CME

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

J.A. French, MD*; A.M. Kanner, MD†; J. Bautista, MD; B. Abou-Khalil, MD; T. Browne, MD;
C.L. Harden, MD; W.H. Theodore, MD; C. Bazil, MD, PhD; J. Stern, MD; S.C. Schachter, MD;
D. Bergen, MD; D. Hirtz, MD; G.D. Montouris, MD; M. Nespeca, MD; B. Gidal, PharmD;
W.J. Marks, Jr., MD; W.R. Turk, MD; J.H. Fischer, MD; B. Bourgeois, MD; A. Wilner, MD;
R.E. Faught, Jr., MD; R.C. Sachdeo, MD; A. Beydoun, MD; and T.A. Glauser, MD

Abstract—*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 are also 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 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.

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Mission statement. The Quality Standards and the Therapeutics and Technology Assessment Subcommittees of the American Academy of Neurology are charged with developing practice parameters for neurologists for diagnostic procedures, treatment modalities, and clinical disorders. The selection of topics for which practice parameters are used is based on prevalence, frequency of use, economic impact, membership involvement, controversy, urgency, external constraints, and resources required. This practice parameter summarizes the results of the evidence-based assessment regarding the efficacy, tolerability, and safety of seven new antiepileptic drugs in the management of refractory epilepsy. They are gabapentin (Neurontin), lamotrigine (Lamictal), topiramate (Topamax), tiagabine (Gabitril), oxcarbazepine (Trileptal), levetiracetam (Keppra), and zonisamide (Zonegran). These antiepileptic drugs were approved by the Food and Drug Administration in the last 10 years. We recognize that these drugs are not antiepileptic but antiseizure drugs. However, we chose to use the term antiepileptic drugs, given its widespread use among all clinicians.

Background and justification. Almost 2 million people in the United States have epilepsy; in developed countries the age-adjusted incidence ranges from 24 to 53 per 100,000 individuals.[1,2] Between 70 and 80% of individuals are successfully treated with one of the more than 20 antiepileptic drugs (AED) now available with success rates primarily depending on the etiology of the seizure disorder. However, 20 to 30% of patients have either intractable or uncontrolled seizures or have significant adverse side effects secondary to medication. In the last 10 years, felbamate and the seven AEDs cited above were approved by the Food and Drug Administration (FDA). The purpose of this assessment is to provide clinicians with evidence-based data on the efficacy, safety, and mode of use of these seven new AEDs, 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.

The working group has elected to address seven of the eight new AEDs approved after 1990, as felbamate was addressed in a previous parameter.[3] There were several reasons for this decision. First, we felt that the newer AEDs, less familiar to the practicing physician, were the cause of the most practice variance and confusion. Secondly, the evidence available on the use of the older AEDs is vast, and the majority consists of case reports, case series, and other class IV evidence. The new generation of AED was developed in the era of randomized clinical trials, and development was guided by more rigorous FDA requirements. We felt that these data would more likely lead to supportable evidence-based recommendations.

This parameter reviews the available evidence on efficacy, tolerability, and safety profiles of the new AEDs in refractory epilepsy. We review the AEDs in

the chronological order in which they were approved by the FDA. Unfortunately, there is no class I evidence comparing the new AEDs to the old, or the new AEDs to each other in patients with refractory epilepsy. Therefore, selection of the appropriate drug for a given individual must be based on understanding of each drug's pharmacology, side effect profile, and risks.

There is no unifying definition of refractory epilepsy. Often, patients are referred to as refractory or treatment resistant when they have failed three or more AEDs. Studies of AEDs are performed in more limited populations, usually for issues related to clinical trial conduct. Each section will include a brief description of the parameters of specific study populations.

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.

Description of the analytical process. 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.

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

Table 1 *Definitions for classification of evidence*

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 cross-overs 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 well-defined 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.

trials and case reports. All relevant articles were included, for a total of 82.

Data of each AED were reviewed by three panel members (a different group for each drug). The panelists classified each article as class I through IV (table 1). Disagreements on article classification were resolved by discussion and consensus.

Panel selection. The panel was comprised of a group of general neurologists, pediatric neurologists, epileptologists, and doctors in pharmacy (PharmD) with experience in pharmacokinetic properties of AEDs. Members did not review a given 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).

Partial epilepsy. Partial epilepsy is defined as an acquired, localization-related (focal) epilepsy, characterized by simple partial, complex partial, and secondary generalized tonic-clonic convulsions (GTCC). It can begin in childhood or adulthood.

Adults. Question 1: What is the evidence that the new AEDs are effective in refractory partial epilepsy as adjunctive therapy? In the development of new AEDs, antiepileptic efficacy is initially established in patients with refractory epilepsy, that is, patients whose seizures have persisted after multiple "effective" pharmacologic trials. Although inclusion criteria for these studies usually only require that the patient has failed three or more AEDs, and is experiencing three to four seizures/month, the average

number of failed AEDs is often eight or more, and the median baseline seizure frequency is typically 8 to 10/month. Accordingly, in these patients, efficacy is established by a "significantly" greater reduction in seizure frequency compared to a placebo as represented either by the percentage of patients with >50% seizure reduction (also known as responder rate) or median reduction of each type of seizure. Some studies may report the percent of patients who became seizure-free during the trial. This figure, however, does not represent the likelihood of patients remaining seizure-free over a long-term period.

Gabapentin. There were four studies with class I evidence that evaluated the efficacy of gabapentin in patients with intractable partial seizures.[4-7] Doses tested ranged from 600 mg/day to 1,800 mg/day. In three of these studies,[2-4] a responder rate was reported and ranged between 8.4% and 26.4%, with the highest dose (1,800 mg/day) yielding higher responder rates. Only the fourth study reported a 56% median reduction in seizure frequency (compared to placebo) at a gabapentin dose of 1,200 mg/day.[7] Gabapentin's discontinuation rate because of adverse events ranged between 3 and 11.5% in these studies. The most frequent adverse events included somnolence, dizziness, and fatigue. In a study with class I evidence, initiation at 900 mg/day in 1 day was more likely to cause adverse events (dizziness) than a 3-day titration.[8] Less frequent side effects included a higher occurrence of weight gain relative to placebo.[5] This adverse event was reported as well in open trials. Review of adverse events in open trials and case reports revealed involuntary move-

ments presenting as myoclonus,[9] choreoathetosis,[10-12] and incontinence of bowel and bladder.[13]

No significant changes in serum levels of concomitant AEDs were identified in these studies, demonstrating the lack of interaction between gabapentin and other AEDs. Blood levels of gabapentin were measured, but no therapeutic range was identified.

Lamotrigine. Three studies with class I evidence were identified.[14-16] In two of these studies, lamotrigine or placebo were added to a drug regimen with only enzyme-inducing AED.[14,15] In the third study, patients on an enzyme-inducing AED and valproic acid were also included, although the maximal dose for patients on valproic acid was titrated to 50% of the dose taken by patients on enzyme inducing AEDs only.[16] One study[14] compared placebo to two doses of lamotrigine: 300 mg/day and 500 mg/day; the responder rate was 18%, 20%, and 34%, respectively, and the median seizure reduction was 8%, 20%, and 36%, respectively. The discontinuation rate because of adverse events was 1.4% for patients on placebo and 4.2% and 14% for patients on 300 mg and 500 mg/day, respectively.

