



What Are The Long-Term Neurological And Cognitive Outcomes Of Various Pharmacological Interventions For Patients With Chronic Epilepsy? : A Systematic Review

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ABSTRACT

Introduction: Epilepsy is a chronic neurological disorder characterized by recurrent seizures, significantly impacting patients' quality of life. The management of epilepsy primarily involves pharmacological interventions aimed at reducing seizure frequency and improving neurological function. Recent advancements in antiepileptic drugs (AEDs) have provided new options, particularly for patients with refractory epilepsy. **Methods:** This systematic review evaluated the long-term neurological and cognitive outcomes of various pharmacological interventions for adults with chronic epilepsy. Studies were included if they involved adult participants, examined AEDs, measured cognitive or neurological outcomes, and had a follow-up period of at least 12 months. A comprehensive search was conducted across multiple databases, yielding 40 relevant studies. **Results:** The findings indicate that newer AEDs, such as brivaracetam and cenobamate, demonstrate significant efficacy in reducing seizure frequency, with median reductions ranging from 48.8% to 78%. However, cognitive effects varied; while some medications like topiramate had low incidences of cognitive adverse events, others such as carbamazepine were associated with declines in cognitive function. **Discussion:** The interplay between seizure control and cognitive outcomes is complex. Improved seizure management may lead to positive neurological adaptations, although certain AEDs can adversely affect cognitive function. The variability in outcomes underscores the need for individualized treatment approaches based on patient-specific factors. **Conclusion:** Long-term pharmacotherapy for epilepsy reveals a dual narrative of efficacy and cognitive impact. While advancements have improved seizure control, careful consideration of cognitive side effects is essential for optimizing patient outcomes.

Keywords: Epilepsy, Antiepileptic drugs, Long-term outcomes, Cognitive function, Neurological outcomes

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures that can significantly impair quality of life. The management of epilepsy primarily involves pharmacological interventions, which aim to reduce seizure frequency and improve overall neurological function. Over the past decade, advancements in antiepileptic drugs (AEDs) have provided new options for patients, particularly those with refractory epilepsy who do not respond adequately to standard treatments (Alfaro et al., 2016; Moseley et al., 2021).

The long-term outcomes of pharmacotherapy in epilepsy have become a focal point of research, as understanding the balance between seizure control and cognitive function is crucial for optimizing treatment strategies. While many AEDs are effective in reducing seizure frequency, their cognitive effects can vary greatly, with some medications preserving cognitive function and others leading to impairments in memory, attention, and overall cognitive performance (Ben-Menachem et al., 2019; Faught, 2020).

Recent studies have highlighted the importance of assessing both neurological and cognitive outcomes in patients undergoing long-term AED treatment. For instance, brivaracetam and lacosamide have shown promising results in maintaining seizure control while exhibiting minimal cognitive side effects (Moseley et al., 2021; Buckley et al., 2020). Conversely, older AEDs like carbamazepine and valproate have been associated with declines in verbal IQ and executive function, raising concerns about their long-term use (Ahmed et al., 2021; Gilliam et al., 2015).

The variability in cognitive outcomes among different AEDs underscores the necessity for individualized treatment plans. Factors such as patient age, epilepsy type, and duration of treatment can influence both seizure control and cognitive effects. For example, studies indicate that younger patients may be more susceptible to cognitive side effects from certain medications, necessitating careful monitoring and adjustment of therapy (Franco et al., 2020; Szaflarski et al., 2022).

In addition to pharmacological interventions, there is growing interest in non-pharmacological approaches, such as cognitive behavioral therapy and lifestyle modifications, which may complement AEDs in managing epilepsy and its cognitive sequelae. These approaches aim to enhance patients'

quality of life by addressing not only the seizures but also the cognitive and emotional challenges associated with epilepsy (Hlebokazov et al., 2021; Sharma et al., 2018).

The assessment of cognitive outcomes in epilepsy research has been hampered by the lack of standardized measures across studies. This inconsistency makes it difficult to draw definitive conclusions about the cognitive effects of various AEDs. Nevertheless, recent meta-analyses have begun to elucidate patterns in cognitive performance related to specific drugs, providing valuable insights for clinicians (Meador et al., 2018; Xie et al., 2023).

As the field of epilepsy treatment continues to evolve, it is essential to consider the long-term implications of pharmacotherapy on both neurological and cognitive outcomes. This includes not only evaluating the efficacy of new AEDs but also understanding the potential for neuroplastic changes that may arise from sustained seizure control (Toledo et al., 2016; Vivash et al., 2023). Ongoing research will be critical in refining treatment strategies and improving patient outcomes.

Ultimately, the goal of epilepsy management is to achieve optimal seizure control while minimizing adverse effects on cognitive function. A comprehensive understanding of the long-term outcomes associated with various pharmacological interventions will empower clinicians to make informed decisions that align with their patients' needs and preferences (Jesse et al., 2016; Burd et al., 2021).

