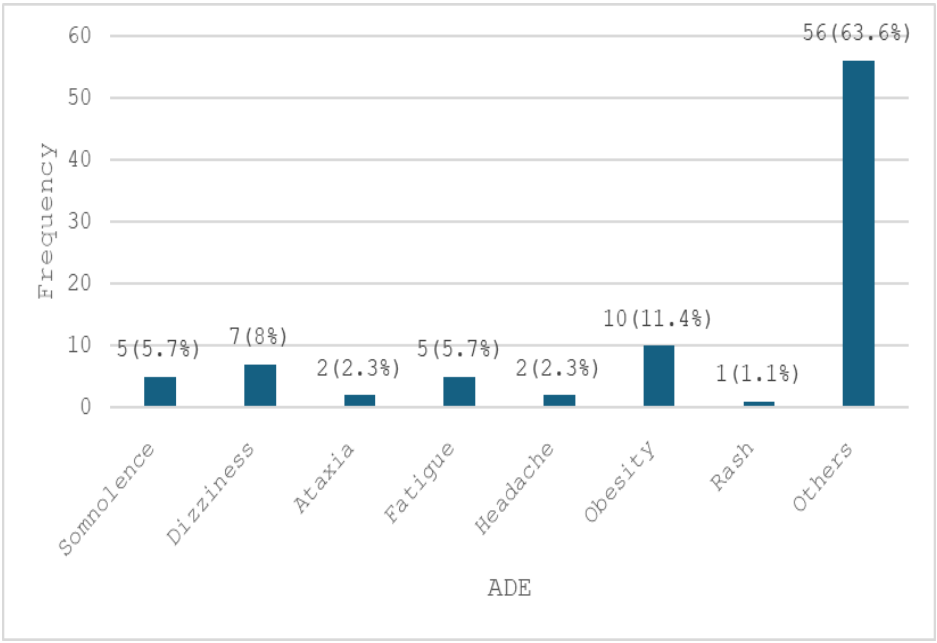


Figure 3: Adverse drug events of newer antiepileptic drugs.

- Other category adverse events involved neurological, behavioural, gastrointestinal, respiratory, visual and other systemic manifestations.
- Levetiracetam was associated with several reported events, including insomnia, increased salivation, behavioural changes, flu-like symptoms, runny nose, mood swings, loss of appetite, coordination problems, stuffy nose, anaemia, rash, falls, aggression, weakness, abdominal pain and polyuria.
- Among these events, behavioural changes, mood swings and aggression are clinically important because levetiracetam has been linked to behavioural and psychiatric adverse events. Co-ordination problems and falls also require careful

clinical observation as they can impair physical movement and elevate the likelihood of trauma or falls.

- Behavioural changes, mood swings, aggression, insomnia and impaired coordination are consistent with recognised adverse effects of levetiracetam.
- Gabapentin was associated with adverse events such as insomnia, slurred speech, acid reflux, tremors, gastrointestinal distress, visual abnormalities, breathing difficulties, increased appetite, and peripheral oedema.
- Tremors, slurred speech, visual disturbances and peripheral oedema are recognised adverse effects of gabapentin.
- Breathing difficulties warrant particular clinical attention because gabapentin may be associated with respiratory depression, especially when used concomitantly with opioids or other central nervous system depressants.
- Neurological symptoms such as slurred speech and tremors warrant evaluation for medicine-related central nervous system effects, interactions with other sedating medicines and underlying neurological conditions.
- Respiratory depression is a potentially serious event and requires particular clinical attention, especially when gabapentin is combined with opioids or other central nervous system depressants.
- Hyperphagia and gastrointestinal symptoms evaluated in the context of dietary habits, comorbidities and concomitant treatment.
- Pregabalin was associated with visual disturbances, increased sleepiness, difficulty concentrating, blurred vision and unsteadiness.
- These findings are consistent with recognised adverse effects, particularly somnolence, visual disturbances and impaired coordination, which may affect alertness and increase the risk of falls.
- Topiramate was associated with altered taste and speech difficulties, both of which are recognised adverse effects of the drug.
- In the Korean pharmacovigilance study published in May 2024, rash or urticaria accounted for 31.8% of reports, followed by dizziness (7.1%), somnolence or drowsiness (5.4%) and hepatotoxic effects (4.8%).
- The proportions of dizziness and somnolence in the present study were numerically similar to those in the Korean dataset, although direct comparison is limited by differences in denominator and study design.

4. UTILIZATION PATTERN OF NEWER ANTIEPILEPTIC DRUGS

Table 4: Utilization pattern of newer antiepileptic drugs.

