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# **Comparative Efficacy and Safety of Antiepileptic Drugs (AEDs) in the Management of Focal and Generalized Seizures: A Systematic Review**

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### Abstract

Epilepsy is a prevalent neurological disorder affecting individuals across all age groups. It is characterized by recurrent, unprovoked seizures that can have a profound impact on quality of life, functional independence, and psychosocial well-being. Effective management of epilepsy relies heavily on antiepileptic drugs (AEDs), which aim to control seizures and prevent recurrence with minimal adverse effects.

This systematic review aims to compare the efficacy and safety profiles of commonly used AEDs in the treatment of both focal and generalized seizures. The focus is on identifying optimal pharmacological options for various patient subgroups, including pediatric, adult, and elderly populations, with considerations for monotherapy versus combination therapy.

A comprehensive search was conducted using PubMed, Scopus, and the Cochrane Library for studies published up to March 2025. Eligible studies included randomized controlled trials (RCTs), cohort studies, and meta-analyses evaluating the use of AEDs for focal or generalized epilepsy. Key outcome measures included seizure freedom rates, adverse events, drug discontinuation due to intolerance, and quality-of-life impacts.

Of 5,438 studies initially identified, 96 met the inclusion criteria and were systematically analyzed. For focal seizures, lamotrigine and levetiracetam demonstrated high efficacy with favorable safety profiles, while carbamazepine, though highly effective, showed increased rates of adverse effects. In generalized seizures, valproate remained the most effective but posed significant teratogenic risks. Levetiracetam emerged as a safer alternative, especially for women of childbearing potential. Combination therapy improved seizure control in drug-resistant cases but increased the risk of cumulative side effects.

Levetiracetam and lamotrigine are effective and well-tolerated across seizure types, making them strong candidates for first-line therapy. Valproate remains highly efficacious in generalized seizures but requires careful consideration due to safety concerns. This review supports individualized treatment plans based on patient characteristics and encourages further comparative research, particularly involving newer AEDs and real-world effectiveness.



Keywords: Epilepsy, antiepileptic drugs, focal seizures, generalized seizures, levetiracetam, lamotrigine, valproate, efficacy, safety, monotherapy, combination therapy

### 1. Introduction

### 1.1 Overview of Epilepsy and Seizure Classification

Epilepsy is a chronic neurological condition that affects approximately 50 million people worldwide and is characterized by recurrent, unprovoked seizures caused by abnormal electrical activity in the brain. These seizures vary in type and severity and can be classified broadly into focal seizures—originating in a specific part of the brain—and generalized seizures, which affect both hemispheres simultaneously. Focal seizures can be further categorized as aware (simple partial) or impaired awareness (complex partial) seizures, while generalized seizures include tonic-clonic, absence, myoclonic, and atonic types. Accurate classification is vital for selecting appropriate therapeutic strategies.

### **1.2 Pathophysiology and Burden of Disease**

The pathophysiology of epilepsy involves an imbalance between excitatory and inhibitory neurotransmission, often involving dysfunction in ion channels, receptor abnormalities, or structural brain anomalies. Common etiologies include genetic predisposition, traumatic brain injury, infections, tumors, and cerebrovascular disease. Beyond physical health, epilepsy imposes significant psychosocial and economic burdens. Patients frequently experience anxiety, depression, and cognitive impairment, while facing stigma and reduced employment and educational opportunities. Therefore, effective seizure control is essential for improving both health and societal outcomes.

- Prevalence: 0.5–1% worldwide; higher in low-income countries.
- Focal seizures: Most common in adults.
- Generalized seizures: Predominant in children and adolescents.

### 1.3 Role of Antiepileptic Drugs (AEDs) and Treatment Challenges

Antiepileptic drugs are the cornerstone of epilepsy management and aim to prevent seizures without impairing cognitive or physiological functions. AEDs exert their effects through various mechanisms, including modulation of voltage-gated sodium or calcium channels, enhancement of GABAergic activity, and inhibition of glutamatergic neurotransmission. Despite over two dozen AEDs being available, around one-third of patients continue to have drug-resistant epilepsy. Adverse effects such as drowsiness, dizziness, gastrointestinal issues, and rare but severe complications (e.g., hepatic failure, dermatologic reactions) complicate long-term treatment. Furthermore, considerations such as teratogenicity, drug-drug interactions, and pharmacokinetics in special populations make AED selection highly individualized.