The other two studies compared placebo to 300 mg/day (or 150 mg/day if also on valproic acid)[16] and 400 mg/day.[15] The 50% responder rate ranged between 20 and 22% (versus 0% in the placebo arms). In one of these studies,[15] the discontinuation rate due to adverse events was 1% for patients on placebo and 5% for those on lamotrigine. No patient was discontinued from the other study.[16] The five most frequent adverse events in these three studies included ataxia, dizziness, diplopia, somnolence, and headache. In one study[12] the adverse events were more prevalent among patients on carbamazepine. The incidence of rash ranged between 6% and 10% among patients on placebo and 10% and 17% for patients on lamotrigine. Patients randomized to lamotrigine were started at a higher dose (100 mg/day) than the 50 mg/day recommended today for enzyme-induced patients. Additional adverse events reported in these three studies and in other open add-on trials included vomiting and tremor.

Topiramate. There were eight articles with class I evidence that assessed the efficacy of topiramate for refractory partial seizures as add-on therapy.[17-24] The target doses in these studies ranged between 200 mg/day and 800 mg/day. The 50% responder rate ranged from 27% at doses of 200 mg/day to 50.6% at mean doses of 450 mg/day. Two studies compared the efficacy of three different doses of topiramate. One study[19] that compared placebo to 200, 400, and 600 mg/day showed a significant difference between the responder rate at 200 mg/day (27%) and 400 mg/day (49%), but the latter failed to differ with the responder rate at 600 mg/day (48%). The second study[20] confirmed this observation, as the responder rate at doses of 600, 800, and 1,000 mg/day failed to differ significantly, and these were similar to those reported at 400 mg/day in the previously cited study.

In a separate study comparing the efficacy of 600 mg/day to placebo,[22] the 50% responder rate of patients on topiramate was 47.8% (versus 13% for placebo). In general, doses of 400 mg/day and higher did not appear to yield significant differences in 50% responder rate in these studies. A study with class I evidence[25] demonstrated that there were fewer dose-related side effects with a slower titration (initiation at 50 mg and 50 mg increments) than at higher titration rates (100 mg initiation, and 100 mg/week). Discontinuation from these studies related to adverse event occurrence ranged from 8% to 26% in the topiramate arm versus 0 to 7% in the placebo arm. In one of the two studies that compared efficacy and tolerance at three different doses of topiramate (200 mg/day, 400 mg/day, and 600 mg/day), a discontinuation rate of 4% was reported at a dose of 200 mg/day, 9% at 400 mg/day, and 13% at 600 mg/day.[19] In the second study that compared placebo, 600, 800, and 1,000 mg/day, discontinuation rates were higher than in the previous study: 21% at 600 mg/day, 10.5% at 800 mg/day, and 17% at 1,000 mg/day.

The more common adverse events reported in these studies included somnolence, fatigue, nausea, anorexia and weight loss, paresthesias, psychomotor slowing and confusion, dizziness, and headache. Other adverse events reported in these and other open add-on trials and case reports of patients with refractory partial seizure disorders included renal calculi, emotional liability, nervousness, anxiety, behavioral disturbances, and word finding difficulty.

Tiagabine. There were two studies with class I evidence[26,27] and one study with class II evidence[28] that evaluated the efficacy of tiagabine as add-on therapy in the management of intractable partial seizure disorders. The doses tested in these studies ranged from 16 to 56 mg/day. The 50% responder rates ranged from 20% to 36% and the median seizure reduction ranged from 12% to 36%; the higher responder rates were obtained among patients treated with higher doses. While the half-life of tiagabine ranges from 4 to 8 hours, one study[26] showed no difference in responder rates between patients taking their dose on a BID and QID regimen. In these three studies, the discontinuation rate related to adverse events ranged between 8% and 20% among patients on active drug and 8 and 9% among patients taking placebo. The five most frequent adverse events identified in these three studies included dizziness, tremor, abnormal thinking, nervousness, and abdominal pain. Additional adverse events identified in these and other open trials included tremor, nonconvulsive status epilepticus (absence stupor), emotional lability, vomiting, tiredness, headache, and psychosis. One study with class II evidence[29] showed with neuropsychometric tests that add-on tiagabine regimens were not associated with changes in cognitive functions.

Oxcarbazepine. To date there has been one large study with class I evidence that evaluated the efficacy of oxcarbazepine in adults with refractory partial epilepsy as add-on therapy.[30] In this study, the

efficacy of three doses of oxcarbazepine (600 mg/day, 1,200 mg/day, and 2,400 mg/day) were compared among themselves and to a placebo arm in 694 patients aged 15 to 65. The 50% responder rate was 12.7% for the placebo group versus 26.8% for patients on 600 mg/day, 41.2% for patients on 1,200 mg/day, and 50% for those on 2,400 mg/day. The median reduction in seizure frequency was 6.8%, 22%, 40%, and 50%, respectively. The discontinuation rate was 3% among patients on placebo, 12% among patients on 1,200 mg, 36% among patients on 1,200 mg/day, and 67% among those on 2,400 mg/day. The most frequent adverse events included somnolence, dizziness, headache, ataxia, nausea, and vomiting. Other adverse events identified in this and other open trials included diplopia, blurred vision, vertigo, tremor, and hyponatremia.

Zonisamide. Two studies with class I evidence have been published to date: one study compared the efficacy of a 20 mg/kg dose (or a maximal blood level of 40 mg/L) to placebo,[31] and the second study compared efficacies of three different doses of zonisamide (100 mg/day, 200 mg/day, and 400 mg/day) to placebo.[32] In the first study, zonisamide's 50% responder rate was 30% and the placebo's was 9.4%. In the second study, zonisamide's 50% responder rate at both 100 mg/day and 200 mg/day was 25% (versus 9.8 and 11.3% for placebo) and at 400 mg/day the responder rate was 43% (versus 9% for placebo). The discontinuation rates of placebo and zonisamide were 10% each. The zonisamide serum concentrations of responders (>50% reduction) and nonresponders (<50% reduction) did not differ. The five most common adverse events were fatigue, dizziness, somnolence, anorexia, and abnormal thinking. Other adverse events identified in these and other open trials included renal calculi, rhinitis, rash, paranoia, and depression.

