



Complete Summary

GUIDELINE TITLE

Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset 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 I: treatment of new onset 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):1252-60. [21 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 and/or warning information has been released.

- [December 12, 2007, Carbamazepine](#): The U.S. Food and Drug Administration (FDA) has provided recommendations for screening that should be performed on specific patient populations before starting treatment with carbamazepine.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

SCOPE

DISEASE/CONDITION(S)

New onset partial and generalized epilepsies

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—reviewed in the order in which these agents received approval by the US Food and Drug Administration) in the treatment of children and adults with newly diagnosed partial and generalized epilepsies

TARGET POPULATION

Children and adults with newly diagnosed 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 published between January 1987 and September 2001. A second, manual search was performed by panel members, covering September 2001 through May 2002. A manual search for class I articles was then updated to include articles published through 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 papers that included the terms epilepsy and either gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, or zonisamide and satisfied the following criteria: 1) relevant to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) human subjects only; 3) type of studies: randomized controlled trials, cohort, case control, observational, or case series; 4) all languages for randomized controlled trials not available in English; and 5) relevant to patients with newly diagnosed epilepsy.

Exclusion Criteria

Articles were excluded from further analysis if they were reviews or meta-analyses, articles related to non-epilepsy uses of antiepileptic drugs (AEDs) unless they describe relevant idiosyncratic reactions or safety concerns, and articles on basic AED mechanisms.

NUMBER OF SOURCE DOCUMENTS

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. Among these studies, there was one gabapentin class I study, three class I or II studies with lamotrigine, two class I studies with topiramate,

and three class I studies and one class II study with oxcarbazepine in patients with new-onset epilepsy.

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 for each antiepileptic drug (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 (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.

Efficacy and Tolerability of the New Antiepileptic Drugs (AEDs) Compared with That of Older AEDs in Patients with Newly Diagnosed Epilepsy

1. 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**).

Note: At present, there is insufficient evidence to determine effectiveness in newly diagnosed patients for tiagabine, zonisamide, or levetiracetam

Effectiveness of New AEDs in Adults or Children with Primary or Secondary Generalized Epilepsy

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

Note: At present there is insufficient evidence to determine effectiveness in newly diagnosed primary or secondary generalized epilepsy for topiramate, oxcarbazepine, tiagabine, zonisamide, or levetiracetam.

Table: Summary of American Academy of Neurology (AAN) Evidence-Based Guidelines Level A or B Recommendation for Use

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.

Definitions:

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.

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 the clinician with evidence-based data on the efficacy, safety, and mode of use of these new antiepileptic drugs (AEDs), 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.
- The newer agents are involved in many fewer drug interactions. Many of the newer agents have little, if any, effect on the cytochrome P450 (CYP450) enzyme system and other metabolic pathways.

POTENTIAL HARMS

Table: Serious and Nonserious Adverse Events Associated with the New Antiepileptic Drugs (AEDs)

- *Gabapentin*
 - Serious adverse events: none
 - Nonserious adverse events: weight gain, peripheral edema, behavioral changes*
- *Lamotrigine*
 - Serious adverse events: rash, including Stevens Johnson and toxic epidermal necrolysis (increased risk for children, also more common with concomitant valproate use and reduced with slow titration); hypersensitivity reactions, including risk of hepatic and renal failure, disseminated intravascular coagulation (DIC), and arthritis
 - Nonserious adverse events: tics* and insomnia
- *Levetiracetam*
 - Serious adverse events: none
 - Nonserious adverse events: irritability/behavior change
- *Oxcarbazepine*
 - Serious adverse events: hyponatremia (more common in elderly), rash
 - Nonserious adverse events: none
- *Tiagabine*
 - Serious adverse events: stupor or spike wave stupor
 - Nonserious adverse events: weakness
- *Topiramate*
 - Serious adverse events: nephrolithiasis, open angle glaucoma, hypohidrosis*
 - Nonserious adverse events: metabolic acidosis, weight loss, language dysfunction
- *Zonisamide*
 - Serious adverse events: rash, renal calculi, hypohidrosis*
 - Nonserious adverse events: irritability, photosensitivity, weight loss

* Predominantly children

Note: This is not meant to be a comprehensive list but represents the most common adverse events, based on consensus of panel. Psychosis and depression are associated with epilepsy and occur in open label studies with all new AEDs. Although these side effects may appear more commonly with some drugs than with others, it is difficult to ascertain whether these relationships are causal. Consequently, these side effects have been omitted from the table.

- Common drug-drug interactions associated with new AEDs are listed in Table 2 of the original guideline document.

- The effects of comorbid conditions or their treatment on the adverse effects or pharmacokinetics of AEDs are listed in Table 4 of the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline subcommittee recognizes that these are antiseizure and not antiepileptic drugs (AEDs). Nevertheless, they have decided to use in this assessment the term AEDs, given its widespread use.
- 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 I: treatment of new onset 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):1252-60. [21 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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Samuel Wiebe, MD; William Weiner, MD; Stephen Ashwal, MD; Jacqueline French, MD; Catherine Zahn, MD

AES 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 [of the panel] did not review a given antiepileptic drug (AED) if they had served as advisors for the pharmaceutical company that manufactured the drug 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, I: treatment of new onset 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 I: treatment of new onset epilepsy. St. Paul (MN): American Academy of Neurology. 2004. 14 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, I: treatment of new onset 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](#).

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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). This summary was updated by ECRI Institute on January 10, 2008, following the U.S. Food and Drug Administration advisory on Carbamazepine.

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