- Focal seizures: Abnormal neuronal activity in one brain hemisphere (e.g., temporal lobe).
- Generalized seizures: Widespread neuronal discharges (e.g., absence, tonic-clonic).

### **1.4 Rationale for Comparative Evaluation**

With the continuous development of newer AEDs promising improved efficacy and safety, clinicians are often faced with the dilemma of choosing the most suitable drug. Levetiracetam and lamotrigine, for



example, are widely used due to their favorable side-effect profiles and minimal drug interactions, while traditional drugs like valproate and carbamazepine remain essential in certain seizure types. The variability in patient response, however, underscores the necessity of comparative studies to inform evidence-based prescribing. Previous reviews and network meta-analyses offer insights, but inconsistencies in study design, outcome definitions, and patient characteristics limit their generalizability.

- First-generation: Carbamazepine, valproate, phenytoin.
- Second-generation: Levetiracetam, lamotrigine, topiramate.
- Third-generation: Brivaracetam, perampanel.

# 1.5 Objectives

Therefore, this systematic review aims to comprehensively evaluate and compare the efficacy and safety of commonly prescribed AEDs in managing focal and generalized seizures across different patient populations.

Specifically, it seeks to:

- (1) Identify the most effective monotherapies and adjunct therapies
- (2) Assess tolerability and adverse event profiles
- (3) Evaluate outcomes across subgroups such as pediatrics, adults, and elderly patients
- (4) Support clinicians in making individualized, evidence-based treatment decisions.

# 2. Methods

### 2.1 Literature Search

A systematic search was performed using PubMed, Scopus, and the Cochrane Library databases from inception to March 2025. The search strategy incorporated both MeSH terms and free-text keywords related to epilepsy, antiepileptic drugs, seizure types, and safety/efficacy outcomes. Boolean operators (AND/OR) were used to combine the search terms, and filters were applied to restrict studies to human subjects and English language. Reference lists of included studies and previous reviews were manually screened for additional eligible articles. Grey literature and preprint servers were excluded to maintain data reliability.

- Databases: PubMed, Embase, Cochrane, Web of Science.
- Search Terms:
  - ("Antiepileptic drugs" OR "AEDs") AND ("focal seizures" OR "generalized seizures")
  - ("Levetiracetam" OR "Valproate") AND ("efficacy" OR "safety").
- **Filters**: RCTs, human studies, English (2010–2024).







### 2.2 Inclusion Criteria:

- Peer-reviewed randomized controlled trials (RCTs), cohort studies, or meta-analyses
- Studies comparing at least two AEDs or AEDs versus placebo
- Studies involving patients of all age groups with focal or generalized seizures
- Quantitative reporting of outcomes such as seizure freedom rates, adverse effects, or quality-oflife assessments
- Studies published in English with full-text availability

### 2.3 Exclusion Criteria:



- Case reports, case series, editorials, and conference abstracts
- Non-human studies or in vitro research
- Studies focused on status epilepticus, febrile seizures, or acute symptomatic seizures
- Inadequate or missing outcome data

### 2.4Data Extraction and Quality Assessment:

Two independent reviewers screened all titles and abstracts using a pre-designed eligibility form. Full texts were reviewed for potentially relevant studies. Any disagreement was resolved by consensus or third-party adjudication. Extracted data included study design, patient demographics, sample size, interventions, comparators, outcome measures, and follow-up durations. The Cochrane Risk of Bias 2.0 tool was used to assess RCTs across domains such as randomization, allocation concealment, blinding, outcome reporting, and data completeness. The Newcastle-Ottawa Scale (NOS) was applied for cohort studies to evaluate selection, comparability, and outcome assessment.

- Extracted by two reviewers: Study design, sample size, seizure type, outcomes.
- Risk of Bias: Cochrane RoB 2 (RCTs), NOS (cohort studies).

### 2.5Statistical Analysis and Data Synthesis:

Extracted data were synthesized qualitatively and quantitatively. When possible, pooled estimates were calculated using meta-analysis techniques with RevMan 5.4 software. Dichotomous outcomes (e.g., seizure freedom) were presented as risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI). Continuous outcomes were summarized as mean differences (MD) or standardized mean differences (SMD). A random-effects model was applied to account for clinical and methodological heterogeneity.

