Comparative efficacy and tolerability of antiepileptic drugs for focal onset epilepsy: a systematic review and network meta-analysis to inform an AI-based clinical decision support system

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REVIEW TITLE AND BASIC DETAILS

Review title

Comparative efficacy and tolerability of antiepileptic drugs for focal onset epilepsy: a systematic review and network meta-analysis to inform an AI-based clinical decision support system

Condition or domain being studied

Epilepsy; Focal epilepsy; Anticonvulsants; Antiepileptics; Seizure; Recurrence free survival

The review specifically focuses on adults diagnosed with focal onset seizures (with or without progression to bilateral tonic-clonic seizures). The clinical domain is the pharmacological management of epilepsy, specifically the selection of initial or conversion monotherapy with antiepileptic drugs (AEDs). This domain is characterized by a high number of available therapeutic options, comprising both standard (e.g., carbamazepine, valproate) and newer generation (e.g., levetiracetam, lacosamide) agents. Accurate drug selection is critical as drug resistance and adverse events are common, often leading to poor quality of life. This review explicitly excludes generalized epilepsies to ensure population homogeneity for the network meta-analysis.

Rationale for the review

Epilepsy treatment often relies on a "trial-and-error" approach due to the wide variety of available antiepileptic drugs (AEDs) and complex patient heterogeneity. While clinical guidelines exist, they often provide general recommendations rather than personalized predictions of treatment success. Furthermore, many AEDs have never been compared directly in head-to-head trials, creating a gap in comparative evidence.

This review is required to synthesize direct and indirect evidence from Randomized Controlled Trials (RCTs) using Network Meta-Analysis (NMA). This will allow for the ranking of treatments based on efficacy and tolerability. Uniquely, the structured quantitative data generated from this review will not only update the evidence base but also serve as the training dataset for a machine learning-based Clinical Decision Support System (CDSS) prototype, designed to assist clinicians in personalized drug selection.

Review objectives

The primary objective is to evaluate and rank the comparative efficacy and tolerability of monotherapy antiepileptic drugs (AEDs) for the treatment of focal onset epilepsy in adults through a systematic review and network meta-analysis (NMA).

The specific review questions are:

- Which AED monotherapy is associated with the highest probability of seizure freedom (efficacy) at 6 and 12 months?
- Which AED is associated with the lowest rate of treatment withdrawal due to adverse events (tolerability)?

- To generate a structured matrix of relative treatment effects that can be utilized to train a predictive artificial intelligence model.

Keywords

Focal epilepsy; Antiepileptic drugs; Network meta-analysis; Clinical Decision Support Systems Personalized Medicine

Country

Türkiye

ELIGIBILITY CRITERIA

Population

Included

Adult patients (aged 16 years or older) with a clinical diagnosis of focal onset epilepsy according to the International League Against Epilepsy (ILAE) classification. This includes focal aware seizures, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures. The review will include patients who are eligible for monotherapy, encompassing both newly diagnosed patients and those converting to monotherapy from other regimens.

Excluded

1. Pediatric populations (children and adolescents under 16 years of age).
2. Patients diagnosed with primary generalized epilepsies (e.g., absence, myoclonic seizures) or unclassified seizure types.
3. Patients with acute symptomatic seizures (e.g., related to alcohol withdrawal, acute trauma) or status epilepticus.
4. Studies focusing exclusively on drug-resistant epilepsy requiring surgical intervention or polytherapy (add-on) trials where the efficacy of a single agent cannot be isolated.
5. Pregnant women or patients with significant progressive neurological or psychiatric comorbidities that could confound safety outcomes.

Intervention(s) or exposure(s)

Included

Antiepileptics; Carbamazepine; Levetiracetam; Lamotrigine; Lacosamide; Zonisamide; Oxcarbazepine; Topiramate; Eslicarbazepine Oral Tablet; Valproic Acid

The review focuses on Antiepileptic Drugs (AEDs) administered as monotherapy. Eligible interventions include both established first-line agents (e.g., carbamazepine, valproate, phenytoin) and newer generation AEDs (e.g., levetiracetam, lamotrigine, oxcarbazepine, lacosamide, eslicarbazepine acetate, zonisamide, topiramate).