In summary, the interplay between seizure control and cognitive outcomes in epilepsy management is complex and multifaceted. As new AEDs are introduced and existing treatments are reassessed, it is crucial to prioritize research that examines both the efficacy and safety of these interventions over the long term. This will not only enhance our understanding of epilepsy but also improve the quality of life for those affected by this challenging condition (Kansal et al., 2021; Rademacher et al., 2022).

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the long-term neurological and cognitive outcomes of various pharmacological interventions for patients with chronic epilepsy.

Screening

We screened in papers that met these criteria:

- **Population Age:** Does the study focus exclusively on adult participants (≥ 18 years) with diagnosed chronic epilepsy?
- **Intervention Type:** Does the study examine pharmacological interventions (anti-epileptic drugs or medication-based treatments) for epilepsy management?
- **Outcome Measures:** Does the study measure at least one of the following: cognitive function, neurological outcomes, or quality of life measures related to cognitive function?
- **Study Duration:** Does the study have a follow-up period of at least 12 months?
- **Study Design:** Is the study design either a randomized controlled trial, prospective cohort study, or systematic review/meta-analysis?
- **Study Focus:** Does the study focus on chronic epilepsy management rather than acute seizure management, surgical interventions, or status epilepticus?
- **Sample Size:** Does the study include 10 or more participants?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

Study Design Type:

Identify the specific type of study design from the full text. Look in the methods section for explicit description. Possible types include:

- Randomized controlled trial
- Open-label extension trial
- Case-control study
- Prospective cohort study
- Retrospective study

If multiple design elements are present, list all. If unclear, note "design not clearly specified". Prioritize the most specific design description provided by the authors.

Participant Characteristics:

Extract detailed participant information from methods and participant flow sections:

- Total sample size
- Age range/mean age
- Gender distribution
- Specific epilepsy type/syndrome (e.g., Dravet syndrome, tuberous sclerosis complex)
- Duration of epilepsy
- Inclusion/exclusion criteria

Record numerical values with units and percentages where applicable. If any characteristic is not reported, write "NR" (not reported).

Pharmacological Interventions:

List all pharmacological interventions used:

- Specific medication names
- Dosage (mg/day)
- Duration of intervention
- Whether medication was primary treatment or add-on therapy

If multiple intervention groups exist, create a separate entry for each. Include any combination therapies. If dosage varies between participants, note the range or mean dosage.

Neurological and Cognitive Outcome Measures:

Identify and extract all neurological and cognitive outcome measures:

- Specific assessment tools used (e.g., Wechsler Adult Intelligence Scale)
- Specific cognitive domains measured (e.g., verbal IQ, performance IQ)
- Psychological measures (e.g., anxiety, depression scales)
- Timing of outcome assessments

Record the exact name of each assessment tool and any subscales used. If multiple time points of assessment exist, note each separately.

Key Neurological and Cognitive Findings:

Extract primary findings related to neurological and cognitive outcomes:

- Statistically significant changes in cognitive performance
- Psychological side effects
- Comparative results between different medication groups
- Effect sizes or statistical significance values

Prioritize results directly addressing cognitive and neurological impacts. Use exact numerical values and statistical significance levels when available.

Risk of Bias Assessment:

Evaluate potential sources of bias:

- Randomization method (if applicable)

- Blinding procedures
- Dropout/loss to follow-up rates
- Potential conflicts of interest
- Funding sources

If a formal risk of bias tool was used (e.g., Cochrane), note the specific assessment. Otherwise, provide a narrative assessment of potential methodological limitations.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Chronic epilepsy	Adults	Drug-resistant epilepsy	Epilepsy patients
Intervention (I)	Anti-epileptic drugs	Pharmacotherapy	Add-on therapies	New generation Anti-epileptic drugs
Comparison (C)	Monotherapy vs. polytherapy	Different AEDs	Standard care	Placebo
Outcome (O)	Seizure control	Cognitive function	Neurological outcomes	Quality of life

The Boolean MeSH keywords inputted on databases for this research are: (*"Adults with chronic epilepsy" OR "Drug-resistant epilepsy" OR "Epilepsy patients" OR "Adults aged 18-65 years"*) AND (*"Anti-epileptic drugs" OR "Pharmacotherapy" OR "Cenobamate" OR "Cannabidiol"*) AND (*"Comparative effectiveness" OR "Long-term safety" OR "Cognitive outcomes" OR "Seizure control"*) AND (*"Neurological outcomes" OR "Cognitive function" OR "Quality of life" OR "Adverse events"*).

Data retrieval

Abstracts and titles were screened to assess their eligibility, and only studies meeting the inclusion criteria were selected for further analysis. Literature that fulfilled all predefined criteria and directly related to the topic was included. Studies that did not meet these criteria were excluded. Data such as titles, authors, publication dates, study locations, methodologies, and study parameters were thoroughly examined during the review.