Sl.No.	Prescription Indicators	Formula	Result
1	Average number of drugs per encounter	Total drug/Total prescription	4
2	Percentages of newer anti-epileptic drugs prescribed by generic names	(Generic drugs/Total drugs) x 100	36.4%
3	Percentages of newer anti-epileptic drug from essential drug list (EDL)	Essential drug list/Total	47.7%

- The average number of drugs per encounter therefore reflects the overall medication burden of the patients, including antiepileptic therapy and medications prescribed for associated comorbidities.
- Patients with multiple comorbid conditions may receive several medications, increasing the likelihood of polypharmacy and potential drug–drug interactions.
- These factors are relevant to adverse drug events assessment because concomitant medications may contribute to adverse drug reactions or complicate the identification of the suspected causative drug.
- Evaluation of prescribing indicators in this study revealed an average of four medications per clinical encounter, with generic prescribing accounting for 36.4% and essential drug list inclusion standing at 47.7%.[40]
- These findings provide an initial description of prescribing practices at the study hospital.

Table 5: Utilization profile of individual antiepileptic medications.

Drug	Frequency	Percentage
Levetiracetam	42	47.7%
Topiramate	4	4.5%
Gabapentin	35	39.8%
Pregabalin	7	8.0%
Total	88	100%

- Levetiracetam was recorded in 42 participants (47.7%), making it the most frequently used medication in the study.
- Gabapentin was recorded in 35 participants (39.8%), followed by pregabalin in seven (8.0%) and topiramate in four (4.5%).
- The high frequency of levetiracetam highlights its status as the most widely utilized agent within the study population.
- These drugs were prescribed either alone or in combination with conventional antiseizure

medications, depending on the patient's clinical conditions and treatment requirements.

NEWER ANTIEPILEPTIC DRUGS

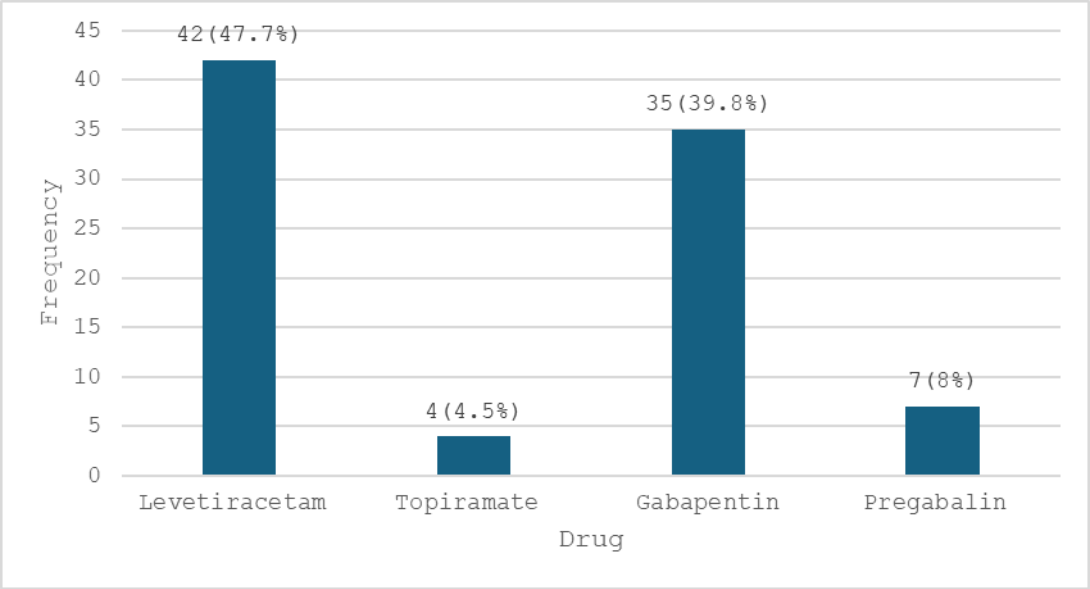


Figure 4: Drug utilization patterns.

- These outcomes align with a recent hospital-based investigation by Waghmare et al. (2026), which noted levetiracetam as the most frequent medication, accounting for 93.51% of all reviewed prescriptions.[70]

5. FREQUENCY OF NEWER ANTIEPILEPTIC DRUGS

Table 6: Frequency of newer antiepileptic drugs.