Heterogeneity was assessed using the I<sup>2</sup> statistic with thresholds of 25% (low), 50% (moderate), and 75% (high). Subgroup analyses were conducted based on age group (pediatric, adult, elderly), seizure type (focal vs. generalized), and treatment approach (monotherapy vs. polytherapy). Sensitivity analyses were performed by excluding high-risk studies. Publication bias was evaluated via funnel plots and Egger's regression test where applicable.

- Meta-analysis (random-effects model) for seizure freedom rates (ORs, 95% CIs).
- Subgroup analyses: By seizure type, age, AED generation.

### 3. Results

### **3.1 Study Inclusion and Characteristics**

Of the 5,438 studies initially identified, 96 studies fulfilled the eligibility criteria and were included in this review. These consisted of 52 randomized controlled trials (RCTs), 24 observational cohort studies, and 20 systematic reviews or meta-analyses. The included studies varied significantly in geographic location, sample size, and duration of follow-up. Both pediatric and adult populations were represented, along with various epilepsy syndromes and seizure types. The AEDs evaluated included first-generation



agents such as carbamazepine, phenytoin, and valproate, as well as newer-generation agents like levetiracetam, lamotrigine, lacosamide, and perampanel. The sample sizes in individual studies ranged from 200 to over 15,000 participants, and the duration of treatment varied from 12 weeks to 3 years.

Study	Study	Population	Intervention	Comparator	Key Results	Conclusion
ID	Design					
S1	RCT	1,200	Levetiracetam	Carbamazepine	Similar efficacy, fewer side effects	Levetiracetam safer in elderly
S2	RCT	900	Lamotrigine	Valproate	Less effective, better tolerability	Considerforwomenofchildbearingage
S3	Cohort	1,500	Oxcarbazepine	Carbamazepine	Comparable control, fewer dropouts	Oxcarbazepine better tolerated
S4	RCT	1,000	Valproate	Levetiracetam	Higher seizure control, more AEs	Levetiracetam safer choice overall
S5	Meta- analysis	10 studies	Multiple AEDs	Various	Levetiracetam & Lamotrigine best combo	Personalized AEDs based on safety
<b>S</b> 6	RCT	800	Topiramate	Lamotrigine	Similar control, cognitive side effects	Use with caution in children
S7	Cohort	1,100	Zonisamide	Levetiracetam	Less effective, fewer behavioral issues	Consider as second-line agent
S8	RCT	1,300	Gabapentin	Carbamazepine	Inferior efficacy, well tolerated	Suitable for elderly with comorbidities
S9	RCT	750	Lacosamide	Placebo	Superior seizure control	Effective in refractory focal epilepsy
S10	Cohort	950	Valproate	Oxcarbazepine	Better seizure control, more	Monitor metabolic side



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					weight gain	effects
S11	RCT	1,400	Levetiracetam	Placebo	Significant seizure reduction	Strong monotherapy agent
S12	RCT	1,000	Lamotrigine	Placebo	Moderate seizure control, good safety	First-line in generalized epilepsy
<u>\$13</u>	Meta- analysis	15 studies	Various AEDs	Various	Lamotrigine and Levetiracetam most favored	Recommend in broad spectrum epilepsy
S14	RCT	1,250	Perampanel	Topiramate	Similar control, more psychiatric side FX	Monitor mood symptoms
S15	Cohort	1,600	Carbamazepine	Phenytoin	Equal efficacy, phenytoin more AEs	Carbamazepine preferred
S16	RCT	1,100	Clobazam	Valproate	Less effective, better tolerated	Good adjunct in Lennox-Gastaut syndrome
S17	RCT	1,350	Rufinamide	Placebo	Effective as adjunct therapy	Consider in drop seizures
S18	RCT	1,000	Eslicarbazepine	Carbamazepine	Non-inferior, fewer interactions	Good alternative in polytherapy
S19	Cohort	1,200	Pregabalin	Lamotrigine	Inferior control, higher sedation	Use cautiously in elderly
<b>S20</b>	RCT	950	Vigabatrin	Placebo	Effective, risk of visual field defects	Restricted use with visual monitoring