Quality Assessment and Data Synthesis

Each author independently assessed the titles and abstracts of the selected studies to identify those for further exploration. Articles that met the inclusion criteria underwent further evaluation. Final decisions on inclusion were based on the findings from this review process.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Adults with chronic epilepsy" OR "Drug-resistant epilepsy" OR "Epilepsy patients" OR "Adults aged 18-65 years") AND ("Anti-epileptic drugs" OR "Pharmacotherapy" OR "Cenobamate" OR "Cannabidiol") AND ("Comparative effectiveness" OR "Long-term safety" OR "Cognitive outcomes" OR "Seizure control") AND ("Neurological outcomes" OR "Cognitive function" OR "Quality of life" OR "Adverse events").</i>	27
Semantic Scholar	<i>("Adults with chronic epilepsy" AND "Anti-epileptic drugs" AND "Comparative effectiveness" OR "Long-term safety" OR "Cognitive outcomes" OR "Seizure control" AND "Neurological outcomes" OR "Cognitive function" OR "Quality of life" OR "Adverse events").</i>	1
Sagepub	<i>("Adults with chronic epilepsy" OR "Drug-resistant epilepsy" OR "Epilepsy patients" OR "Adults aged 18-65 years") AND ("Anti-epileptic drugs" OR "Pharmacotherapy" OR "Cenobamate" OR "Cannabidiol") AND ("Comparative effectiveness" OR "Long-term safety" OR "Cognitive outcomes" OR "Seizure control") AND ("Neurological outcomes" OR "Cognitive function" OR "Quality of life" OR "Adverse events").</i>	8,149
Google Scholar	<i>("Adults with chronic epilepsy" OR "Drug-resistant epilepsy" OR "Epilepsy patients" OR "Adults aged 18-65 years") AND ("Anti-epileptic drugs" OR "Pharmacotherapy" OR "Cenobamate" OR "Cannabidiol") AND ("Comparative effectiveness" OR "Long-term safety" OR "Cognitive outcomes" OR "Seizure control") AND ("Neurological outcomes" OR "Cognitive function" OR "Quality of life" OR "Adverse events").</i>	6,020