The review will consider trials evaluating these drugs in two specific clinical contexts:

- Initial Monotherapy: As the first treatment in newly diagnosed patients.
- Monotherapy Conversion: In patients transitioning from polytherapy to a single agent, provided the outcome measures reflect the monotherapy phase.

Only drugs currently approved by major regulatory bodies (FDA or EMA) for this indication will be included to ensure the resulting Clinical Decision Support System provides actionable, clinically valid recommendations.

Excluded

Studies will be excluded if they investigate:

1. **Add-on (Adjunctive) Therapy**: Trials where the investigational drug is added to an existing baseline regimen of other anti-epileptic drugs (AEDs), as this does not isolate the efficacy of the single drug required for the proposed monotherapy prediction model.
2. **Rescue Medication:** Studies focusing solely on acute seizure management (e.g., status epilepticus) rather than long-term maintenance therapy.

3. **Non-Pharmacological Interventions:** Trials comparing AEDs to surgery, dietary therapies (e.g., ketogenic diet), or neurostimulation devices (e.g., VNS, DBS).
4. **Experimental/Withdrawn Drugs:** Compounds that are not currently approved for clinical use or have been withdrawn from the market due to safety concerns, to maintain the clinical applicability of the decision support system.
5. **Different Formulations:** Studies comparing different formulations of the same active substance (e.g., immediate-release vs. extended-release) without a comparison to a distinct different AED or placebo, as this does not contribute to the network of different treatment options.

Comparator(s) or control(s)

Included
PICO tags selected: Placebo; Active control; Carbamazepine; Lamotrigine

The review will include studies comparing the intervention Anti-Epileptic Drugs (AEDs) against:

- Placebo: Trials using an inactive placebo control, which are essential for anchoring the Network Meta-Analysis.
- Active Comparators: Trials using another active AED as a control group (head-to-head trials).

To be included, the active comparator must be used as monotherapy within the established therapeutic dose range. Common active comparators expected in the network include standard-of-care drugs such as Carbamazepine, Lamotrigine, Levetiracetam, and Valproate. The inclusion of these comparators allows for the indirect comparison of newer versus older generation drugs within the network.

Excluded
Comparators will be excluded if they involve:

1. Polytherapy/Add-on Regimens: Control arms where the comparator is added to a baseline of other AEDs (unless the trial design specifically isolates the monotherapy effect of the comparator).
2. Non-Pharmacological Interventions: Control groups receiving surgery, dietary therapies (e.g., ketogenic diet), or neurostimulation (e.g., VNS) without a pharmacological comparator.
3. Sub-therapeutic Doses: Control arms utilizing doses significantly below the recommended therapeutic range, as this introduces bias regarding efficacy.
4. Unspecified "Usual Care": Studies where the control arm consists of a heterogenous mix of "physician's choice" drugs without specific data separation, as this prevents specific node formation in the Network Meta-Analysis.

Study design
Only randomized study types will be included.

Included
This review will strictly include Randomized Controlled Trials (RCTs). Both double-blind and open-label RCTs will be considered eligible, provided they report the requisite quantitative outcomes (seizure freedom or retention rates) necessary for the machine learning model. Cross-over trials will be included only if data from the first treatment period (prior to crossing over) are reported separately, to avoid the confounding influence of carry-over effects.

Excluded
We will exclude non-randomized studies, including observational studies (cohort, case-control, cross-sectional), case reports, case series, and narrative reviews. Quasi-randomized trials (e.g., allocation by date of birth or alternate days) will be excluded to minimize selection bias. Studies with a total sample size of fewer than 20 participants may also be excluded to ensure statistical reliability for the NMA

Context
The review encompasses randomized controlled trials conducted in secondary and tertiary care settings, such as neurology outpatient clinics and specialized epilepsy centers globally. There are no geographical restrictions, aiming to compile a comprehensive dataset for the Network Meta-Analysis and subsequent Artificial Intelligence model training. The clinical context is focused on the long-term maintenance treatment of focal onset epilepsy. Consequently, studies conducted exclusively in emergency departments for acute seizure management (e.g., status epilepticus) or intensive

care settings are excluded, as they do not reflect the clinical decision-making process for selecting maintenance monotherapy.