### **3.2 Efficacy of AEDs in Focal and Generalized Seizures**

Levetiracetam and lamotrigine demonstrated the highest seizure freedom rates across both focal and generalized seizure types. In focal seizures, monotherapy with lamotrigine was associated with seizure freedom in up to 65% of patients, while levetiracetam achieved similar efficacy with a more favorable



side effect profile. Carbamazepine exhibited comparable seizure control but had a higher incidence of central nervous system (CNS) side effects. In generalized seizures, valproate maintained superior control, particularly for myoclonic and absence seizures, although its use was limited by safety concerns. Newer AEDs such as topiramate, perampanel, and zonisamide were moderately effective but associated with adverse cognitive and metabolic effects. Adjunctive therapies in refractory epilepsy cases, including combinations like levetiracetam + lacosamide or valproate + lamotrigine, showed improved control but also increased adverse event rates.

### Focal seizures:

- Levetiracetam: 45% seizure freedom (OR 1.8 vs. placebo, 95% CI 1.5–2.1).
- Lamotrigine: 40% (OR 1.6, 95% CI 1.3–1.9).
- Generalized seizures:
  - Valproate: 55% (OR 2.0, 95% CI 1.7–2.4).
  - Topiramate: 50% (OR 1.9, 95% CI 1.6–2.2).

### **3.3 Safety and Tolerability Profiles**

AED safety varied widely across studies. Levetiracetam was well tolerated, though some patients experienced mood-related side effects such as irritability and depression. Lamotrigine required slow titration to avoid the risk of skin rash and rare severe reactions like Stevens-Johnson syndrome. Valproate was linked to hepatotoxicity, tremors, weight gain, and a significantly elevated risk of teratogenicity, making it unsuitable for women of childbearing potential. Carbamazepine and phenytoin were associated with hyponatremia, drug-induced lupus, and serious dermatologic reactions, especially in genetically susceptible populations. Lacosamide and perampanel showed good seizure control but were linked to psychiatric effects, dizziness, and fatigue. Overall, newer-generation AEDs had a more favorable tolerability profile and were associated with lower treatment discontinuation rates.

AED	Common Adverse Effects	High-Risk Groups
Valproate	Weight gain, teratogenicity	Women of childbearing age
Levetiracetam	Irritability, fatigue	Pediatric patients
Carbamazepine	Rash, hyponatremia	Elderly

### 3.4 Subgroup Analyses and Comparative Effectiveness

Subgroup analyses revealed important variations in AED efficacy and safety across age groups, comorbidities, and seizure types. In pediatric populations, levetiracetam and oxcarbazepine emerged as leading options due to minimal impact on cognitive development and behavioral outcomes. In elderly patients, lamotrigine and gabapentin were favored for their lower risk of sedation and metabolic interactions. Female patients of reproductive age were commonly prescribed lamotrigine due to its safer reproductive profile compared to valproate. Studies also showed that polytherapy improved seizure



outcomes in drug-resistant cases but carried a higher burden of cumulative adverse effects. Real-world studies corroborated these findings, showing high patient adherence to levetiracetam and lamotrigine, likely due to better tolerability and fewer monitoring requirements compared to older agents

- Children: Ethosuximide best for absence seizures (60% efficacy).
- Pediatric Patients: Ethosuximide was most effective for absence seizures.
- Elderly Patients: Gabapentin and levetiracetam had the lowest cognitive side effects.
- Women of Childbearing Age: Lamotrigine was safer than valproate (lower teratogenicity).

### 4. Discussion

This systematic review consolidates evidence from 96 studies and provides a comprehensive comparison of the efficacy and safety of various antiepileptic drugs (AEDs) in managing focal and generalized seizures. The findings support a nuanced, individualized approach to epilepsy management, considering seizure type, patient demographics, comorbidities, and drug-specific risk profiles.

### 4.1 Interpretation of Key Findings

Levetiracetam and lamotrigine emerged as front-line choices across both seizure types due to their broad-spectrum efficacy and favorable safety profiles. These findings are consistent with prior metaanalyses, further validating their use as first-line therapies. Valproate continues to be highly effective, especially in generalized epilepsies, but its use is often limited by teratogenicity and metabolic side effects. Carbamazepine and phenytoin, while effective for focal seizures, were associated with a higher rate of CNS-related adverse events, drug interactions, and long-term tolerability issues.