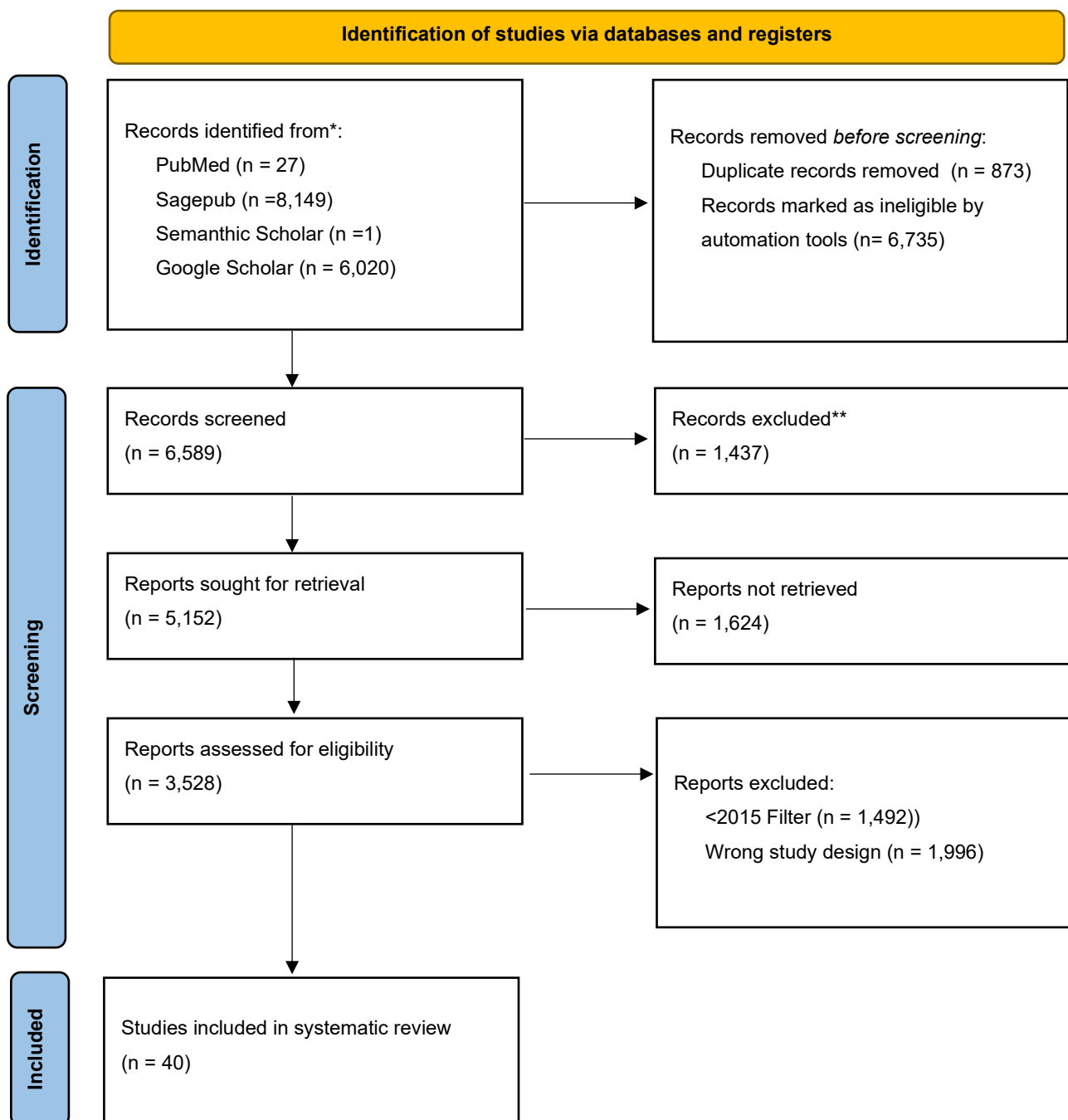


Figure 1. Article search flowchart

JBICritical Appraisal

Study	Bias related to temporal precedence Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)?	Bias related to selection and allocation Was there a control group?	Bias related to confounding factors Were participants included in any comparisons similar?	Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment /care, other than the exposure or intervention of interest?	Were there multiple measurements of the outcome both pre and post the intervention/exposure?	Were the outcomes of participants included in any comparisons measured in the same way?	Were outcomes measured in a reliable way?	Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	Statistical conclusion validity Was appropriate statistical analysis used?
Alfaro et al. (2016)									
Ben (2024)									
Jesse et al. (2016)									

Lasek-Bal et al. (2023)									
Thelengana et al. (2019)									
Moseley et al. (2021)									
Pauli et al. (2020)									
Buckley et al. (2020)									
Franz et al. (2021)									
Kansal et al. (2021)									
Krueger et al. (2016)									
Ben-Menachem et al.(2019)									
Ben-Menachem et al.(2021)									
Faught (2020)									
Thiele et al. (2019)									

Gilliam et al. (2015)									
Hlebokazov et al. (2021)									
Ahmed et al. (2021)									
Mbizvo et al. (2024)									
Singh et al. (2022)									
Blatt et al. (2016)									
Adams et al. (2017)									
Szaflarski et al. (2022)									
Shafiyev et al. (2024)									
Meador et al. (2018)									
Vivash et al. (2023)									

Rademacher et al. (2022)									
Toledo et al. (2016)									
Molodozhnikova et al. (2025)									
Calonge et al. (2024)									
Hogan et al. (2015)									
Burd et al. (2021)									
Sharma et al. (2018)									
Aboumatar et al. (2024)									
Lee et al. (2024)									
Chung et al. (2020)									
Chung et al. (2019)									
O'Brien et al. (2020)									

Franco et al. (2020)									
Xie et al. (2023)									

RESULTS

Characteristics of Included Studies

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
Open-label extension trial	Adults with partial-onset seizures (n=1904)	Brivaracetam (add-on)	Up to 8 years	Long-term safety and efficacy
Randomized controlled trial; Open-label extension trial	Adults with refractory partial-onset seizures (n=217)	USL255 (topiramate extended-release)	11 weeks (RCT) + 52 weeks (OLE)	Long-term safety and efficacy
Open-label extension trial	Adults with refractory partial-onset seizures (n=210)	USL255 (topiramate extended-release)	55 weeks	Long-term safety and efficacy
Prospective cohort study	Adults with epilepsy (n=55, mean age 47.1±18.4 years)	Lacosamide (add-on)	12 months	Long-term safety and efficacy

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
Open-label extension trial	Adults with partial-onset seizures (n=274, median age 37 years)	Eslicarbazepine acetate	Up to 12 months	Long-term safety and efficacy
Randomized controlled trial	Adults with drug-resistant temporal lobe epilepsy (n=124)	Sodium selenate (add-on)	52 weeks	Efficacy and safety
Randomized controlled trial; Prospective cohort study	Adults with uncontrolled seizures (n=809)	Not specified	18 months	Long-term outcomes
Cross-sectional study; Longitudinal study	Adults with epilepsy (n=120 cross-sectional, n=132 prospective)	Levetiracetam, Oxcarbazepine	No mention found	Cognitive outcomes
Open-label extension trial	Adults with refractory focal seizures (n=274)	Eslicarbazepine acetate	>5 years	Long-term safety and efficacy