Frequency of drugs	Frequency	Percentage
OD	25	28.4%
BD	57	64.8%
TID	6	6.8%
Total	88	100%

FREQUENCY

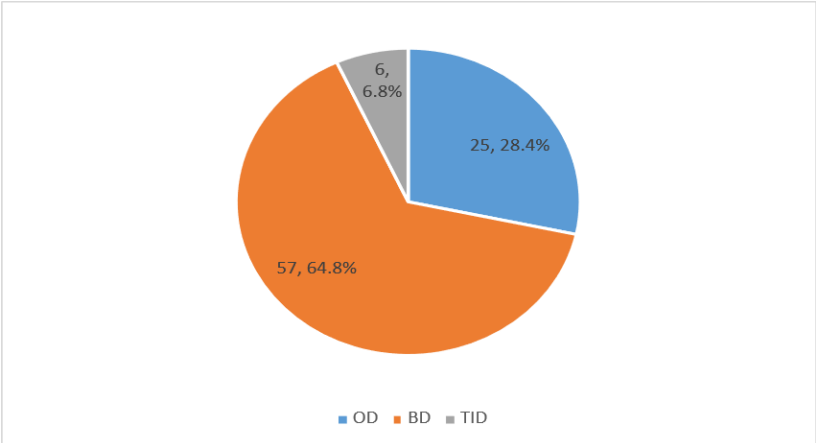


Figure 5: Frequency of newer antiepileptic drugs.

- Twice-daily administration was the most common regimen, reported in 57 participants (64.8%).
- Once-daily dosing was documented in 25 participants (28.4%), while six participants (6.8%) received medication three times daily.
- These results illustrate how the various dosing schedules are distributed across the study population.
- The results can be discussed alongside the real-world COMPARE study by Roberti et al. (2024)

which reported that 19.7% of 960 patients receiving third-generation antiseizure medications experienced at least one adverse event. Dizziness, irritability and somnolence were among the commonly reported adverse events.[71]

6. DISTRIBUTION OF DURATION OF TREATMENT

Table 7: Distribution of duration of treatment.

Duration of treatment	Frequency	Percentage
<1 yr	13	14.8%
1-2 yr	7	8.0%
3-5 yr	23	26.1%
6-10 yr	26	29.5%
>10 yr	19	21.6%
Total	88	100.0%

DURATION OF TREATMENT

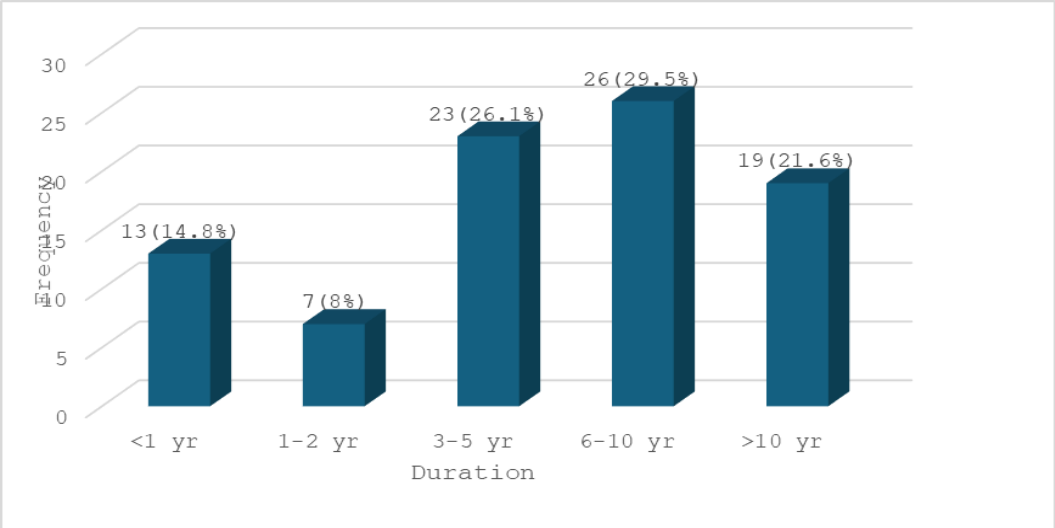


Figure 6: Distribution of duration of treatment.

- Treatment lasting 6–10 years was the most frequently recorded duration category, accounting for 26 participants (29.5%).
- This was followed by 3–5 years in 23 participants (26.1%) and more than 10 years in 19 participants (21.6%).
- The remaining participants had undergone therapy for either a duration under one year or between one and two years.
- The distribution reflects the treatment histories of the enrolled population.
- Krauss et al. (2025) highlighted that adverse effects associated with newer antiseizure medications may influence dose optimization, treatment adherence and medication continuation.
- This study emphasizes the importance of ongoing adverse-event monitoring during long-term antiseizure therapy.[72]

7. CAUSALITY OF ADVERS DRUG EVENTS

Table 8: Causality of adverse drug events.

