2004-2018: Updated summary by subcommittee of the American Academy of Neurology and the American Epilepsy Society in the management of epilepsy

2004: Report of the Therapeutics and Technology assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society

New AED I: Treatment of new onset epilepsy[1]

Purpose: To provide the clinician with evidence-based data on the efficacy, safety and mode of use of new AEDs (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam and zonisamide), which can facilitate the choice of the appropriate drugs **in the management of children and adults with newly diagnosed partial seizure disorders and primary generalized epilepsy.**

A 23-member committee evaluated the available evidence based on a structured literature review including relevant articles from 1987 until September 2002, with selected manual searches up until 2003. Data for each AED were reviewed by three panel members, with a different group assembled for each drug. These three panelists classified each article as class I through IV (Table 1).

Rating of recommendation	Translation of evidence to recommendations	Rating of therapeutic article
A = Established as effective, ineffective, or harmful for the given condition in the specified population	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for drop-outs and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
B = Probably effective, ineffective, or harmful for the given condition in the specified population	Level B rating requires at least one convincing class II study or at least three consistent class III studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criterion a–d
C = Possibly effective, ineffective, or harmful for the given condition in the specified population	Level C rating requires at least two convincing and consistent class III studies	Class III: All other controlled trials (including welldefined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
U = Data inadequate or conflicting; given current knowledge, treatment is unproven		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

RCT = randomized controlled trial.

Table 1: Definitions for classification of evidence

Recommendations: Based on findings in terms of efficacy and tolerability of new AEDs in comparison to that of old AEDs in patients with newly diagnosed epilepsy

- Patients with newly diagnosed epilepsy who require treatment can be initiated on standard AEDs such as carbamazepine, phenytoin, valproic acid, phenobarbital, or on the new AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate.
- Choice of AED will depend on individual patient characteristics (Level A).

Recommendation: Based on the evidence about effectiveness of new AEDs in adults or children with primary or secondary generalized epilepsy

- Lamotrigine can be included in the options for children with newly diagnosed absence seizures (Level B).

Table 2 includes information regarding the difference between the recommendations in this guideline and FDA approved indications for the drugs addressed in this parameter at the time of its publication.

Drug	Newly diagnosed monotherapy partial/mixed	Newly diagnosed absence
Gabapentin	Yes*	No
Lamotrigine	Yes*	Yes*
Topiramate	Yes*	No
Tiagabine	No	No
Oxcarbazepine	Yes	No
Levetiracetam	No	No
Zonisamide	No	No

*Not Food and Drug Administration–approved for this indication.

Table 2: Summary of AAN evidence-based guidelines level A or B recommendation for use

The results of this evidence-based assessment provide guidelines for the prescription of AEDs for patients with newly diagnosed epilepsy and identify those seizure types and syndromes where more evidence is necessary.

New AED II: Treatment of refractory epilepsy[2]

Purpose: To provide clinicians with evidence-based data on the efficacy, safety and mode of use of seven new AEDs (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide), which can facilitate their choice of the appropriate drug in the management of children and adults with refractory partial seizure disorders, primary generalized epilepsy and the Lennox-Gastaut syndrome.

A 23-member committee evaluated the available evidence based on a structured literature review including relevant articles from 1987 until March 2003. Data of each AED were reviewed by three panel members (a different group for each drug). The panel lists classified each article as class I through IV (Table 1).

PARTIAL EPILEPSY (Adults)

Recommendations: Based on the evidence of effectiveness of new AEDs in refractory partial epilepsy as adjunctive therapy

- It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy (Level A).

Recommendations: Based on the evidence of effectiveness of new AEDs as monotherapy in patients with refractory partial epilepsy

- Oxcarbazepine and topiramate can be used as monotherapy in patients with refractory partial epilepsy (Level A).
- Lamotrigine can be used as monotherapy in in patients with refractory partial epilepsy (Level B, downgraded due to dropouts).

