

AAN/AES GUIDELINES ON USE OF NEW AEDS

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

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OBJECTIVE: 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 United States Food and Drug Administration) in the treatment of children and adults with newly diagnosed partial and generalized epilepsies.

METHODS: A 23-member committee, including general neurologists, pediatric neurologists, epileptologists, and doctors in pharmacy, evaluated the available evidence based on a structured literature review including MEDLINE, Current Contents, and Cochrane library for relevant articles from 1987 until September 2002, with selected manual searches up until 2003.

RESULTS: There is evidence from either comparative or dose-controlled trials that gabapentin, lamotrigine, topiramate, and oxcarbazepine have efficacy as monotherapy in newly diagnosed adolescents and adults with either partial or mixed seizure disorders. Evidence also exists that lamotrigine is effective for newly diagnosed absence seizures in children. Evidence for effectiveness of the new AEDs in newly diagnosed patients with other generalized epilepsy syndromes is lacking.

CONCLUSIONS: 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 for which more evidence is necessary.

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

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, Wilner A, Faught RE Jr, Sachdeo RC, Beydoun A, Glauser TA; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society

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OBJECTIVE: 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.

METHODS: A 23-member committee including general neurologists, pediatric neurologists, epileptologists, and doctors in pharmacy evaluated the available evidence based on a structured literature review including MEDLINE, Current Contents, and Cochrane library for relevant articles from 1987 until March 2003.

RESULTS: All of the new AEDs were found to be appropriate for adjunctive treatment of refractory partial seizures in adults. Gabapentin can be effective for the treatment of mixed seizure disorders, and gabapentin, lamotrigine, oxcarbazepine, and topiramate, for the treatment of refractory partial seizures in children. Limited evidence suggests that lamotrigine and topiramate also are effective for adjunctive treatment of idiopathic generalized epilepsy in

adults and children, as well as treatment of the Lennox–Gastaut syndrome.

CONCLUSIONS: The choice of AED depends on seizure or syndrome type or both, 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 for which more evidence is necessary.

COMMENTARY

Currently, approximately 10 new antiepileptic drugs (AEDs) and numerous older agents are available to patients and physicians for the treatment of epilepsy. The committee reports by the American Academy of Neurology (AAN)/American Epilepsy Society (AES) review seven of the new AEDs. Selecting the best drug for a particular patient and for a specific seizure type can be confusing for the physician. Thus an urgent need exists to make some sense of the plethora of clinical trials and flood of information regarding these agents. Most often, AED clinical trials are designed for regulatory purposes, and drugs are marketed as having the best efficacy and fewest side effects—so how does the physician sort it out? The AAN/AES subcommittee should be complimented for their heroic attempt to make sense out of the enormous amount of information generated from regulatory clinical trials during the last 10 years and for making the findings available to practicing physicians in a readable and useable fashion. The subcommittee's report emphasizes the new AEDs, as these drugs have undergone extensive randomized clinical trials (RCTs), whereas many of the older drugs were approved for use in the preclinical-trial-testing era. The articles offer guidelines on efficacy as well as on safety and mode of use.

Recently, evidence-based medicine has become the paradigm for understanding the role of old and new procedures or drugs in the treatment of various disorders, including epilepsy. With careful analysis of clinical trials and other published experiments, recommendations for a procedure or drug are designated by two conventionally accepted categories: Levels of Evidence 1–4 and Recommendation Levels A–C or U. In the two AAN/AES subcommittee articles, these levels of evidence and recommendation were used; the levels are specified as follows:

Levels of Evidence, Class 1–4.

Class 1 includes prospective, randomized, controlled clinical trials with a representative population and masked outcome. At this level, four criteria must be met: (1) designation of primary

outcomes, (2) clear definition of exclusion and inclusion factors, (3) adequate counting of dropouts, and (4) presentation of baseline characteristics that indicate enough similarity between groups to make a valid comparison. Class II studies are prospective, matched-group, cohort studies, or an RCT performed in a representative population and with a masked outcome. Class II lacks the four criteria required in class I. Class III evidence indicates all other controlled trials, such as studies based on natural history, in which the outcome assessment is independent of the treatment. Class IV evidence includes uncontrolled studies, case reports, and consensus or expert opinion groups.