Causality	Frequency	Percentage
Certain	15	17.0%
Probable	27	30.7%
Possible	36	40.9%
Unlikely	10	11.4%
Total	88	100.0%

- The WHO–UMC assessment classified 36 cases (40.9%) as possible and 27 (30.7%) as probable.
- 15 cases (17.0%) were categorised as certain, while ten (11.4%) were considered unlikely to be related to the suspected medication.
- Thus, possible causality was the most frequent classification.

CAUSALITY OF ADVERSE DRUG EVENTS

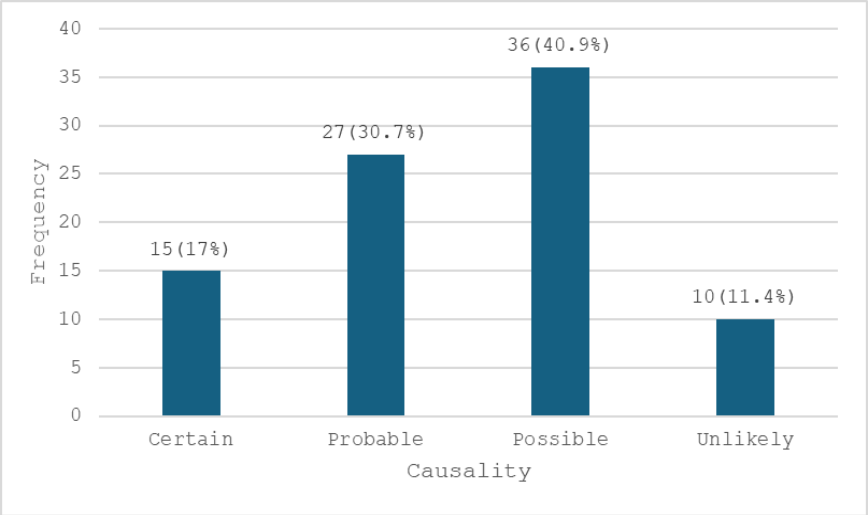


Figure 7: Causality of adverse drug events.

- Somnolence and dizziness were classified as probable or certain for all four medications, suggesting that these are frequently acknowledged side effects linked to their administration.
- Ataxia, unsteadiness and fatigue were classified as probable for all four drugs, while headache, rash or hypersensitivity, and abdominal pain were classified as possible.
- Weight gain was classified as unlikely with levetiracetam and topiramate but probable with gabapentin and pregabalin.
- In contrast, altered taste (dysgeusia) was classified as probable/certain with topiramate, possibly related to its carbonic anhydrase inhibition, and unlikely with levetiracetam.
- Other reactions included behavioural changes or aggression, which showed a probable or certain relationship with levetiracetam and a probable relationship with topiramate.
- Nasopharyngitis was classified as probable with levetiracetam, gabapentin, and pregabalin, and possible with topiramate.
- Insomnia was classified as possible with all four drugs. Visual disturbances and slurred speech were more strongly linked with topiramate, while polyuria or frequent urination was classified as possible with pregabalin and topiramate.

8. SEVERITY OF ADVERSE DRUG EVENTS

Table 9: Severity of adverse drug events.

Severity	Frequency	Percentage
Mild	61	69.3%
Moderate	27	30.7%
Total	88	100%

- 61 cases (69.3%) were mild in severity assessment.
- 27 cases (30.7%) were moderate in severity assessment.
- Thus, mild adverse drug reactions constituted the majority of reported events, accounting for approximately two-thirds of the total population.
- No severe cases were reported in the study population.

SEVERITY OF ADVERSE DRUG EVENTS

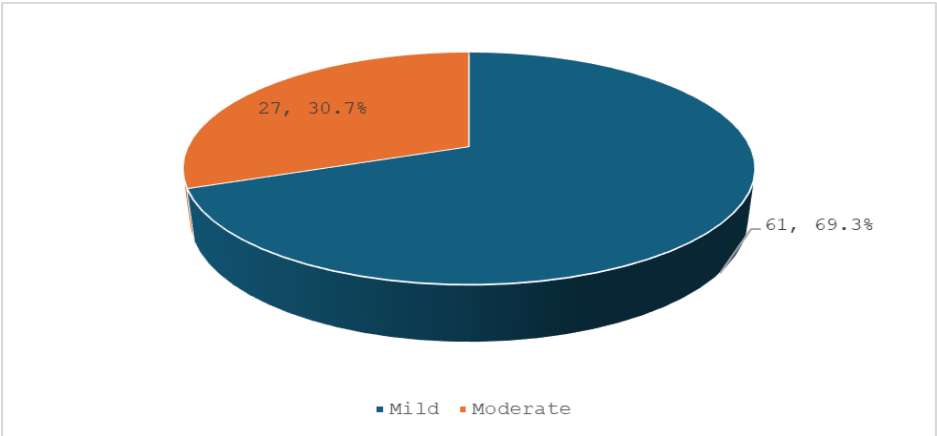


Figure 8: Severity of adverse drug events.