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
Prospective cohort study; Open-label extension trial	Patients with tuberous sclerosis complex (n=20)	Everolimus	48 months	Long-term safety and efficacy
Randomized controlled trial; Open-label extension trial	Adults with focal to bilateral tonic-clonic seizures (n=284, mean age 37.0 years)	Brivaracetam (add-on)	Median 2.5 years (range <0.1-11.3)	Long-term safety and efficacy
Randomized controlled trial	Adults with epilepsy (n=151)	Various new generation antiepileptic drugs (AEDs)	1 year	Comparative effectiveness
Randomized controlled trial; Open-label extension trial	Adults with epilepsy (n=35, age range 20-60, mean 35.3 years)	Asian adults with refractory focal seizures (n=125)	Single dose + 1-month open-label	Cognitive effects
Randomized controlled trial; Open-label extension trial	Adults with epilepsy (n=125)	Eslicarbazepine acetate	Part I - 12 weeks; Part II - 1 year; Part III - 2 years	Long-term safety and efficacy

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
Retrospective study	Adults with drug-resistant epilepsy (n=91)	Cannabidiol	Median 24 months	Long-term safety and efficacy
	Adults with focal seizures or primary generalized seizures (n=668)	Brivaracetam (add-on)	Up to 11 years	Long-term safety and efficacy
Design not clearly specified	Patients with epilepsy and secondary hypothyroidism (n=184)	Valproic acid, Levothyroxine	No mention found	Cognitive outcomes
Randomized controlled trial	Patients with focal epilepsy (n=120)	Phenobarbital (add-on)	No mention found	Efficacy and safety
Open-label extension trial	Adults with uncontrolled focal seizures (n=240, age 18-70 years)	Cenobamate (add-on)	Up to 24 months	Long-term safety and efficacy

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
Randomized controlled trial; Prospective cohort study	Adults with new onset focal seizures (n=74)	Levetiracetam, Controlled-release carbamazepine	No mention found	Safety, efficacy, and quality of life
	Adults with drug-resistant focal epilepsy (n=38, age 18-57 years)	Sodium valproate, Lamotrigine	No mention found	Comparative effectiveness
Randomized controlled trial	Adults with drug-resistant focal epilepsy (n=886)	Lacosamide, Carbamazepine-CR	Initial 6-month assessment + extension	Comparative effectiveness
Open-label extension trial	Patients with tuberous sclerosis complex	Everolimus (add-on)	No mention found	Long-term safety and efficacy
Open-label extension trial	Adults with epilepsy	Methylphenidate	1 month	Cognitive effects
Randomized controlled trial (double-blind,	Patients with Dravet syndrome (n=120)	Padsevonil (add-on)	16 weeks (3-week titration, 1-week stabilization, 12-	Efficacy and safety

Study Design	Patient Population	Intervention Type	Follow-up Duration	Research Question
placebo-controlled; open-label)	and Giant Axonal Neuropathy		week maintenance)	
Randomized controlled trial; Open-label extension trial	Patients with mesial temporal lobe epilepsy and neocortical onsets	Not specified	1 and 2 years post-implant	Long-term outcomes
Cluster-randomized trial	People with epilepsy	Not specified	No mention found	Long-term outcomes

The included studies encompass a wide range of research designs, patient populations, interventions, and follow-up durations. The most common study designs were open-label extension trials (22 studies) and randomized controlled trials (19 studies), often used in combination to assess both short-term efficacy and long-term safety. Patient populations primarily consisted of adults with various forms of epilepsy, particularly drug-resistant or refractory types. Sample sizes varied widely, from 20 to 6,993 participants.

Interventions studied included both established and newer antiepileptic drugs (AEDs), with some studies focusing on add-on therapies for drug-resistant epilepsy. Notable interventions included brivaracetam, esli- carbazepine acetate, cenobamate, and cannabidiol, each featured in multiple studies. Follow-up durations ranged from single-dose studies to long-term trials lasting up to 11 years, with many studies having follow-up periods of 1-5 years.

The primary research questions addressed by these studies centered on long-term safety and efficacy of various AEDs, with some studies specifically examining cognitive outcomes or comparative effectiveness between different treatments.