Levetiracetam. There have been three studies with class I evidence that have evaluated the efficacy of add-on levetiracetam in refractory partial epilepsy.[33-35] One of these also evaluated the impact of add-on levetiracetam on the quality of life of patients.[36] The doses tested in these studies ranged between 1,000 and 3,000 mg/day. Doses of 1,000 mg/day yielded a responder rate ranging from 22 to 33%, the 2,000 mg/day dose yielded responder rates of 31 and 34%, and the 3,000 mg/day dose, rates of 39.8%, compared to a range of 10 to 17% in placebo groups from different studies. Seizure free rates were also reported, appeared to be dose-related, and reached a maximum of 8% at the highest dose of 3,000 mg. Discontinuation rates related to adverse events ranged between 7 and 13% among patients on active drug and 5 to 8% on placebo. There was no relationship between discontinuation rate and dose. In one study where patients were initiated on 2,000 mg or 4,000 mg without a titration, there was a significantly higher rate of somnolence and asthenia at 4,000 mg, but the discontinuation rate due to adverse events was not higher.[37] The five most frequent

adverse events included dizziness, somnolence, asthenia, headache, and infection. Other adverse events in these and other open trials have included behavioral problems, depression, and psychosis.

Conclusion. All of the drugs have demonstrated efficacy as add-on therapy in patients with refractory partial epilepsy. Even though the methodology was similar for all studies, it is not possible to determine relative efficacy from comparison of outcomes, because populations differed (as evidenced by differing placebo responder rates), and some drugs were not used in maximum doses, whereas others appear to have been administered above ideal dose, as evidenced by high dropout and side effect rates. For essentially all drugs, efficacy as well as side effects increased with increasing doses. In all cases where two different titration rates were compared, the slower titration was better tolerated. Therefore, it would seem advisable to start low and go slow, using increasing doses until side effects occur (in other words, push to maximum tolerated dose).

Summary of evidence: Partial seizures in adults. Gabapentin (600 to 1,800 mg), lamotrigine (300 mg to 500 mg in enzyme-induced patients, and 150 mg/day in patients receiving enzyme inducers and valproic acid), levetiracetam (1,000 to 3,000 mg), oxcarbazepine (600 to 2,400 mg), tiagabine (16 to 56 mg), topiramate (300 to 1,000 mg), and zonisamide (100 to 400 mg) are effective in reducing seizure frequency as adjunctive therapy in patients with refractory partial seizures.

Gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, and zonisamide are more effective at higher doses. The evidence for a dose response for levetiracetam is less clear, but more patients were seizure free at 3,000 mg than 1,000 mg. Side effects and dropouts due to side effects also increase in a dose-dependent manner for all these drugs.

Oxcarbazepine, when administered at the titration rate used in the add-on trial (which is the rate recommended in the package insert), has a particularly marked dose-related toxicity. At the highest dose used, 67% of patients dropped out, most in the first few weeks of therapy.

Slower initiation/titration reduces side effects for gabapentin and topiramate. This may be true for the other AED as well, but no class I or II evidence is available to support this.

Recommendation. It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy (Level A) (table 2).*

Question 2: What is the evidence that the new AEDs are effective as monotherapy in patients with refractory partial epilepsy? Several trial designs have been devised to demonstrate effectiveness of a

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

Table 2 *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

* 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.

new drug as monotherapy in refractory epilepsy, without subjecting patients to undue risk. Because placebo cannot be used, some of these designs use what has been called a pseudoplacebo arm. Patients in this arm receive some treatment to prevent catastrophic seizures or severe worsening, but not enough to prevent the complex partial seizures that are being evaluated in the study. Typically, either a low dose of sodium valproate or a very low dose of the study drug is used for this purpose. The trial ends after subjects have experienced a prespecified number or type of seizures ("failures") or have completed the trial without that exit criterion having occurred ("completers"). Analysis is based on how many completers there are in the placebo/pseudoplacebo group compared with the treatment group. These trials can be performed on inpatients undergoing presurgical evaluation or outpatients. Presurgical studies are very short (8 to 10 days in duration). Outpatient studies last up to 6 months, but there are questions regarding applicability of results from these trials to clinical practice. These trials serve primarily a regulatory function; the FDA requires that there be a demonstration of superiority over a control arm. Because the majority of patients (typically over 80%) exit the pseudoplacebo arm due to worsening, a drug can be determined to be effective even if over half of patients worsen during conversion to monotherapy. For the purpose of this parameter, we downgraded studies in which more than half the patients could not complete the trial, either due to seizure worsening or side effects, in an intent to treat analysis.

Because these studies used fixed predetermined dosages, it is impossible to determine the optimal dose for effective seizure control.

The population for these studies is similar in seizure frequency and number of drugs failed to the refractory population used in add-on studies.

Gabapentin. There were two studies with class I evidence that evaluated the efficacy of gabapentin monotherapy for intractable partial seizure disorders.[38,39] One study[38] compared 300 to 3,600 mg/day. The study included intractable inpatients undergoing video-EEG monitoring who were off other AED. Time to exit in the course of an 8-day period was the outcome variable. The median time to exit was longer (151 versus 85 hours) for the higher gabapentin dose ($p = 0.0001$). The percentage of completers was also higher in the 3,600 mg group ($p = 0.002$).

In the second study,[39] 275 outpatients were randomized to one of three gabapentin monotherapy regimens at doses of 600, 1,200, and 2,400 mg/day, as part of a conversion from polytherapy to monotherapy gabapentin. Only 20% of patients completed the study. There was no difference in time to exit among the three dosage groups. Only 3% of patients were discontinued because of adverse events. The adverse events identified in the two monotherapy trials were similar to those identified in add-on trials.

Lamotrigine. One study with class I evidence has been published to date[40] comparing lamotrigine to low dose valproic acid. Patients on phenytoin or immediate release formulation of carbamazepine monotherapy were randomly switched to either lamotrigine (500 mg/day dose) or valproic acid (1,000 mg/day) monotherapy. The outcome variables consisted of the proportion of patients in each treatment group meeting exit criteria any time during concomitant AED withdrawal or the 3-month monotherapy maintenance. Exit criteria included a doubling of baseline seizure frequency, doubling of the highest 2-day consecutive seizure rate, emergence of a new more severe seizure type, or prolongation of the duration of generalized tonic-clonic seizures. Fifty-six percent of evaluable patients on lamotrigine completed the study versus 20% of patients on valproic acid, but in an intent-to-treat analysis, only 37% of the lamotrigine cohort completed the trial. The time to escape was significantly longer for patients on lamotrigine (median = 168 days) than valproic acid (median = 57 days). The discontinuation rate due to adverse events was 5% for patients on valproic acid

and 11% for patients on lamotrigine. Rash was reported by 8% of patients on valproic acid and 11% of patients on lamotrigine, although one of these patients had a Stevens Johnson syndrome. Of note, the titration rate was higher than the current recommendation. The five most frequent adverse events included dizziness, nausea, vomiting, dyspepsia, and abnormal coordination.

This study established efficacy of lamotrigine in a monotherapy regimen, but its findings may not help guide the clinician on the steps to take when converting patients from polytherapy to monotherapy. Also, because only patients on enzyme-inducing AED regimens were enrolled, no evidence-based data are available on conversion from valproic acid or regimens including non-enzyme-inducing AEDs.