- Mild reactions include somnolence, dizziness, fatigue, headache, mild insomnia, altered taste, mild abdominal pain, and mild nasopharyngitis when these reactions do not require additional treatment or significant changes in therapy.
- Such adverse events can present with levetiracetam, gabapentin, pregabalin, or topiramate. Furthermore, minor weight fluctuations and short-term visual blurriness are categorized as mild if medical intervention is unnecessary.
- Moderate reactions include significant somnolence, persistent dizziness, ataxia or unsteadiness affecting daily activities, clinically significant weight gain, behavioural changes or aggression, persistent insomnia, and abdominal pain requiring medical treatment.
- Rash or hypersensitivity reactions requiring drug withdrawal or specific treatment may also be moderate.
- These adverse events are associated with levetiracetam, gabapentin, pregabalin, or topiramate, contingent upon the specific agent prescribed and the individual clinical profile of the patient. Speech difficulties and vision changes demanding professional medical management can similarly be grouped under this classification.

9. PREVENTABILITY OF ADVERSE DRUG EVENTS

Table 10: Preventability of adverse drug events.

Preventability	Frequency	Percentage
Definitely preventable	54	61.4%
Probably preventable	34	38.6%
Total	88	100%

- 54 cases (61.4%) of adverse drug events were definitely preventable.
- 34 cases (38.6%) of adverse drug events were probably preventable.
- Consequently, every documented adverse event was deemed to exhibit a certain level of potential preventability.

PREVENTABILITY OF ADVERSE DRUG EVENTS

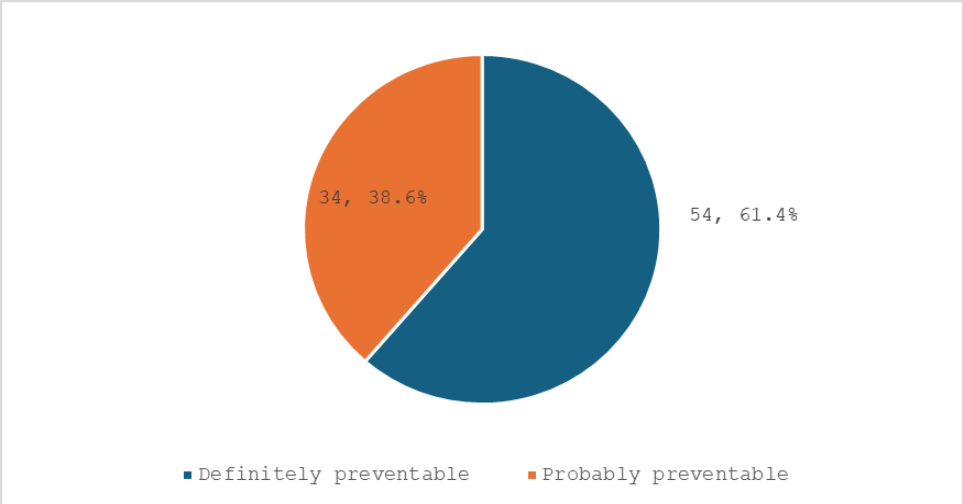


Figure 9: Preventability of adverse drug events.

- Definitely preventable events such as somnolence due to levetiracetam, dizziness and ataxia due to excessive dosing gabapentin. sedation due to an avoidable drug interaction of pregabalin and cognitive impairment due to topiramate
- Reactions such as somnolence, dizziness, fatigue, ataxia, and weight gain are definitely preventable or their severity reduced through appropriate dose titration, renal function assessment where indicated, review of concomitant medications, and regular clinical monitoring.
- Hyperphagia and gastrointestinal symptoms evaluated in the context of dietary habits, comorbidities and concomitant treatment.
- Therefore, each adverse drug events should be evaluated individually rather than assigning preventability solely on the basis of the suspected drug or the type of adverse event.
- Probably preventable adverse events are somnolence associated with levetiracetam due to unrecognised drug interaction. Dizziness due to pregabalin, ataxia associated with inadequate follow-up by gabapentin, Difficulty concentrating associated with topiramate, Behavioural changes during treatment of

levetiracetam, Weight gain not monitored despite relevant clinical risk pregabalin or gabapentin.

- Gabapentin was associated with slurred speech, insomnia, gastric reflux, tremors, gastrointestinal upset, respiratory depression, visual disturbances, hyperphagia and swollen limbs.
- These adverse drug events can manage through appropriate clinical assessment, monitoring, supportive measures, and clinician-directed modification of treatment when necessary.
- However, the classification of an adverse drug reaction as preventable was based on individual patient assessment using established preventability criteria, such as the Schumock and Thornton criteria.