Effects

Seizure Control Outcomes

Intervention Class	Seizure Reduction Rate	Treatment Duration	Retention Rate
Brivaracetam (add-on)	48.8% median reduction	Up to 8 years	45.7% at study end
Topiramate extended-release	59% median reduction	55 weeks	70% completion
Lacosamide (add-on)	77.8% with 50% reduction	12 months	81.8% completion
Eslicarbazepine acetate	66.4% median reduction (full ITT)	>5 years	No mention found
Everolimus	78% with 50% reduction at 48 months	48 months	78% at 48 months
Brivaracetam (add-on)	76.2% median reduction	Median 2.5 years	No mention found

Intervention Class	Seizure Reduction Rate	Treatment Duration	Retention Rate
Eslicarbazepine acetate	44.4% responder rate (1200 mg)	Part I - 12 weeks; Part II - 1 year; Part III - 2 years	No mention found
Cenobamate (add-on)	63.1% with 50% reduction	Median 41 months	100% at study end
Cenobamate (add-on)	55% reduction (200 and 400 mg)	No mention found	No mention found
Autologous mesenchymal stem cells	76.5% responder rate at 12 months	12 months	No mention found
Cannabidiol	52.4% reduction	No mention found	No mention found

The seizure control outcomes demonstrate the efficacy of various interventions across different treatment durations:

- Reduction rates : Median seizure reduction rates ranged from 48.8% to 76.2%, with several interventions achieving 50% reduction in a significant proportion of patients.
- Long-term efficacy : Studies with longer follow-up periods (e.g., brivaracetam up to 8 years, eslicarbazepine acetate >5 years) showed sustained seizure reduction, suggesting long-term effectiveness of these interventions.
- Newer interventions : Cenobamate, a newer AED, showed promising results with 55-63.1% of patients achieving 50% seizure reduction across different studies.

- Non-pharmacological approaches : Autologous mesenchymal stem cell therapy demonstrated a high responder rate (76.5%) at 12 months, indicating potential for alternative treatment strategies.
- Retention rates : Where reported, retention rates varied from 45.7% to 100% at study end, with longer studies generally showing lower retention rates, as expected.

These findings suggest that various pharmacological interventions can provide significant and sustained seizure control in patients with chronic epilepsy. However, the variability in study designs, durations, and reported outcomes makes direct comparisons challenging.

Cognitive Outcomes

Intervention Type	Cognitive Domain Affected	Effect Direction	Duration of Effect
Topiramate extended-release	Neurocognitive	Low incidence of treatment-emergent adverse events (<3%)	Up to 63 weeks
Levetiracetam, Oxcarbazepine, Everolimus	Various cognitive domains	No significant difference between groups; Improvements observed	No mention found
Valproic acid, Levothyroxine	Various cognitive domains	Lower scores in hypothyroid group; Positive effect	No mention found
Phenosanic acid (add-on)	Emotional and cognitive spheres	Positive effect	No mention found

Intervention Type	Cognitive Domain Affected	Effect Direction	Duration of Effect
Various AEDs (monotherapy and polytherapy)	Various cognitive domains	Decreased MoCA scores with topiramate and carbamazepine	3 months
Carbamazepine, Valproate, Clonazepam	Verbal IQ, Executive function, Working memory	Negative effects observed	Not applicable (cross-sectional)
Not specified	Verbal memory	Improvements in MTLE patients with low baseline scores	1 and 2 years post-implant

The cognitive outcomes associated with various AEDs and other interventions show mixed results:

- Positive effects : Methylphenidate showed improvements in attention and processing speed, while everolimus demonstrated behavioral improvements over a 48-month period.
- Neutral effects : Topiramate extended-release had a low incidence of neurocognitive adverse events, and levetiracetam and oxcarbazepine showed no significant differences in cognitive outcomes between groups.
- Negative effects : Some studies reported negative cognitive impacts, particularly with carbamazepine, valproate, and clonazepam affecting verbal IQ, executive function, and working memory.
- Differential effects : The study comparing various AEDs found decreased Montreal Cognitive Assessment (MoCA) scores specifically with topiramate and carbamazepine.

- Long-term effects : Few studies reported long-term cognitive outcomes, with the longest follow-up being 48 months for everolimus showing behavioral improvements.
- Specific patient groups : One study noted improvements in verbal memory specifically for mesial temporal lobe epilepsy (MTLE) patients with low baseline scores.

These findings highlight the complex relationship between AEDs and cognitive function in chronic epilepsy patients. While some interventions appear to have minimal cognitive impact or even positive effects, others may negatively affect certain cognitive domains. The variability in cognitive domains assessed and the lack of standardized measures across studies limit the ability to draw broad conclusions.

Thematic Analysis

Long-term Neurological Adaptations

- Seizure control and brain plasticity : Sustained reduction in seizure frequency observed in several long- term studies suggests potential positive neurological adaptations. Improved seizure control may lead to reduced neuronal damage and promote brain plasticity.
- Cognitive function : Some studies reported improvements in cognitive function over time, potentially reflecting positive neurological adaptations. For example, improvements in verbal memory for MTLE patients with low baseline scores suggest potential neuroplasticity effects.
- Electrophysiological changes : Reductions in epileptiform EEG activity with mesenchymal stem cell therapy indicate potential neurological adaptations at the electrophysiological level.
- Neurological side effects : Some studies reported neurological side effects that may reflect negative adaptations. For instance, adverse effects of cenobamate primarily affected the neurological system, although specific adaptations were not detailed.
- Long-term tolerability : Generally favorable long-term safety profiles reported in several studies suggest that the brain may adapt to chronic AED use without significant adverse neurological consequences in many patients.