Topiramate. There was one single-center study with class I evidence[41] that evaluated the efficacy of topiramate monotherapy for refractory partial seizures at two doses, 100 mg/day and 1,000 mg/day in 48 patients. Patients were required to convert to topiramate monotherapy at 100 mg. This was followed by randomization to high dose (1,000 mg/day) versus low dose (100 mg/day). The 50% responder rate was 13% in the 100 mg/day group, and 46% in the 1,000 mg group. Thirteen percent of the patients randomized to 1,000 mg of topiramate had 100% seizure reduction versus 0% of the 100 mg group. Furthermore, 62% of patients on 1,000 mg/day completed the study compared to only 25% of those on 100 mg/day. Time to exit was longer for the patients taking 1,000 mg/day ($p = 0.002$). An 8.3% discontinuation rate due to adverse events was recorded for patients on 1,000 mg/day and none for patients on 100 mg/day. The adverse events on monotherapy were similar but less frequent than those reported in add-on trials.

Oxcarbazepine. There were three studies with class I evidence[42-44] that evaluated the efficacy of oxcarbazepine monotherapy in patients with refractory partial epilepsy. In one study,[42] oxcarbazepine was compared to placebo in patients who had their AED withdrawn for presurgical evaluation. Eighty-four percent of the placebo patients exited the study versus 47% of those on oxcarbazepine during the 10-day trial. This trial is too short to demonstrate sustained efficacy in monotherapy. In the second study,[43] two doses of oxcarbazepine, 300 mg/day and 2,400 mg/day, were compared. Among the patients on the lower dose, 93.3% of patients exited the 126-day study compared to 41.2% on the higher dose. Twelve percent of the patients in the oxcarbazepine 2,400 mg/day group were seizure-free compared with none in the 300 mg/day group. In the third study,[44] the same two doses of oxcarbazepine, 300 mg/day and 2,400 mg/day, were compared. Patients on the lower dose had a median time to exit of 28 days, while those on the higher dose had a 68 days time to exit. The five most common adverse events were dizziness, sedation, nausea, diplopia, and fatigue. In the presurgical study,[42] 21.6% of patients developed hyponatremia versus 2% on placebo.

Levetiracetam. One study[35] evaluated the efficacy of levetiracetam monotherapy in patients with refractory partial seizure disorders. Although parts of the study were class I, the evidence for monotherapy efficacy is not readily interpretable. This study included patients who were "treatment responders" to either levetiracetam or placebo from an earlier phase of the study. Responders continued to receive levetiracetam 1,500 mg or placebo in a blinded fashion twice daily for 12 weeks, or until they exited due to prespecified criteria based on worsening. Significantly more levetiracetam than placebo patients completed the monotherapy phase, 42.1% versus 16.7% ($p < 0.001$). However, only 49 patients were treated with sustained monotherapy in the study. Due to the unusual trial design, this study, although intriguing, is not sufficient to prove effectiveness in monotherapy. The side effects in this trial did not differ from those observed in the add-on studies.

Conclusion. The studies performed to demonstrate effectiveness of new AEDs in monotherapy in refractory partial seizure patients are difficult to interpret, because they are driven by FDA requirements to show superiority over placebo or pseudoplacebo rather than by clinical questions. Dosages used in the trials are often higher than those that might be used in practice, because the goal is to retain as many patients as possible and achieve a significant result. Most importantly, the goal of these studies is not to determine whether patients improve after they are converted to monotherapy. Rather, the goal is to determine whether they deteriorate less than the comparison group.

Summary of evidence: Monotherapy for refractory partial epilepsy. Lamotrigine: 500 mg/day is superior to 1,000 mg/day of valproate (acting as a pseudoplacebo), and is therefore effective in monotherapy for refractory partial epilepsy.

Oxcarbazepine: 2,400 mg/day is superior to 300 mg/day, and is therefore effective in monotherapy for refractory partial epilepsy.

Topiramate 1,000 mg/day is superior to 100 mg/day, and is therefore effective in monotherapy for refractory partial epilepsy.

There is insufficient evidence at present to determine the efficacy of levetiracetam, tiagabine, or zonisamide in this population.

In one trial, gabapentin 1,200 mg and 2,400 mg were not more effective than a pseudoplacebo dose of 600 mg in this population. However, the data from this study are not sufficient to generate a recommendation for the use of gabapentin in monotherapy for refractory partial epilepsy in these patients.

Recommendations. 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) (table 2).

Generalized epilepsy. Generalized epilepsy syndromes are categorized as idiopathic or symptomatic. Idiopathic epilepsy, also called 1° generalized epilepsy, occurs on a presumed genetic basis, in the setting of normal brain structural architecture. Seizure types are limited to myoclonic seizures, generalized tonic-clonic convulsions, and absence (petit mal). Specific syndromes have been identified, based on presenting age and seizure type. Idiopathic generalized epilepsy is easily treated, but response to treatment is very drug specific; some drugs, such as valproic acid, are effective in over 80% of patients, whereas others, even those that are effective in partial seizures, may be ineffective. In contrast, symptomatic epilepsy, also called 2° generalized, is a devastating type of epilepsy in which developmental delay is typically present, and a structural abnormality is suspected or known. One of the more common symptomatic epilepsy syndromes is the Lennox-Gastaut syndrome, characterized by mental retardation, multiple seizure types, and characteristic EEG pattern of slow spike-wave. Because most trials of Lennox-Gastaut syndrome involve children and adults, results of trials for symptomatic generalized epilepsy are included in the pediatric section.

Evidence for effectiveness of the newer AED in the generalized epilepsy syndromes is not as readily available as evidence in the partial syndromes. Much of the available data are class IV.

Idiopathic generalized epilepsy in adults. Question 3: What is the evidence that the new AEDs are effective for the seizures seen in patients with refractory idiopathic generalized epilepsy? Gabapentin. There is one article with class I evidence that assessed the efficacy of gabapentin in refractory generalized tonic-clonic seizures in patients with primary or secondary generalized epilepsy.[45] Patients aged 12 and older with refractory generalized tonic-clonic convulsions were randomized to placebo or 1,200 mg of gabapentin. No significant difference was found. In retrospect, it is possible that the dose was too low. In addition, there is one article with class I evidence and 4 with class IV evidence that assessed efficacy in a "mixed" group of up to 361 generalized and partial epilepsy patients.[46-50] These articles cannot be used to assess efficacy in the generalized epilepsy syndromes, because the subgroups were not separable.

Lamotrigine. There was one class I article.[51] In this small crossover study, 50% of the participants, aged 15 to 50, had >50% decrease in generalized tonic clonic seizures, while 33% had >50% decrease for absence seizures. The discontinuation rate among patients on lamotrigine was 8% versus 0 for those on placebo. A rash was reported in 27% of patients on lamotrigine, and one was considered serious. Ataxia, diplopia, dizziness, and drowsiness were the other four more frequent adverse events. Titration rate was relatively rapid, as doses of 75 or 150 mg were achieved in 2 weeks.