10. ASSOCIATION BETWEEN ADVERSE DRUG EVENTS AND AGE OF THE PATIENTS

Table 11: Association between adverse drug events and age of the patients.

ADE	Age					Total
	18-30	31-40	41-50	51-60	>60	
Somnolence	1(20%)	1(20%)	0(0%)	1(20%)	2(40%)	5
Dizziness	1(14.3%)	1(14.3%)	2(28.6%)	3(42.9%)	0(0%)	7
Ataxia	1(50%)	0(0%)	1(50%)	0(0%)	0(0%)	2
Fatigue	2(40%)	0(0%)	2(40%)	1(20%)	0(0%)	5
Headache	0(0%)	1(50%)	0(0%)	0(0%)	1(50%)	2
Obesity	3(30%)	1(10%)	1(10%)	2(20%)	3(30%)	10
Rash	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	1
Others	5(8.9%)	4(7.1%)	10(17.9%)	15(26.8%)	22(39.3%)	56
Total	14(15.9%)	8(9.1%)	16(18.2%)	22(25%)	28(31.8%)	88

Fisher's exact test p value =0.019

- Somnolence exhibited the highest reporting frequency in participants older than 60 years (40%).
- Dizziness was predominantly observed in individuals aged 51 to 60 years (42.9%), whereas ataxia and fatigue were documented among patients in the 18–30 and 41–50 age groups.
- Headache cases were distributed across the 31–40 and >60 age brackets
- Obesity showed a relatively broader age distribution, with the highest proportions in the 18-30 and >60-year groups (30% each).
- The largest adverse drug events category "others" was predominantly observed among participants aged >60 years (39.3%).
- These results demonstrate a statistically meaningful correlation linking adverse drug event categories with specific patient age demographics.

11. ASSOCIATION BETWEEN ADVERSE DRUG EVENTS AND GENDER OF THE PATIENTS

Table 12: Association between adverse drug events and gender of the patients.

ADE	Gender		Total
	Male	Male	
Somnolence	3(60%)	2(40%)	5
Dizziness	5(71.4%)	2(28.6%)	7
Ataxia	1(50%)	1(50%)	2
Fatigue	2(40%)	3(60%)	5
Headache	2(100%)	0(0%)	2
Obesity	4(40%)	6(60%)	10
Rash	1(100%)	0(0%)	1
Others	29(51.8%)	27(48.2%)	56
Total	47(53.4%)	41(46.6%)	88

Fisher's exact test p value =0.545

- 47(53.4%) occurred in males and 41(46.6%) in females.
- A higher proportion of male patients experienced somnolence (60%), dizziness (71.4%), headache (100%), and rash (100%).
- Whereas fatigue and obesity were more frequently reported among females (60% each).
- Ataxia showed an equal distribution between males and females (50% each).
- However, there was no statistically significant association between adverse drug event type and gender.

12. ASSOCIATION BETWEEN ADVERSE DRUG EVENTS AND NEWER ANTIEPILEPTIC DRUGS

Table 13: Association between adverse drug events and newer antiepileptic drugs.

ADE	Drug				Total
	Levetiracetam	Topiramate	Gabapentin	Pregabalin	
Somnolence	5(100%)	0(0%)	0(0%)	0(0%)	5
Dizziness	5(71.4%)	0(0%)	2(28.6%)	0(0%)	7
Ataxia	0(0%)	0(0%)	2(100%)	0(0%)	2
Fatigue	2(40%)	0(0%)	3(60%)	0(0%)	5
Headache	2(100%)	0(0%)	0(0%)	0(0%)	2
Obesity	0(0%)	0(0%)	10(100%)	0(0%)	10
Rash	1(100%)	0(0%)	0(0%)	0(0%)	1
Others	27(48.2%)	4(7.1%)	18(32.1%)	7(12.5%)	56
Total	42(47.7%)	4(4.5%)	35(39.8%)	7(8%)	88

Fisher's exact test p value =0.230.

- Levetiracetam was the most frequently implicated drug (47.7%), followed by Gabapentin (39.8%), Pregabalin (8%), and Topiramate (4.5%).
- Somnolence, headache, and rash were reported exclusively with Levetiracetam.
- Whereas ataxia and obesity were reported exclusively with Gabapentin.
- Fatigue was more frequently associated with Gabapentin (60%) than Levetiracetam (40%).
- Despite these variations, there was no statistically significant association between adverse drug event type and the implicated drug.

13. ASSOCIATION BETWEEN ADVERSE DRUG EVENTS AND DURATION OF NEWER ANTIEPILEPTIC DRUGS

Table14: Association between adverse drug events and duration of newer antiepileptic drugs.