GENERALIZED EPILEPSY (Adults)

Idiopathic generalized epilepsy in adult

Recommendations: Based on the evidence of effectiveness of new AEDs with respect to seizures seen in patients with refractory idiopathic generalized epilepsy

- Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children (Level A).

Refractory epilepsy (Children)

Recommendations: Based on the evidence of effectiveness of new AEDs in refractory partial epilepsy as adjunctive therapy in children

- Gabapentin, lamotrigine, oxcarbazepine and topiramate may be used as adjunctive treatment of children with refractory partial seizures (Level A).

Lennox-Gastaut syndrome (Children)

Recommendations: Based on the evidence of effectiveness of new AEDs in children and/or adults with Lennox-Gastaut syndrome

- Topiramate and lamotrigine may be used to treat drop attacks associated with the Lennox Gastaut syndrome in adults and children (Level A).

Drug	Partial adjunctive adult	Partial monotherapy	Primary generalized	Symptomatic generalized	Pediatric partial
Gabapentin	Yes	No	No	No	Yes
Lamotrigine	Yes	Yes	No	Yes	Yes
Topiramate	Yes	Yes†	Yes (only generalizedtonic-clonic)	Yes	Yes
Tiagabine	Yes	No	No	No	No
Oxcarbazepine	Yes	Yes	No	No	Yes
Levetiracetam	Yes	No	No	No	No
Zonisamide	Yes	No	No	No	No

* NB: In a previous parameter, felbamate was recommended for intractable partial seizures in patients over age 18 and patients over 4 with the Lennox-Gastaut syndrome. Felbamate is associated with significant and specific risks, and risk-benefit ratio must be considered.[3]

† Not Food and Drug Administration approved for this indication.

Table 3: Summary of AAN evidence-based guidelines level A or B recommendation for use*

The choice of AED depends upon seizure and/or syndrome type, patient age, concomitant medications, AED tolerability, safety, and efficacy. The results of this evidence-based assessment provide guidelines for the prescription of AEDs for patients with refractory epilepsy and identify those seizure types and syndromes where more evidence is necessary.

2018: Report of the American Epilepsy Society and the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology[3]

Purpose: Since the 2004 publications, new studies emerged in the 8 second-generation and 6 newer (third- generation) AEDs. **This is an updated 2018 recommendation of AAN guideline for treatment of new-onset focal or childhood absence epilepsy with new generation AEDs.**

The 2004 AAN criteria were used to systematically review literature (January 2003 to November 2015), classify pertinent studies according to the therapeutic rating scheme, and link recommendations to evidence strength.

Recommendation: For childhood absence epilepsy

- Unless there are compelling reasons based on adverse effects profile, ethosuximide or valproic acid use should be considered before lamotrigine use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy.

Recommendation: Monotherapy in adults with new-onset epilepsy with focal epilepsy or unclassified tonic-clonic seizures

In patients aged ≥60 years: Lamotrigine and gabapentin is effective and better tolerated than immediate-release carbamazepine

- To decrease seizure frequency in adults; consider:
  - Lamotrigine
  - Levetiracetam
  - Zonisamide
- To decrease seizure frequency in patients aged ≥60 years; consider:
  - Lamotrigine
  - Gabapentin

References:

1. French JA, Kanner AM, Bautista J, et al; American Academy of Neurology Therapeutics and Technology Assessment Subcommittee; American Academy of Neurology Quality Standards Subcommittee; American Epilepsy Society Quality Standards Subcommittee; American Epilepsy Society Therapeutics and Technology Assessment Subcommittee. Efficacy and tolerability of the new antiepileptic drugs, I: Treatment of new-onset epilepsy: report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2004 May;45(5):401-9. Available at: https://pubmed.ncbi.nlm.nih.gov/15101821/
2. French JA, Kanner AM, Bautista J, Abou-Khalil B, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004 Apr 27;62(8):1261-73. Available at: https://pubmed.ncbi.nlm.nih.gov/15111660/
3. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Epilepsy Currents. 2018;18(4):260-268. Available at: https://journals.sagepub.com/doi/pdf/10.5698/1535-7597.18.4.260

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