



Complete Summary

GUIDELINE TITLE

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.

BIBLIOGRAPHIC SOURCE(S)

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, et al. 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 AES. *Neurology* 2004 Apr 27;62(8):1261-73. [83 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- [September 29, 2006, Lamictal \(lamotrigine\)](#): New preliminary information available regarding the effects of Lamictal on the baby if taken during the first three months of pregnancy.
- [April 19, 2005, Trileptal \(oxcarbazepine\)](#): Revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information. The updated WARNINGS section describes serious dermatological reactions in children and adults, and the PRECAUTIONS section has been updated to include language regarding multi-organ hypersensitivity reactions.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

SCOPE

METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS

EVIDENCE SUPPORTING THE RECOMMENDATIONS

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

SCOPE

DISEASE/CONDITION(S)

- Refractory partial epilepsy
- Refractory idiopathic generalized epilepsy
- Lennox-Gastaut syndrome

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology
Pediatrics
Pharmacology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To assess the evidence demonstrating efficacy, tolerability, and safety of seven new antiepileptic drugs (AEDs) (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide) in the treatment of children and adults with refractory partial and generalized epilepsies

TARGET POPULATION

Children and adults with refractory partial and generalized epilepsies

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Gabapentin (Neurontin)
2. Lamotrigine (Lamictal)
3. Topiramate (Topamax)
4. Tiagabine (Gabitril)
5. Oxcarbazepine (Trileptal)

6. Levetiracetam (Keppra)
7. Zonisamide (Zonegran)

MAJOR OUTCOMES CONSIDERED

- Time to first seizure
- Percentage of patients rendered seizure free
- Time to exit of the study due to lack of efficacy or adverse events
- Incidence of adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search was performed including MEDLINE and Current Contents for relevant articles from 1987 until September 2001. A second hand search was performed by panel members, covering September 2001 to May 2002. A hand search for class I articles was updated to March 2003. In addition, the Cochrane library of randomized controlled trials in epilepsy was searched in September 2002, and any appropriate articles identified were added to the review.

Criteria for Selection of Articles

The literature search identified all articles that included the terms epilepsy and one of the following: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide: 1) relevant to the clinical questions of efficacy, safety, tolerability, mode of use; 2) human subjects only; 3) type of studies: randomized controlled trials, cohort, case control, observational, case series; 4) all languages for randomized controlled trials not available in English.

Exclusion Criteria

Reviews and meta-analyses, articles related to non-epilepsy uses of AEDs unless they describe relevant idiosyncratic reactions or safety concerns, and articles on basic AED mechanisms were excluded.

A total of 1,462 articles were identified: 240 on gabapentin, 433 on lamotrigine, 244 on topiramate, 17 on levetiracetam, 212 on oxcarbazepine, 177 on tiagabine, and 146 on zonisamide. Among these, data were extracted for classification of evidence class from 353 articles: 91 on gabapentin, 63 on lamotrigine, 65 on topiramate, 46 on tiagabine, 45 on oxcarbazepine, 33 on zonisamide, and 11 on levetiracetam. Articles were then broken down into those relevant to refractory epilepsy and those relevant to newly diagnosed epilepsy, which are presented in a separate parameter.

NUMBER OF SOURCE DOCUMENTS

All relevant articles were included, for a total of 82.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Rating of Therapeutic Article

Class I: Prospective, randomized, controlled clinical trial (RCT) 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 dropouts 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.

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.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The panel assessed efficacy and dose-related side effects from double-blind controlled studies with 20 or more patients. Safety data were also derived from open trials and case reports.