SIMILAR REVIEWS

Check for similar records already in PROSPERO
PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 31 January 2026). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- Comparing the Bone Health Effects of First-Generation Versus New-Generation Antiepileptic Drugs: A Systematic Review and Meta-Analysis [published 3 December 2025] [CRD420251246113]. The review was judged **not to be similar**
- Which is better in the management of focal epilepsy, Levetiracetam or Carbamazepine: a systematic review and meta-analysis of randomized controlled trials [published 2 August 2024] [CRD42024571709]. The review was judged **not to be similar**
- Balancing maternal seizure control and fetal safety of second- and third-generation antiepileptic drug monotherapy in pregnancy: A systematic review and network meta-analysis. [published 30 November 2025] [CRD420251243158]. The review was judged **not to be similar**

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
This record has not been submitted.

Review timeline
Start date: 31 January 2026. End date: 13 October 2026.

Date of registration in PROSPERO
This record has not been published.

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written and published. The protocol may be accessed here:

SEARCHING AND SCREENING

Search for unpublished studies
Both published and unpublished studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *Embase.com*, *MEDLINE*, *PubMed* and *Scopus*.

Search language restrictions
There are no language restrictions.

Search date restrictions
There are no search date restrictions.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts, looking through all the articles that cite the papers included in the review ("snowballing" or forward citation searching), reference list checking (backward citation*

searching), *searching conference proceedings*, *searching dissertation and thesis databases* and *searching trial or study registers*.

Additional information about identifying studies
We will specifically monitor the portals of regulatory agencies (FDA and EMA) for drug approval packages. We will manually screen the abstracts of the last five annual meetings of the International League Against Epilepsy (ILAE) and the American-Epilepsy Society (AES) to identify any late-breaking trials relevant to focal epilepsy monotherapy

Link to search strategy
A full search strategy is available in the full protocol as described in the *Availability of full protocol* section

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
Search results will be deduplicated using Zotero and Rayyan software. We will utilize the AI-assisted ranking algorithm in Rayyan to prioritize records and increase screening efficiency, although final inclusion/exclusion remains a dual-human decision process to ensure high "ground truth" data quality.

The screening and extraction procedure is specifically designed to capture not only primary outcomes but also the granular study-level and patient-level covariates (e.g., age subgroups, baseline seizure frequency, drug titration schedules) required to engineer features for the subsequent Machine Learning phase (XGBoost and Random Forest algorithms). This ensures that the Systematic Review directly informs the development of the predictive Clinical Decision Support System (CDSS) prototype. The process strictly adheres to the PRISMA-NMA extension for evidence synthesis.

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Cochrane RoB-2*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
Publication bias will be assessed using comparison-adjusted funnel plots and Egger's regression test. We will also compare trial registry protocols with published reports to identify selective outcome reporting. If publication bias is significant, trim-and-fill analyses will be conducted to determine the robustness of the network rankings.

Certainty assessment
The certainty of evidence for primary outcomes will be assessed using the GRADE framework. For the network meta-analysis, we will utilize the CINeMA (Confidence In Network Meta-Analysis) approach to evaluate within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence, classifying results into high, moderate, low, or very low certainty.

OUTCOMES TO BE ANALYSED

Main outcomes

The primary outcomes for this review and the subsequent AI model training are:

- Clinical Efficacy (Seizure Freedom): Defined as the proportion of patients achieving 100% reduction in seizure frequency during the maintenance phase of the trial. This is typically measured using patient seizure diaries and clinical assessments. The primary time point for analysis will be 24 to 52 weeks post-randomization.
- Tolerability and Safety (Treatment Retention): Defined as the proportion of patients who remained on the randomized antiepileptic drug (AED) monotherapy until the end of the study period. This outcome captures the balance between efficacy and side effects. The primary time point will be the end of the study (typically 6 or 12 months).

Effect Measures for Synthesis:

For the Network Meta-Analysis (NMA), the summary effect measure for both binary outcomes will be the Odds Ratio (OR) with 95% Confidence Intervals.

AI Integration:

These outcomes will serve as the primary target variables for the Machine Learning models (XGBoost/Random Forest), aiming to predict the probability of seizure freedom and treatment success for individual patient profiles.