ADE	Duration					Total
	<1 yr	1-2 yr	3-5 yr	6-10 yr	>10 yr	
Somnolence	1(20%)	1(20%)	0(0%)	3(60%)	0(0%)	5
Dizziness	1(14.3%)	1(14.3%)	4(57.1%)	1(14.3%)	0(0%)	7
Ataxia	2(100%)	0(0%)	0(0%)	0(0%)	0(0%)	2
Fatigue	2(40%)	0(0%)	1(20%)	1(20%)	1(20%)	5
Headache	1(50%)	0(0%)	1(50%)	0(0%)	0(0%)	2
Obesity	1(10%)	1(10%)	4(40%)	3(30%)	1(10%)	10
Rash	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)	1
Others	5(8.9%)	4(7.1%)	13(23.2%)	18(32.1%)	16(28.6%)	56
Total	13(14.8%)	7(8%)	23(26.1%)	26(29.5%)	19(21.6%)	88

Fisher's exact test p value =0.193

- The largest proportion occurred among patients with a treatment duration of 6-10 years (29.5%), followed by 3-5 years (26.1%) and >10 years (21.6%).
- Adverse drug events patterns were varied across duration categories.
- Somnolence was most frequently observed with 6-10 years of therapy (60%), whereas dizziness was most frequent with 3-5years (57.1%).
- Ataxia was reported exclusively among those with <1 year of treatment, while rash was reported exclusively among those with >10 years of treatment.
- However, there was no statistically significant association between adverse drug event type and duration of therapy.

14. ASSOCIATION BETWEEN ADVERSE DRUG EVENTS AND FREQUENCY OF NEWER ANTIEPILEPTIC DRUGS

Table15: Association between adverse drug events and frequency of newer antiepileptic drugs.

ADE	Frequency			Total
	OD	BD	TID	
Somnolence	0(0%)	5(100%)	0(0%)	5
Dizziness	2(28.6%)	4(57.1%)	1(14.3%)	7
Ataxia	2(100%)	0(0%)	0(0%)	2

Fatigue	2(40%)	3(60%)	0(0%)	5
Headache	0(0%)	2(100%)	0(0%)	2
Obesity	4(40%)	5(50%)	1(10%)	10
Rash	0(0%)	1(100%)	0(0%)	1
Others	15(26.8%)	37(66.1%)	4(7.1%)	56
Total	25(28.4%)	57(64.8%)	6(6.8%)	88

Fisher's exact test p value =0.422

- 57 (64.8%) occurred with twice daily (BD) dosing, followed by once-daily (OD) dosing in 25 (28.4%) and three-times-daily (TID) dosing in 6 '96.8%0.
- BD dosing was predominant across most adverse drug reaction categories, particularly somnolence and headache (100% each).
- Ataxia occurred exclusively among patients receiving OD dosing.
- However, there was no statistically significant association between adverse drug event type and dosing frequency.

SUMMARY

- Demographic Characteristics: The mean age of the study participants was 49.88 ± 14.56 years, with ages ranging from 18 to 86 years.
- The majority belonged to the age group above 60 years (31.8%), followed by 51–60 years (25.0%), 41–50 years (18.2%), 18–30 years (15.9%), and 31–40 years (9.1%). Males constituted 53.4% (n = 47), while females accounted for 46.6% (n = 41).
- Primary Outcome – Assessment of Adverse Drug Events: Among the specifically identified adverse drug events, obesity was the most frequently reported (11.4%), followed by dizziness (8.0%), somnolence (5.7%), fatigue (5.7%), ataxia (2.3%), headache (2.3%), and rash (1.1%).
- Other adverse events constituted 63.6% of the reported categories.
- The study identified a range of adverse events during treatment with newer antiepileptic drugs.
- Although several reported events were consistent with the known safety profiles of the respective medicines, their classification as suspected adverse drug reactions depended on the causality assessment findings.
- A statistically significant association was observed between adverse drug event type and age group (Fisher's exact test, p = 0.019).
- No statistically significant associations were observed between adverse drug event type and the other assessed parameters.
- Secondary Outcomes – Causality, Severity, Preventability, and Drug Utilisation: According to the WHO–UMC causality assessment, 40.9% of cases were classified as possible, 30.7% as probable, 17.0% as certain, and 11.4% as unlikely to be related to the suspected medication.
- Severity assessment using the Hartwig and Siegel scale showed that 69.3% of events were mild and 30.7% were moderate, with no severe cases reported.
- According to the Schumock and Thornton preventability assessment, 61.4% were classified as definitely preventable and 38.6% as probably preventable.
- Regarding drug utilisation, levetiracetam was the most frequently used drug (47.7%), followed by gabapentin (39.8%), pregabalin (8.0%), and topiramate (4.5%).
- Twice-daily administration was the most common dosing frequency (64.8%). Treatment duration of 6–10 years was the most frequent category (29.5%).
- The average number of medicines per encounter was four, with 36.4% prescribed by generic name and 47.7% reported as belonging to the essential drug list.