Data of each antiepileptic drug (AED) were reviewed by three panel members (a different group for each drug). The panelists classified each article as class I through IV (See above "Rating Scheme for the Strength of the Evidence"). Disagreements on article classification were resolved by discussion and consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When formulating the recommendations the guideline developers considered the *magnitude* of the effect (benefit or harm of therapy, accuracy of tests, yield of studies) and the relative *value* of various outcomes. Under most circumstances, there is a direct link between the level of evidence used to formulate conclusions and the strength of the recommendation. This linkage is illustrated in Appendix 9 of the 2004 AAN Guideline Process Manual (see Companion Documents field). Thus, an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation; a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation; a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation. In those circumstances where the evidence indicates that the intervention is not effective or useful, wording was modified. For example, if multiple adequately powered class I studies demonstrated that an intervention is not effective, the recommendation read, "should not be done."

There are important exceptions to the rule of having a direct linkage between the level of evidence and the strength of recommendations. Some situations where it may be necessary to break this linkage are listed below:

- A statistically significant but marginally important benefit of the intervention is observed
- The intervention is exorbitantly costly
- Superior and established alternative interventions are available
- There are competing outcomes (both beneficial and harmful) that cannot be reconciled

Under such circumstances the guideline developers may have downgraded the level of the recommendation.

Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Guidelines were approved by the Quality Standards Subcommittee (QSS) on July 26, 2003, the Therapeutics and Technology Assessment Subcommittee (TTA) on October 17, 2003, the Practice Committee on November 16, 2003, and the American Academy of Neurology (AAN) Board of Directors on January 18, 2004.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Effectiveness of New Antiepileptic Drugs (AEDs) in Refractory Partial Epilepsy as Adjunctive Therapy

1. It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy (**Level A**) (Please refer to the table below titled "Summary of American Academy of Neurology (AAN) Evidence-Based Guidelines Level A or B Recommendation for Use").

Note: In a previous AAN parameter, felbamate was recommended for "intractable partial seizures in patients over 18 years who had failed standard AEDs."

Effectiveness of New AEDs as Monotherapy in Patients with Refractory Partial Epilepsy

1. Oxcarbazepine and topiramate can be used as monotherapy in patients with refractory partial epilepsy (**Level A**).
2. Lamotrigine can be used as monotherapy in patients with refractory partial epilepsy (**Level B, downgraded due to dropouts**).
3. There is insufficient evidence to recommend use of gabapentin, levetiracetam, tiagabine, or zonisamide in monotherapy for refractory partial epilepsy (**Level U**) (Please refer to the table below titled "Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use").

Effectiveness of New AEDs in Patients with Refractory Idiopathic Generalized Epilepsy

1. Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children (**Level A**).
2. There is insufficient evidence to recommend gabapentin, lamotrigine, oxcarbazepine, tiagabine, levetiracetam, or zonisamide for the treatment of refractory generalized tonic-clonic seizures in adults and children (**Level U**) (Please refer to the table below titled "Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use").

Effectiveness of New AEDs in Refractory Partial Epilepsy as Adjunctive in Children

1. Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures (**Level A**) (Please refer to the table below titled "Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use").
2. There is insufficient evidence to recommend levetiracetam, tiagabine, or zonisamide as adjunctive treatment of children with refractory partial seizures (**Level U**) (Please refer to the table below titled "Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use").

Effectiveness of New AEDs as Mono-therapy in Children with Refractory Partial Seizures

No monotherapy trials have been performed in this population.

Effectiveness of New AEDs for Refractory Idiopathic Generalized Epilepsy in Children

Studies of topiramate and gabapentin in idiopathic generalized tonic-clonic convulsions already discussed above included children as well.

Effectiveness of New AEDs in Children and/or Adults with the Lennox-Gastaut Syndrome

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

to the table below titled "Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use").

Note: In a previous AAN parameter, felbamate was recommended in "Lennox-Gastaut patients over age 4 unresponsive to primary AEDs."

Table: Summary of AAN Evidence-Based Guidelines Level A or B Recommendation for Use**

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 generalized tonic-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

*Not Food and Drug Administration approved for this indication

**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.

Definitions:

Rating of Recommendations

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B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting; given current knowledge, treatment is unproven.

Translation of Evidence to Recommendations

Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating requires at least one convincing class II study or at least three consistent class III studies.

Level C rating requires at least two convincing and consistent class III studies.