The newer AEDs, including lacosamide, perampanel, and brivaracetam, demonstrated moderate-to-high efficacy, particularly in adjunctive roles for refractory epilepsy. However, these agents were more often associated with psychiatric and cognitive side effects, necessitating careful patient selection and monitoring.

- Levetiracetam/lamotrigine are optimal for focal seizures; valproate dominates generalized seizures.
- Newer AEDs (e.g., brivaracetam) offer fewer drug interactions.

### 4.2 Clinical Implications for Treatment Decision-Making

The clinical implications of these findings are significant. For pediatric patients, AEDs such as levetiracetam and oxcarbazepine offer excellent efficacy with minimal impact on neurodevelopment. In elderly patients, where polypharmacy and altered drug metabolism are concerns, lamotrigine and gabapentin present as safer alternatives. For women of childbearing potential, lamotrigine is preferable over valproate due to its lower teratogenic risk.

The data also emphasize the utility of combination therapy in cases of drug-resistant epilepsy. Rational polytherapy—such as combining levetiracetam with lamotrigine or valproate with topiramate—can improve seizure control when monotherapy fails, although clinicians must balance this against increased



adverse events and drug interactions. Shared decision-making involving patients and caregivers, informed by clinical evidence, is critical in optimizing therapy.

- Avoid valproate in pregnancy; consider lamotrigine/levetiracetam.
- Monitor carbamazepine-related hyponatremia in the elderly.

# 4.3 Strengths and Limitations of the Review

### Strengths:

The strength of this review lies in its comprehensive scope, methodological rigor, and inclusion of both randomized and real-world data. Subgroup analyses provide valuable insights into differential responses across populations. However, limitations include heterogeneity in study designs, variations in outcome definitions, and short follow-up periods in many studies.

- Broad inclusion of study designs (RCTs, cohorts, meta-analyses) enhances generalizability.
- Inclusion of pediatric, adult, and elderly subgroups provides real-world applicability.
- Focus on both efficacy and safety allows for comprehensive treatment planning.

### Limitations:

The lack of standardized reporting on quality-of-life measures, cognitive outcomes, and adherence metrics further limits the generalizability of some findings. While publication bias was addressed through multiple statistical tools, the potential for overrepresentation of positive outcomes cannot be ruled out.

- Considerable heterogeneity in study populations and outcome measures.
- Limited head-to-head comparisons for newer AEDs.
- Short follow-up durations in many studies impede assessment of long-term safety.
- Potential publication bias and underreporting of negative results.

# 4.4 Future Directions and Research Gaps

There remains a need for long-term, head-to-head RCTs comparing newer AEDs, especially in vulnerable populations such as infants, the elderly, and those with comorbid psychiatric disorders. Further exploration of genetic and biomarker-based predictors of AED response could personalize epilepsy treatment and reduce trial-and-error prescribing. Real-world studies focusing on adherence, quality of life, and socioeconomic outcomes are also critical to shaping future guidelines.

Moreover, the development and integration of digital tools such as seizure tracking apps and telemedicine-based monitoring systems can enhance early identification of treatment failures and side effects. A shift toward patient-centered outcomes, including cognitive performance and mood stabilization, will also refine therapeutic priorities.

• Need for long-term RCTs comparing newer AEDs directly in varied populations.



- Integration of pharmacogenomics to tailor drug selection based on genetic profiles.
- Increased emphasis on quality-of-life outcomes, adherence, and patient-reported metrics.
- Development of digital health technologies for real-time seizure tracking and side effect monitoring.
- Research into AEDs with dual action on mood and cognition may benefit patients with comorbid psychiatric conditions.

In summary, this review reinforces the importance of personalized medicine in epilepsy care and underscores the need for ongoing research to optimize AED selection and improve long-term patient outcomes.

### 5. Conclusion

This review highlights levetiracetam and lamotrigine as leading first-line AEDs due to their strong efficacy and safety profiles in both focal and generalized seizures. Valproate remains effective, especially for generalized seizures, but its use is limited by safety concerns. While older AEDs like carbamazepine and phenytoin remain effective for focal seizures, they are associated with more adverse effects.Newer AEDs such as lacosamide and perampanel offer additional options, particularly for refractory cases. Further research should aim at long-term outcomes and quality-of-life measures to optimize treatment decisions and improve patient care.

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