Recommendation Levels A–C or U.

Recommendation Level A indicates that the treatment is well established as being effective, ineffective, or even harmful in the population studied (requiring at least one convincing class I study or at least two consistent, convincing class II studies). Recommendation B designates treatment that *probably* is effective, ineffective, or harmful (requiring at least one convincing class II study or at least three consistent class III studies), and Recommendation C implies *possibly* is effective, ineffective, or harmful (requires at least two convincing and consistent class III studies). Finally, Recommendation U denotes data that, given current knowledge, are conflicting, unproven, or inadequate.

After establishing standards of evidence-based medicine, the primary purpose of most guidelines is to improve medical decision making. Other rationales for establishing guidelines include providing recommendations for patient management, developing standards to assess clinical practice, and keeping cost–benefit ratios at an acceptable level. In the two AAN/AES subcommittee articles, useful tables of the most common serious and nonserious side effects, drug–drug interactions, effects of comorbid conditions, and pharmacokinetic profiles of the seven AEDs are provided to help in clinical decision making.

As mentioned in the articles, ample evidence exists for the efficacy of most AEDs for the treatment of partial seizures, whereas the number of controlled trials on any AED is

significantly lower for the idiopathic forms of epilepsy. For juvenile myoclonic epilepsy, no RCT has evaluated efficacy for any AED, new or old. Furthermore, patients with generalized seizures, such as absence and myoclonic, may have seizure exacerbations if prescribed drugs recommended for partial-onset seizures (e.g., carbamazepine, phenytoin, tiagabine, and vigabatrin), emphasizing the need for research on patients with idiopathic epilepsies. Unfortunately, not even substantial head-to-head comparisons of the new drugs exist, for either monotherapy or adjunctive use. However, Cramer et al. compared the demographics in the RCTs of new AEDs and found the populations of refractory patients with partial seizures to be similar between groups (1,2).

Are the gains in efficacy great enough to justify the increased cost of the new AEDs? The AAN/AES guidelines did not address the issue of cost. However, the authors of a similar article, the National Institute of Clinical Excellence (NICE) guidelines, published in the United Kingdom, concluded that the difference in efficacy between the older and newer drugs is not significant (3). Consequently, in the absence of a compelling clinical justification, NICE guidelines recommend that the older drugs be used first.

How much trust and confidence can we place in the AAN/AES recommendations? Of concern is the method used by the committee to analyze individual trials. Various factors (e.g., calculations of statistical power, length of observation time) can influence results or change the statistical significance of a study. Of special concern are the monotherapy studies reviewed by the subcommittee. In these studies, drugs are compared, and the outcomes sometimes are reported as not being statistically different. Yet if a study is designed to compare efficacy of two AEDs and is underpowered, a finding of no significant difference between the drugs does not necessarily mean that no difference exists. The AAN/AES authors determined the outcomes of such studies by consensus, without disclosing specific details of their decision-making procedure. In addition,

responder rate (i.e., the percentage of patients with a 50% seizure reduction) is often the main outcome measure used for studies on patients with refractory seizures. Not all the studies in the AAN/AES report provide responder rates. Further evidence-based research will be required to evaluate the importance of these guidelines.

The AAN/AES recommendations were published in two journals, *Epilepsia* and *Neurology*. In addition, the guidelines can be found in their entirety on several Internet sites (4). An advantage to website accessibility is the ability to update findings regularly. Physicians, particularly primary care doctors less familiar with AEDs, will need to be provided with brief treatment algorithms. Guidelines should be available for and understandable by all physicians, not just neurologists.

Regardless of the overall recommendations found in the AAN/AES report, patient individuality is most important and determines the choice of drug, regardless of recommendations or guidelines. Pertinent factors, such as expense, availability, ease of use, and severity of condition, can vary considerably among patients. The guidelines must be used in combination with the skill, knowledge, and experience of the treating physician. There are really no shortcuts.

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References

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