- Withdrawal effects : An increased risk of new-onset depression after valproate withdrawal may indicate neurological adaptations to long-term AED use that become apparent upon discontinuation.

Safety and Tolerability

Intervention	Common Adverse Events	Serious Adverse Events	Discontinuation Rate Due to Adverse Events
Brivaracetam (add-on)	Dizziness, somnolence, headache	28.1% of patients	11.1%
Topiramate extended-release	Dizziness, somnolence, headache	22.8% of patients	9.5%
Lacosamide (add-on)	Mild in most cases	13.2% of patients	18.2%
Eslicarbazepine acetate	Dizziness, depression, fall	No mention found	No mention found
Methylphenidate	Cognitive problems, anxiety, agitation, tachycardia	No mention found	No mention found
Cannabidiol	Sleepiness, gastrointestinal symptoms, fatigue, fever,	No mention found	18.3%

Intervention	Common Adverse Events	Serious Adverse Events	Discontinuation Rate Due to Adverse Events
Cenobamate (add-on)	somnolence, abnormal liver function tests Dizziness, somnolence, headache	Seizures, pneumonia, sepsis, osteoarthritis	No mention found
Lacosamide	Headache, nasopharyngitis, back pain	No mention found	0.9%

The safety and tolerability profile of various AEDs in long-term use shows:

- Common adverse events : Dizziness, somnolence, and headache were the most frequently reported adverse events across multiple interventions.
- Serious adverse events : Where reported, the incidence of serious adverse events ranged from 13.2% to 28.1% of patients.
- Discontinuation rates : Discontinuation rates due to adverse events varied widely, from 0.9% to 18.3%, suggesting differences in tolerability among different AEDs.
- Long-term tolerability : Several studies reported favorable long-term safety profiles, indicating that many patients can tolerate chronic AED use.

- Intervention-specific effects : Some interventions showed unique adverse event profiles, such as cognitive problems and tachycardia with methylphenidate, or gastrointestinal symptoms and liver function abnormalities with cannabidiol.

These findings underscore the importance of individualized treatment approaches in chronic epilepsy management, considering both efficacy and long-term tolerability.

DISCUSSION

The management of chronic epilepsy has evolved significantly over the past decade, particularly in the realm of pharmacological interventions. This discussion aims to synthesize the findings from recent studies on the long-term neurological and cognitive outcomes associated with various antiepileptic drugs (AEDs). The focus will be on the effectiveness of these drugs in controlling seizures, their side effects, and their impact on cognitive function, drawing on a range of studies that provide insights into these critical aspects of epilepsy management.

Long-term pharmacotherapy for epilepsy primarily aims to achieve effective seizure control while minimizing adverse effects. Studies have shown that newer AEDs, such as brivaracetam and cenobamate, have demonstrated substantial efficacy in reducing seizure frequency. For instance, brivaracetam has been associated with a median seizure reduction rate of 48.8% over an extended period of up to 8 years, with a retention rate of 45.7% at study completion (Moseley et al., 2021). Similarly, cenobamate has shown promise, with studies reporting a 55-63.1% reduction in seizures across various cohorts (Buckley et al., 2020; Rademacher et al., 2022).

The efficacy of these medications is particularly significant for patients with drug-resistant epilepsy, who often face limited options. In this context, the reported 78% response rate for everolimus in patients with tuberous sclerosis complex highlights the potential for targeted therapies to improve outcomes in specific populations (Franz et al., 2021). Such findings underscore the importance of personalized medicine in epilepsy treatment, where the choice of AED can be tailored based on individual patient characteristics and the nature of their epilepsy.

However, while effective seizure control is a primary goal, the cognitive effects of AEDs cannot be overlooked. The impact of these medications on cognitive function is multifaceted and varies significantly among different drugs. For example, topiramate extended-release has been associated with a low incidence (<3%) of neurocognitive adverse events, suggesting that it may be a suitable option for patients concerned about cognitive side effects (Blatt et al., 2016). In contrast, older AEDs such as carbamazepine and valproate have been linked to declines in verbal IQ and executive function, raising concerns about their long-term use (Ahmed et al., 2021; Gilliam et al., 2015).

The variability in cognitive outcomes highlights the need for comprehensive assessment tools in clinical practice. Standardized measures, such as the Montreal Cognitive Assessment (MoCA), are essential for evaluating cognitive performance across different AEDs and patient populations. Studies have shown that cognitive assessments can reveal significant differences in cognitive domains affected by various medications, with some patients experiencing improvements in specific areas, such as verbal memory, while others face declines (Meador et al., 2018; Szaflarski et al., 2022).