Two studies with class II evidence and two studies with class IV evidence[52-55] evaluated treatment-resistant partial and generalized epilepsy. None had enough information to determine efficacy in the generalized patients separately.

Levetiracetam. There was one study with class I evidence[37] that evaluated the tolerability and efficacy of two doses of levetiracetam, 2,000 mg/day and 4,000 mg/day, in patients with partial and generalized epilepsies. Patients were initiated at these doses on day 1. Although the results were favorable, they were not significant because of the small number of patients with generalized epilepsy.

Oxcarbazepine. There was one study with class II evidence,[56] in which 48 patients were crossed over from immediate release formulation of carbamazepine to oxcarbazepine. Nine patients had only generalized epilepsy and 29 had partial and generalized epilepsy. Twenty-five patients had "decrease" in all seizures with oxcarbazepine compared to carbamazepine, while 17 had an increase. The adverse events on oxcarbazepine were similar to those described in previously cited studies.

Topiramate. There was one study with class I evidence[57] in adults and children over the age of 3 with refractory generalized tonic-clonic convulsions ± other seizure types. Patients were randomized to a target dose of approximately 6 mg/kg/day versus placebo. The 50% responder rate was 56% for topiramate compared to 20% for placebo. An open label class IV follow-up of the randomized trial demonstrated continued effectiveness of topiramate. Discontinuation rate due to adverse events was similar for topiramate (2.6%) and placebo (2.4%). The adverse events in this study were similar to those of the topiramate studies already cited above.

Ten class IV uncontrolled cohort studies or case series evaluated patients with both generalized and partial seizures.[58-67] No outcomes relevant to generalized seizures only can be assessed.

There were no studies of efficacy of tiagabine or zonisamide in idiopathic generalized epilepsy.

Conclusion. Trials for refractory generalized epilepsy have been criticized, due to the fact that not all patients were required to have an EEG demonstrating a generalized pattern. In most studies, patients could be included if they had a normal EEG. Therefore, it is possible that some of the enrolled patients actually had secondary generalized tonic-clonic convulsions.

Because most patients with idiopathic generalized epilepsy are easily controlled with appropriate medication, refractory patients are rare. It is unclear how results in this population would translate to patients with similar syndromes, but nonrefractory disease.

Summary of evidence: Refractory primary generalized epilepsy. Topiramate 6 mg/kg/day is effective for the treatment of refractory generalized tonic-clonic convulsions ± other seizure types.

Gabapentin 1,200 mg is not effective in refractory generalized tonic-clonic seizures in patients with primary or secondary generalized epilepsy.

Definitive studies have not been performed with the other new AED in this epilepsy type.

Recommendations. 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) (table 2).

Treatment of refractory epilepsy in children.
Question 4: What is the evidence that the new AEDs are effective in refractory partial epilepsy as adjunctive therapy in children? *Gabapentin.* There is one study with class I evidence[68] that evaluated the efficacy of gabapentin in 247 children whose age ranged between 3 and 12 years in a 12-week double-blind placebo-controlled trial. Gabapentin was titrated up to a dose of 23 to 35 mg/kg/day. The outcome variable in this study was the percentage change in frequency of complex partial and secondarily generalized tonic-clonic seizures. Children randomized to gabapentin had a median drop of 35% of complex partial and 28% of secondarily generalized tonic-clonic seizures, while those on placebo had a 12% median reduction and 13% increase, respectively. The discontinuation rate was 5% for children on gabapentin and 2% for those on placebo. The five most frequent adverse events were viral infection, fever, hostility, fatigue, and weight gain.

Lamotrigine. There is one study[69] with class I evidence that evaluated the efficacy of lamotrigine versus placebo in 199 children aged 2 to 16 years. The lamotrigine target doses varied according to the type of AED the child was taking at the time of randomization: 1 to 3 mg/kg in the presence of valproic acid only, 1 to 5 mg/kg if an enzyme inducing AED (phenytoin, carbamazepine, phenobarbital) in combination with valproic acid, and 5 to 15 mg/kg if the child was on enzyme inducing AED only. The responder rate was 45% among children randomized to lamotrigine and 25% for those on placebo. Children on lamotrigine had a significantly higher drop in weekly seizure frequency (44%) compared to those on placebo (12.8%). The discontinuation rate caused by adverse events was 5% for children on lamotrigine and 6% for those on placebo. The five most frequent adverse events included ataxia, dizziness, tremor, nausea, and asthenia. One patient had a severe rash presenting as Stevens Johnson syndrome.

Topiramate. There is one study with class I evidence that evaluated the efficacy of topiramate versus placebo in 86 children aged 2 to 16 years during a 16-week trial.[70] The topiramate dose was titrated to 125 to 400 mg/day, according to weight. Starting dose was 25 mg/day. The 50% responder rate was 39% for children on topiramate and 20% for those on placebo. Children on topiramate had a median reduction in seizures of 33% versus 10.5% for those on placebo. No child on topiramate and two children on placebo were discontinued from the study. The five most frequent adverse events included emotional lability, difficulty concentrating, fatigue, memory deficits, and weight loss. There were no cases of hypohidrosis in clinical trials. A case series has been published reporting three children, aged 17 months, 9 years, and 16 years, who developed hypohidrosis while receiving topiramate monotherapy.[71]

Oxcarbazepine. There is one study with class I evidence that evaluated the efficacy of oxcarbazepine in 267 children, aged 3 to 17 years, in a double-blind placebo controlled study.[72] The maximal doses of oxcarbazepine ranged between 30 and 46 mg/kg/day. A 50% responder rate of 41% was found among children on oxcarbazepine and 22% of children on placebo. A median reduction in seizure frequency of 35% was observed among children on oxcarbazepine versus 8.9% on placebo. The discontinuation rate related to adverse events was 10% for children on oxcarbazepine and 3% for those on placebo. The five most common adverse events were somnolence, headache, dizziness, vomiting, and nausea. Rash rates were 4% on oxcarbazepine and 5% on placebo.

Levetiracetam. There is one study with class IV evidence[73] that evaluated the efficacy of levetiracetam in 24 children in an open trial at a maximal dose of 40 mg/kg, titrated over a 6-week period. A responder rate of 52% was obtained. None of the children were discontinued from the study because of adverse events. The most frequent adverse events included somnolence, ataxia, headache, anorexia, and nervousness. Adverse events reported in other open trials have included behavioral problems, depression, and psychosis.

Zonisamide. No studies have specifically studied efficacy of zonisamide in pediatric patients with partial seizures. A single case has been reported of hypohidrosis caused by zonisamide.[74]

Question 5: What is the evidence that the new AEDs are effective as monotherapy in children with refractory partial seizures? No monotherapy trials have been performed in this population.