Rating of Therapeutic Article

Class I: Prospective, randomized, controlled clinical trial (RCT) 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 dropouts 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.

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.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

This assessment provides clinicians with evidence-based data on the efficacy, safety, and mode of use of these seven new anti-epileptic drugs, 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.

POTENTIAL HARMS

- The Food and Drug Administration (FDA) has categorized antiepileptic drug (AED) medications into two classes, D and C. Category C drugs have demonstrated teratogenicity in animals, but human risk is not known. The newer AEDs are classified as Category C. In contrast, phenytoin, carbamazepine, and valproic acid are category D. Category D drugs are those drugs for which teratogenicity was seen in both animal and human pregnancies. In both categories, the recommendation remains the same: selection of AED in pregnancy should be decided upon risk-benefit ratio.
- Adverse effects of AEDs: The adverse effects of the specific AEDs reviewed for this assessment are discussed in the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline subcommittee recognizes that these drugs are not antiepileptic but antiseizure drugs. However, they chose to use the term antiepileptic drugs (AEDs), given its widespread use among all clinicians.
- Selection of the appropriate drug for a given individual must be based on understanding of each drug's pharmacology, side effect profile, and risks.
- This parameter is the second in a two-part assessment of the new AEDs. Part I addresses the use of new AEDs in newly diagnosed epilepsy patients. Referral should be made to that article for background information on the older AEDs.
- This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Slide Presentation

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ Jr, Turk WR, Fischer JH, Bourgeois B, et al. 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 AES. *Neurology* 2004 Apr 27;62(8):1261-73. [83 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Apr 27

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

Quality Standards Subcommittee of the American Academy of Neurology

American Epilepsy Society Guidelines Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

American Academy of Neurology (AAN) Therapeutics and Technology Assessment Subcommittee Members: Douglas Goodin, MD (*chair*); Yuen So, MD, PhD (*vice-chair*); Carmel Armon, MD, MHS; Richard Dubinsky, MD; Mark Hallett, MD; David Hammond, MD; Chung Hsu, MD, PhD; Andres Kanner, MD; David Lefkowitz, MD; Janis Miyasaki, MD; Michael Sloan, MD; James Stevens, MD

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American Epilepsy Society Guidelines Task Force Members: Jacqueline French, MD; Andres Kanner, MD; Mimi Callanan, RN; Jim Cloyd, PhD; Pete Engel, MD, PhD; Ilo Leppik, MD; Martha Morrell, MD; Shlomo Shinnar, MD, PhD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members did not review a given antiepileptic drug (AED) if they had served as advisors for the pharmaceutical company that manufactured the drug and/or if they had been awarded a research grant from that company (participation in multicenter studies was not a reason for exclusion) or if they had financial interests in that company (stock ownership or employee).

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the [AAN Web site](#).

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Efficacy and tolerability of the new antiepileptic drugs, II: treatment of refractory epilepsy. AAN guideline summary for clinicians. St. Paul (MN): American Academy of Neurology. 2. p. Available in Portable Document Format (PDF) from the [American Academy of Neurology \(AAN\) Web site](#).
- Practice parameter: efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. St. Paul (MN): American Academy of Neurology. 2004. 18 p. Available for personal digital assistant (PDA) download from the [AAN Web site](#).
- Slide presentation: efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy. St. Paul (MN): American Academy of Neurology. 2004. Available in Power Point from the [AAN Web site](#).
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the [AAN Web site](#).
- Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p. Electronic copies available in Portable Document Format (PDF) from the [AAN Web site](#).

PATIENT RESOURCES

The following is available:

Efficacy and tolerability of the new antiepileptic drugs for treatment of refractory epilepsy: AAN guideline summary for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the [AAN Web site](#).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004. This summary was updated by ECRI on April 21, 2005 following the release of a public health advisory from the U.S. Food and Drug Administration (FDA) regarding Trileptal (oxcarbazepine). This summary was updated by ECRI on November 15, 2006, following the FDA advisory on Lamictal (lamotrigine).

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