CONCLUSION

- The cross-sectional study assessed the adverse drug events of newer antiepileptic drug in patients with epilepsy.
- According to the WHO–UMC causality assessment scale, 27 (30.7%) ADRs were classified as probable, 36 (40.9%) as possible, 15 (17.0%) as certain, and 10 (11.4%) as unlikely to be related to the suspected drug.
- Among the specifically identified adverse drug reactions, Obesity was the most frequently reported.
- The "Others" category accounted for the largest proportion of reported adverse reactions and included neurological, behavioural, gastrointestinal, respiratory, visual, and other systemic manifestations.
- 61 (69.3%) adverse drug reactions were classified as mild and 27 (30.7%) as moderate, with no severe adverse drug events reported.
- According to the Schumock and Thornton preventability assessment, 54 (61.4%) adverse drug reactions were classified as definitely preventable, while 34 (38.6%) were classified as probably preventable.
- Levetiracetam: Somnolence, dizziness, fatigue, and impaired coordination were among the reported adverse reactions. Behavioural changes, mood swings, and aggression showed a probable or certain association with levetiracetam, while nasopharyngitis was classified as probable. Weight gain was classified as unlikely to be related to levetiracetam in this assessment.

- Gabapentin: Reported adverse reactions included somnolence, dizziness, fatigue, ataxia, tremors, slurred speech, gastrointestinal disturbances, visual abnormalities, and peripheral oedema. Somnolence and dizziness were classified as probable or certain, while ataxia, unsteadiness, and fatigue were considered probable ADRs. Weight gain and nasopharyngitis were also classified as probable.
- Pregabalin: The reported adverse reactions included somnolence, dizziness, fatigue, unsteadiness, blurred vision, difficulty concentrating, and weight gain. Somnolence and dizziness were classified as probable or certain, while ataxia, unsteadiness, and fatigue were considered probable ADRs. Weight gain and nasopharyngitis were classified as probable, whereas insomnia and frequent urination were classified as possible.
- Topiramate: Reported adverse reactions included somnolence, dizziness, fatigue, altered taste, speech difficulties, visual disturbances, and insomnia. Somnolence and dizziness were classified as probable or certain, while ataxia, unsteadiness, and fatigue were classified as probable. Altered taste showed a probable or certain association with topiramate. Visual disturbances and speech difficulties were more strongly associated with topiramate in the study's assessment, while frequent urination was classified as possible.
- Overall, the causality assessment identified several reported events as probable or certain ADRs associated with the newer antiepileptic drugs studied. Somnolence and dizziness showed stronger causal associations across the four drugs. Weight gain was considered more likely to be associated with gabapentin and pregabalin than with levetiracetam and topiramate.
- But their occurrence indicates the need for continuous monitoring during therapy.

These findings emphasise the importance of regular adverse drug reaction monitoring, appropriate drug selection, patient counselling, adherence monitoring, and active pharmacist involvement to promote safe and effective antiepileptic therapy.

LIMITATIONS

- **Single-center design:** As the study was restricted to a single tertiary care hospital, the results may not represent variations across different populations, geographical areas, or healthcare settings.
- **Patient-reported measures:** The assessment of adverse drug reactions based on patient-reported information may be influenced by recall bias, differences in individual perceptions of symptoms, and variations in patients' ability to recognize and report adverse events.
- **Potential under-reporting of adverse drug events:** Some adverse events may have been missed because patients might not have reported mild or less noticeable symptoms, and some events may not have been documented in the medical records.
- **Limited statistical associations:** Several categories contained relatively few patients. This may have reduced the ability to identify statistically significant associations between adverse drug events and factors such as drug type, treatment duration, and dosing frequency.
- De-challenge and re-challenge were not done due to ethical considerations, which may influence the scoring and results.

FUTURE PERSPECTIVES

- **Larger, multi centric studies**: Conducting Prospective study with a larger sample size across multiple institutions would improve the external validity and generalizability of the results.
- **Pharmacoeconomics assessments:** Cost-effectiveness analyses would provide valuable information for policymakers and clinicians, particularly in resource-limited settings.
- **Early detection:** Strengthen pharmacovigilance and systematic adverse drug event monitoring for early detection and reporting.
- **Patient counselling:** Promote patient counselling and appropriate monitoring to minimize potentially preventable adverse drug events.

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