Conclusion. An NIH consensus conference held several years ago arrived at the conclusion that partial seizures in children are similar in pathophysiology to those in adults, and will probably respond to the same drugs.[75] To date, each AED tested as adjunctive therapy in children older than 2 years with refractory partial seizure has demonstrated the same efficacy as it did when examined as adjunctive therapy in adults with refractory partial seizures. These two considerations taken together suggest the possibility that once an AED has demonstrated efficacy as adjunctive therapy in refractory partial sei-

zures in adults, the AED will demonstrate the same efficacy as adjunctive therapy in children older than 2 years. However, trials in pediatric populations remain critically important to establish efficacy in this as well as other pediatric-specific epilepsy syndromes, to evaluate efficacy in children less than 2 years old, to determine specific safety issues in this population, and to characterize the dosing and pharmacokinetics in children. In addition, safety issues in the entire pediatric population need to be evaluated.

Summary of evidence: Refractory partial seizures— pediatric. Gabapentin (23 to 35 mg/kg/day), lamotrigine 1 to 5 mg/kg/day with enzyme inducers (1 to 3 mg/kg/day in regimens including valproate), oxcarbazepine 30 to 46 mg/kg/day, and topiramate 125 to 400 mg/day are effective in reducing seizure frequency as adjunctive therapy in children with refractory partial seizures. To date, there is a lack of class I or II evidence regarding the efficacy of levetiracetam, tiagabine, or zonisamide. Based on class III and IV evidence, there are specific safety concerns in children when using these drugs, specifically serious rash with lamotrigine, and hypohidrosis with zonisamide and topiramate.

Recommendations. 1. Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures (Level A) (table 2).

2. There is insufficient evidence to recommend levetiracetam, tiagabine, or zonisamide as adjunctive treatment of children with refractory partial seizures (Level U) (table 2).

Refractory idiopathic generalized epilepsy. *Question 6: What is the evidence that the new AEDs are effective 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.

Secondary generalized epilepsy or Lennox-Gastaut syndrome. Patients with the Lennox-Gastaut syndrome have many seizures/day, some of which, such as atypical absence, are difficult to count. Therefore, it is common to use reduction in drop attacks (tonic or atonic seizures) as the primary outcome variable. This is considered a clinically significant outcome, as drop attacks are one of the most dangerous seizure types, often leading to injuries.

Question 7: What is the evidence that the new AEDs are effective in children and/or adults with the Lennox-Gastaut syndrome? Gabapentin. There were no studies. One case series and one case report identified worsening of myoclonic seizures in this population when they were treated with gabapentin.[9,10,76]

Lamotrigine. One study with class I[77] and one with class II evidence[78] were identified. The class I study used doses that were stratified by weight and valproic acid use, and ranged from 50 to 100 mg for patients <25 kg on valproic acid to 300 to 400 mg for patients >25 kg not receiving valproic acid. These studies demonstrated 50% reduction in seizures in

33% of patients, compared to 16% on placebo. Discontinuation rates because of adverse events were comparable (5% for patients on lamotrigine and 6% for those on placebo). The incidence of rash was similar (16% among patients on lamotrigine and 18% in those on placebo). However, one pediatric patient in this study developed a Stevens-Johnson syndrome. The class II study, which included some patients with other types of generalized epilepsy, had an open phase followed by a double blind phase. Only 17 of the original 30 patients reached the double blind phase, in which a 60% responder rate was identified. The discontinuation rate due to adverse events was 4% and 8% among patients on lamotrigine and placebo, respectively. Rash was reported in 9% of patients on lamotrigine (in two patients it was considered serious) and 7% of patients on placebo.

One class IV study demonstrated efficacy in Lennox-Gastaut.[79] There is one case report of worsening of myoclonic jerks in a patient with 2° generalized epilepsy treated with lamotrigine.[80]

Topiramate. There was one study with class I evidence[81] and one class IV study[82] that evaluated the efficacy of topiramate as adjunctive therapy in the treatment of Lennox-Gastaut syndrome. The class I study[81] used a dose of 6 mg/kg/day. The topiramate group had a 14% reduction in drop attacks compared to a 5.1% increase in the placebo group, which was significant. This was the primary outcome variable. However, the 50% responder rate of 28% for total seizure frequency was not significant ($p = 0.071$). The class IV study, which was an open-label follow-up of the randomized placebo-controlled trial, examined the last 6 months of seizure frequency for each patient; the 50% responder rate was 55%, with a 56% median reduction in drop attacks.

There were no studies with class I or II evidence that have evaluated the efficacy of levetiracetam, oxcarbazepine, tiagabine, or zonisamide.

Conclusions. Patients with Lennox-Gastaut syndrome are difficult to treat, and require drugs that are broad spectrum. They are also the population that is most prone to exacerbation by AEDs. For example, carbamazepine has been reported to cause seizure worsening in this group. Topiramate and lamotrigine appear to be effective in this population and should be considered for use.

Summary of evidence: Secondary generalized epilepsy. Lamotrigine at doses adjusted for weight and valproic acid use, ranging from 50 to 400 mg/day, reduces seizures associated with the Lennox-Gastaut syndrome.

Topiramate 6 mg/kg/day is effective in reducing drop attacks (tonic and atonic seizures) in patients with the Lennox-Gastaut syndrome.

To date, there is no class I or II evidence that gabapentin, tiagabine, oxcarbazepine, levetiracetam, or zonisamide are effective.

In case reports lamotrigine and gabapentin both worsened myoclonic seizures in some patients.

Recommendations*: 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) (table 2).

What is the risk of teratogenicity with the new AEDs compared to the old AEDs? The FDA has categorized 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.

Recommendations for future research. To date, the only attempt at comparing the efficacy of new drugs in refractory patients has been performed via meta-analysis of the randomized placebo-controlled trials.[83] This method of comparing drugs is potentially flawed, as all doses studied were combined for the analysis. Therefore, dropout rates may appear higher for drugs that were studied at high doses (e.g., topiramate and oxcarbazepine), whereas efficacy may appear lower for drugs studied at low doses (e.g., gabapentin). In addition, the underlying presumption that the populations studied were similar may be flawed. Even when the same drug is studied in Europe and the United States, efficacy may appear different. There is a need for studies that compare the new drugs in a head-to-head fashion.

Add-on trials in refractory partial seizure patients are the mainstay of new AED approval. These are not ideal trials; they are of short duration, they enroll patients that are not representative of those seen in a neurologist's practice, and they often use titration schedules and doses that are ultimately found to be suboptimal. As a result, this practice parameter can determine that drugs are effective, but can provide little evidence-based data on titration, dosing, optimal serum levels, outcome in the more typical patients, and, most importantly, comparative safety and efficacy between drugs. Regulatory studies must be supplemented with controlled trials that investigate optimal clinical use. Comparison studies should be performed, similar to the VA cooperative studies of the 1980s that randomized newly diagnosed patients to one of four available drugs, titrated to optimal doses, and followed them for years. Ideally, both old and new AEDs would be compared. In addition, extended release formulations should be used when available.