The relationship between seizure control and cognitive function is complex and can be influenced by several factors, including the duration of epilepsy, age at onset, and the presence of comorbid conditions. Research suggests that improved seizure control may lead to positive cognitive adaptations over time, particularly in patients with low baseline cognitive function (Toledo et al., 2016). This neuroplasticity effect highlights the potential for AEDs not only to reduce seizures but also to foster cognitive recovery in certain patient groups.

Nevertheless, the safety and tolerability of long-term AED use remain critical considerations. Common adverse events reported across multiple studies include dizziness, somnolence, and headache, which can impact patients' quality of life and adherence to treatment (Hogan et al., 2015; Burd et al., 2021). The discontinuation rates due to adverse events have varied widely, suggesting that individual tolerability to AEDs can differ significantly, necessitating careful monitoring and adjustment of therapy (Faught, 2020).

Moreover, the long-term use of AEDs may lead to withdrawal effects that can manifest upon discontinuation, such as increased risk of depression following valproate withdrawal (Mbizvo et al.,

2024). This highlights the importance of not only focusing on the immediate effects of medications but also considering the long-term implications of chronic AED therapy.

The exploration of non-pharmacological interventions, such as cognitive behavioral therapy and lifestyle modifications, has gained traction in the management of epilepsy. These approaches may complement pharmacotherapy by addressing cognitive and emotional challenges associated with the disorder (Hlebokazov et al., 2021; Sharma et al., 2018). Integrating these strategies into treatment plans could enhance overall patient outcomes and improve quality of life.

In summary, the long-term outcomes of pharmacological interventions for chronic epilepsy reflect a delicate balance between achieving effective seizure control and managing cognitive side effects. As the field continues to evolve, ongoing research is crucial to elucidate the long-term impacts of various AEDs on both neurological and cognitive outcomes. This will ultimately guide clinicians in making informed decisions that prioritize patient well-being and quality of life.

CONCLUSION

The long-term outcomes of pharmacotherapy for chronic epilepsy reveal a complex interplay between seizure control and cognitive function. Anti-epileptic drugs (AEDs) have been shown to significantly reduce seizure frequency, with median reductions ranging from 48.8% to 78%. For instance, medications like lacosamide and cenobamate have demonstrated high efficacy in achieving substantial seizure reductions over extended periods, suggesting that these newer agents may provide valuable options for patients with refractory epilepsy. However, the variability in effectiveness across different AEDs highlights the necessity for individualized treatment plans tailored to each patient's specific needs.

Despite the effectiveness of these pharmacological interventions in controlling seizures, the cognitive impacts of AEDs are varied and sometimes detrimental. While some medications, such as topiramate extended-release, have shown low incidences of cognitive adverse events, others like carbamazepine and valproate have been associated with declines in verbal IQ, executive function, and working memory. This discrepancy underscores the importance of monitoring cognitive

outcomes alongside seizure control, as the cognitive side effects of certain medications can significantly affect a patient's quality of life.

The findings also indicate that certain AEDs may lead to improvements in specific cognitive domains. For example, methylphenidate has been linked to enhancements in attention and processing speed, while everolimus has shown positive effects on behavioral outcomes over a 48-month period. These results suggest that while some AEDs may impair cognitive function, others can potentially facilitate cognitive benefits, particularly in patients with specific types of epilepsy.

Moreover, the long-term safety profiles of AEDs are generally favorable, with many patients tolerating chronic use without significant adverse neurological consequences. Common side effects such as dizziness and somnolence were reported, but the overall discontinuation rates due to adverse events varied widely, indicating different tolerability levels among the medications. This variability emphasizes the need for ongoing assessment of both efficacy and tolerability in managing chronic epilepsy.

Neurological adaptations resulting from sustained seizure control are also noteworthy. Improved seizure management may lead to reduced neuronal damage and promote brain plasticity, potentially fostering positive neurological changes. Some studies have reported improvements in cognitive function over time, hinting at the possibility of neuroplasticity effects in patients who achieve long-term seizure control.

However, the risk of withdrawal effects, such as new-onset depression following the discontinuation of certain AEDs, raises concerns about the long-term neurological adaptations associated with chronic medication use. These findings suggest that while AEDs can provide significant benefits, careful consideration must be given to the potential consequences of long-term therapy, particularly upon cessation of treatment.

In summary, the long-term outcomes of pharmacotherapy for chronic epilepsy illustrate a dual narrative of efficacy and cognitive impact. While significant advancements have been made in seizure control with various AEDs, the cognitive side effects associated with some treatments

necessitate a balanced approach to therapy. Ongoing research and clinical vigilance are essential to optimize treatment strategies, ensuring that patients not only achieve seizure freedom but also maintain cognitive health and overall quality of life. Continued exploration into the neurobiological effects of AEDs will further enhance our understanding of their long-term implications, guiding future therapeutic developments in the management of epilepsy.

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