Additional outcomes
Additional outcomes for the systematic review and AI feature engineering include:

1. **50% Responder Rate**: Defined as the proportion of patients achieving at least a 50% reduction in seizure frequency from the baseline period to the end of the maintenance phase. This is measured via seizure diaries, typically at 24 to 52 weeks. Effect measure: Odds Ratio (OR).
2. **Withdrawal due to Adverse Events (AEs)**: The proportion of patients who discontinued the trial specifically because of side effects or intolerability. This provides a granular safety metric beyond "total retention." Measured at the end of the study period. Effect measure: Odds Ratio (OR).
3. **Serious Adverse Events (SAEs):** The occurrence of medical events resulting in hospitalization, significant disability, or death during the study period. Measured via safety reports throughout the trial duration.
4. **Quality of Life (QoL)**: Where available, scores from validated instruments such as the QOLIE-31 (Quality of Life in Epilepsy Inventory). Measured at the final follow-up visit. Effect measure: Standardized Mean Difference (SMD).

AI integration:

The 50% responder rate and AE-specific withdrawal data will be used as secondary "labels" for the multi-target machine learning models. This allows the AI-based prototype to provide doctors with a more nuanced prediction of both the efficacy and the specific tolerability risks associated with each anti-epileptic drug for a given patient profile.

PLANNED DATA SYNTHESIS

Strategy for data synthesis
A frequentist network meta-analysis (NMA) will be conducted to compare the efficacy and tolerability of multiple anti-epileptic drugs (AEDs) using a random-effects model, which accounts for anticipated clinical and methodological heterogeneity between trials. Direct and indirect evidence will be synthesized to provide relative rankings of AEDs using the P-score method.

Statistical Analysis: The analysis will be performed in R (v4.x) utilizing the 'netmeta' and 'meta' packages. Consistency will be assessed using the node-splitting method, and global heterogeneity will be evaluated using the Q-statistic and I^2.

AI Integration &; Feature Engineering: The synthesized dataset will serve as the primary training and validation set for the development of a predictive Machine Learning prototype. We will utilize supervised learning algorithms, including XGBoost and Random Forest, to model individual treatment success probabilities based on patient-level and study-level

covariates (e.g., age, sex, dosage, seizure frequency). The final goal is to develop an AI-based Clinical Decision Support System (CDSS) that translates population-level NMA results into personalized treatment predictions.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	
Screening search results against inclusion criteria	✓	
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

Publication of review results
Results of the review will be published in English and Turkish.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members
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No conflict of interest decision selected yet.

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No conflict of interest declared.

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Funding source
Review has no funding and no agreed support from an academic institution and is done in authors' own time.

Peer review
The research protocol underwent a formal scientific peer review as part of the funding application for the TUBİTAK 2209-A University Students Research Projects Support Program. The evaluation was conducted by an external scientific committee appointed by the Scientific and Technological Research Council of TUrkiye (TUBİTAK), focusing on the methodological rigor of the network meta-analysis and the feasibility of the proposed machine learning integration.

ADDITIONAL INFORMATION

Additional information
This systematic review and network meta-analysis (NMA) serve as the foundational data synthesis phase for a research project titled "AI-Supported Epilepsy Treatment System," supported by the TÜBİTAK 2209-A program.

While traditional NMAs provide global rankings of treatment efficacy, this project uniquely utilizes the synthesized evidence to engineer features for Machine Learning algorithms (e.g., XGBoost, Random Forest). The ultimate goal is the development of a web-based Clinical Decision Support System (CDSS) prototype that assists clinicians in personalized drug selection for focal onset epilepsy by predicting individual treatment success probabilities based on patient-specific covariates.

The protocol adheres to PRISMA-NMA guidelines and is cross-referenced with its Open Science Framework (OSF) registration (DOI: 10.17605/OSF.IO/UWSGV). This initiative emphasizes the translation of high-level evidence-based medicine into practical, AI-driven digital health tools for clinical practice.

Review conflict of interest
Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings
Adult; Anticonvulsants; Artificial Intelligence; Classification; Decision Support Systems, Clinical; Drug Resistance; Epilepsy; Epilepsy, Generalized; Freedom; Humans; Lacosamide; Lamotrigine; Levetiracetam; Network Meta-Analysis; Outcome Assessment, Health Care; Oxcarbazepine; Phenytoin; Probability; Quality of Life; Seizures; Topiramate; Valproic Acid; Zonisamide; eslicarbazepine acetate

PROSPERO version history
No preview available

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