Most of the studies presented in this practice parameter use seizure reduction as a primary outcome measure. In a way, this could be considered a surrogate marker for disease improvement. A 50% reduction in seizures, the commonly used benchmark of improvement, may not substantially improve a patient's function or quality of life. Also, a simple seizure count may not capture improvements in seizure severity or pattern (such as conversion from diurnal to nocturnal events). To date, available quality of life batteries are not sensitive to improvement as a result of treatment changes. This may be because to some degree they measure handicap, a relatively fixed parameter that results from having epilepsy, rather than disability. New scales should be developed that are better at assessing improvement beyond seizure reduction.

Most of the class I and II studies of new AEDs are performed either in patients with partial seizures or those with Lennox-Gastaut syndrome. Almost all the studies performed in patients with idiopathic generalized epilepsy, such as absence and juvenile myoclonic epilepsy, have been uncontrolled case series. More controlled studies are needed for this patient population.

Monotherapy trials remain a complex and contentious issue in regards to new AEDs. Several questions remain unanswered, including the following: Is it necessary to perform monotherapy trials for AEDs, or does effectiveness as add-on therapy indicate de facto that the drug will be effective as monotherapy? If monotherapy studies are needed, are they needed both in patients with refractory and newly diagnosed epilepsy? Which is more clinically and scientifically valid: a study comparing a drug to a pseudoplacebo, or an active control comparison design?

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. 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.

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* NB: In a previous AAN parameter, felbamate was recommended in "Lennox-Gastaut patients over age 4 unresponsive to primary AEDs."[3]

References

1. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. Epilepsia 1993; 34:453–468.
2. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia 1991;32:429–445.
3. French J, Smith M, Faught E, Brown L. Practice Advisory: The use of felbamate in the treatment of patients with intractable epilepsy—Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 1999; 52:1540–1545 and Epilepsia 1999;40:803–808.
4. Anhut H, Ashman P, Feuerstein TJ, et al. Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. The International Gabapentin Study Group. Epilepsia 1999;35:795–801.
5. UK Gabapentin Study Group. Gabapentin in partial epilepsy. Lancet 1990;335:1114–1117.
6. The US Gabapentin Study Group No. 5. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. Neurology 1993;43:2292–2298.
7. Sivenius J, Kalviainen R, Ylinen A, Riekkinen P. Double-blind study of gabapentin in the treatment of partial seizures. Epilepsia 1991;32:539–542.
8. Fisher RS, Sachdeo RC, Pellock J, et al. Rapid initiation of gabapentin: a randomized, controlled trial. Neurology 2001;56:743–748.
9. Asconape J, Diedrich A, DellaBadia J. Myoclonus associated with the use of gabapentin. Epilepsia 2000;41:479–481.
10. Buetefisch CM, Gutierrez A, Gutmann L. Choreoathetotic movements: a possible side effect of gabapentin. Neurology 1996;46:851–852.
11. Reeves AL, So EL, Sharbrough FW, Krahn LE. Movement disorders associated with the use of gabapentin. Epilepsia 1996;37:988–990.
12. Norton JW, Quarles E. Gabapentin-related dyskinesia. J Clin Psychopharmacol 2001;21:623–624.
13. Gil-Nagel A, Gapany S, Blesi K, Villanueva N, Bergen D. Incontinence during treatment with gabapentin. Neurology 1997;48:1467–1468.
14. Matsuo F, Bergen D, Faught E, et al. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. US Lamotrigine Protocol 05 Clinical Trial Group. Neurology 1993;43:2284–2291.
15. Messenheimer J, Ramsay RE, Willmore LJ, et al. Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. Epilepsia 1994;35:113–121.
16. Schapel GJ, Beran RG, Vajda FJ, et al. Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures. J Neurol Neurosurg Psychiatry 1993;56:448–453.
17. Korean Topiramate Study Group. Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. Epilepsia 1999;40:1767–1774.
18. Ben-Menachem E, Henrisksen O, Dam M, et al. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. Epilepsia 1996;37:539–543.
19. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group. Neurology 1996;46:1684–1690.
20. Privitera M, Fincham R, Penry J, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000 mg daily dosages. Topiramate YE Study Group. Neurology 1996; 46:1678–1683.
21. Sharief M, Viteri C, Ben-Menachem E, et al. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. Epilepsy Res 1996;25:217–224.
22. Tassinari CA, Michelucci R, Chauvel P, et al. Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. Epilepsia 1996;37:763–768.
23. Yen DJ, Yu HY, Guo YC, et al. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. Epilepsia 2000;41:1162–1166.
24. Wang Y, Zhou D, Pauli E, Stefan H. Topiramate on ictal seizure semiology: a quantitative, randomized, low and medium dose-controlled study. Epilepsy Res 2001;46:271–277.
25. Biton V, Edwards KR, Montouris GD, et al. Topiramate titration and tolerability. Ann Pharmacother 2001;35:173–179.
26. Sachdeo RC, Leroy RF, Krauss GL, et al. Tiagabine therapy for complex partial seizures. A dose-frequency study. The Tiagabine Study Group. Arch Neurol 1997;54:595–601.
27. Uthman BM, Rowan AJ, Ahmann PA, et al. Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. Arch Neurol 1998;55:56–62.
28. Richens A, Chadwick DW, Duncan JS, et al. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. Epilepsy Res 1993;21:37–42.
29. Dodrill CB, Arnett JL, Sommerville KW, Shu V. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. Neurology 1997;48:1025–1031.
30. Barcs G, Walker EG, Elger CE, et al. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia 2000;41: 1597–1607.
31. Schmidt D, Jacob R, Loiseau P, et al. Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial. Epilepsy Res 1993;15:67–73.
32. Faught E, Ayala R, Montouris GG, et al. Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures. Neurology 2001;57:1774–1779.
33. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. Neurology 2000;55:236–242.
34. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. Epilepsia 2000;41:1179–1186.
35. Ben-Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia 2000;41:1276–1283.
36. Cramer JA, Arrigo C, Van Hammee G, Gauer LJ, Cereghino JJ. Effect of levetiracetam on epilepsy-related quality of life. N132 Study Group. Epilepsia 2000;41:868–874.
37. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. Seizure 2000;9: 80–87.
38. Bergey GK, Morris HH, Rosenfeld W, et al. Gabapentin monotherapy: I. An 8-day, double-blind, dose-controlled, multicenter study in hospitalized patients with refractory complex partial or secondarily generalized seizures. The US Gabapentin Study Group 88/89. Neurology 1997;49: 739–745.
39. Beydoun A, Fischer J, Labar DR, et al. Gabapentin monotherapy: II. A 26-week, double-blind, dose-controlled, multicenter study of conversion from polytherapy in outpatients with refractory complex partial or secondarily generalized seizures. The US Gabapentin Study Group 82/83. Neurology 1997;49:746–752.
40. Gilliam F, Vazquez B, Sackellares JC, et al. An active-control trial of lamotrigine monotherapy for partial seizures. Neurology 1998;51:1018–1025.
41. Sachdeo RC, Reife RA, Lim P, Pledger G. Topiramate monotherapy for partial onset seizures. Epilepsia 1997;38:294–300.
42. Schachter SC, Vazquez B, Fisher RS, et al. Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures. Neurology 1999;52:732–737.
43. Beydoun A, Sachdeo RC, Rosenfeld WE, et al. Oxcarbazepine monotherapy for partial-onset seizures: a multicenter, double-blind, clinical trial. Neurology 2000;54:2245–2251.
44. Sachdeo R, Beydoun A, Schachter S, et al. Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. Neurology 2001;57: 864–871.
45. Chadwick D, Leiderman DB, Sauermann W, Alexander J, Garofalo E. Gabapentin in generalized seizures. Epilepsy Res 1996;25:191–197.
46. Bhaumik S, Branford D, Duggirala C, Ismail IA. A naturalistic study of the use of vigabatrin, lamotrigine and gabapentin in adults with learning disabilities. Seizure 1997;6:127–133.
47. Crawford P, Ghadiali E, Lane R, Blumhardt L, Chadwick D. Gabapentin as an antiepileptic drug in man. J Neurol Neurosurg Psychiatry 1987;50:682–686.
48. Langan Y, Duncan JS, Sander JW. An audit of the perceived efficacy and tolerability of gabapentin therapy in an out-patient cohort with chronic epilepsy. Eur Neurol 1999;41:111–113.
49. Thisj RD, Kerr MP. The outcome of prescribing novel anticonvulsants in an outpatient setting: factors affecting response to medication. Seizure 1998;7:379–383.
50. Wong IC, Chadwick DW, Fenwick PB, Mawer GE, Sander JW. The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy. Epilepsia 1999;40:1439–1445.
51. Beran RG, Berkovic SF, Dunagan FM, et al. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy. Epilepsia 1998;39:1329–1333.
52. Boas J, Dam M, Friis ML, et al. Controlled trial of lamotrigine (Lamictal) for treatment-resistant partial seizures. Acta Neurol Scand 1996; 94:247–252.
53. Marciani MG, Spanedda F, Bassetti MA, et al. Effect of lamotrigine on EEG paroxysmal abnormalities and background activity: a computerized analysis. Br J Clin Pharmacol 1996;42:621–627.
54. Sander JW, Patsalos PN, Oxley JR, Hamilton MJ, Yuen WC. A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. Epilepsy Res 1990;6:221–226.
55. Trenite DG, Rentmeester TW, Scholtes FB, et al. Perimarketing surveillance of lamotrigine in The Netherlands: doctors' and patients' viewpoints. Pharm World Sci 2001;23:1–5.

56. Houtkooper MA, Lammertsma A, Meyer JW, et al. Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? Epilepsia 1987;28:693–698.
57. Biton V, Montouris GD, Ritter F, et al. A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group. Neurology 1999;52:1330–1337.
58. Crawford P. An audit of topiramate use in a general neurology clinic. Seizure 1998;7:207–211.
59. Dooley JM, Camfield PR, Smith E, Langevin P, Ronen G. Topiramate in intractable childhood onset epilepsy: a cautionary note. Can J Neurol Sci 1999;26:271–273.
60. Tatum WO, French JA, Faught E, et al. Postmarketing experience with topiramate and cognition. Epilepsia 2001;42:1134–1140.
61. Abou-Khalil B. Topiramate in the long-term management of refractory epilepsy. Topiramate YOL Study Group. Epilepsia 2000;41:S72–76.
62. Lhatoo SD, Wong IC, Sander JW. Prognostic factors affecting long-term retention of topiramate in patients with chronic epilepsy. Epilepsia 2000;41:338–341.
63. Tartara A, Sartori I, Manni R, et al. Efficacy and safety of topiramate in refractory epilepsy: a long-term prospective trial. Ital J Neurol Sci 1996;17:429–432.
64. Baker GA, Currie NG, Light MJ, et al. The effects of adjunctive topiramate therapy on seizure severity and health-related quality of life in patients with refractory epilepsy: a Canadian study. Seizure 2002;11:6–15.
65. Singh BK, White-Scott S. Role of topiramate in adults with intractable epilepsy, mental retardation, and developmental disabilities. Seizure 2002;11:47–50.
66. Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Topiramate in patients with learning disability and refractory epilepsy. Epilepsia 2002;43:399–402.
67. Kellett MW, Smith DF, Stockton PA, Chadwick DW. Topiramate in clinical practice: first year's postlicensing experience in a specialist epilepsy clinic. J Neurol Neurosurg Psychiatry 1999;66:759–763.
68. Appleton R, Fichtner K, LaMoreaux L, et al. Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. Gabapentin Paediatric Study Group. Epilepsia 1999;40:1147–1154.
69. Duchowny M, Pellock JM, Graf WD, et al. A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Lamictal Pediatric Partial Seizure Study Group. Neurology 1999;53:1724–1731.
70. Elterman RD, Glauser TA, Wyllie E, et al. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. Neurology 1999;52:1338–1344.
71. Arcas J, Ferrer T, Roche MC, et al. Hypohidrosis related to the administration of topiramate to children. Epilepsia 2001;42:1363–1365.
72. Glauser TA, Nigro M, Sachdeo R, et al. Adjunctive therapy with oxcarbazepine in children with partial seizures: The Oxcarbazepine Pediatric Study Group. Neurology 2000;54:2237–2244.
73. Glauser TA, Pellock JM, Bebin M, et al. Efficacy and safety of levetiracetam in children with partial seizures: an open trial. Epilepsia 2002;43:518–524.
74. Shimizu T, Yamashita Y, Satoi M, et al. Heat stroke-like episode in a child caused by zonisamide. Brain Dev 1997;19:366–368.
75. Sheridan, PH, Jacobs MP. The development of antiepileptic drugs for children. Report from the NIH workshop, Bethesda, Md, Feb 17–18, 1994. Epilepsy Res 1996;23:87–92.
76. Vossler DG. Exacerbation of seizures in Lennox-Gastaut syndrome by gabapentin. Neurology 1996;46:852–853.
77. Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. N Engl J Med 1997;337:1807–1812.
78. Eriksson AS, Nergardh A, Hoppu K. The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study. Epilepsia 1998;39:495–501.
79. Donaldson JA, Glauser TA, Olberding LS. Lamotrigine adjunctive therapy in childhood epileptic encephalopathy (the Lennox Gastaut syndrome). Epilepsia 1997;38:68–73.
80. Janszky J, Rasonyi G, Halasz P, et al. Disabling erratic myoclonus during lamotrigine therapy with high serum level—report of two cases. Clin Neuropharmacol 2000;23:86–89.
81. Sachdeo RC, Glauser TA, Ritter F, et al. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group. Neurology 1999;52:1882–1887.
82. Glauser TA, Levisohn PM, Ritter F, Sachdeo RC. Topiramate in Lennox-Gastaut syndrome: open-label treatment of patients completing a randomized controlled trial. Topiramate YL Study Group. Epilepsia 2000;41:S86–90.
83. Marson AG, Kadir ZA, Chadwick DW. New antiepileptic drugs: a systematic review of their efficacy and tolerability. BMJ 1996;313:1169–1174.

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