

CME

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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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—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. **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 either from 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. There is also evidence 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 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 new onset partial or generalized 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 are antiseizure and not antiepileptic drugs. Nevertheless, we have decided to use in this assessment the term antiepileptic drugs, given its widespread use.

Background and justification. Almost 2 million people in the United States have epilepsy. A large epidemiologic study of Rochester, MN, showed an age-adjusted epilepsy prevalence of 6.8/1,000 population, and the cumulative incidence through age 74 was 3.1%.^{1,2} In the last 10 years, felbamate and seven antiepileptic drugs (AEDs) (gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide) were approved by the Food and Drug Administration (FDA). The purpose of this assessment is to provide the clinician with evidence-based data on the efficacy, safety, and mode of use of these new 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 development of new AEDs for epilepsy over the last decade has been spurred by the fact that the available AEDs did not provide optimal care for patients with epilepsy. Many patients "failed" all available options, either because their seizures were not adequately controlled, or they were experiencing side effects. Prior to 1990, six major AEDs were available for the treatment of all forms of epilepsy. These included carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, and for absence seizures ethosuximide. The older drugs, while effective in patients with newly diagnosed epilepsy, share some characteristics. For example, older AEDs as a class have complex pharmacokinetics. Four of the six AEDs available prior to 1990 (phenytoin, carbamazepine, phenobarbital, and primidone) are hepatic enzyme inducers. Induction not only complicates combination AED therapy but also changes internal hormonal milieu in possibly important ways. Intrinsic compounds, such as sex steroids and vitamin D,

are hypermetabolized. This can lead to reproductive dysfunction and osteopenia.³ Enzyme-inducing AEDs produce important interactions with many commonly used medications, such as warfarin, oral contraceptives, calcium channel antagonists, and chemotherapeutic agents, to name a few.⁴ Valproic acid, in contrast, is a potent hepatic inhibitor. There is controversy about the impact of valproic acid on the hormonal milieu,^{5,6} and inhibition leads to important drug interactions with AED as well as other classes. The newer agents are involved in many fewer drug interactions. Many of the newer agents have little, if any, effect on the CYP450 enzyme system and other metabolic pathways.

Tables 1 through 4 provide a listing of serious and nonserious adverse events, common drug-drug interactions, effect of comorbid conditions, and pharmacokinetics for the drugs discussed in this parameter.

Recent studies^{7,8} have indicated that patients with newly diagnosed epilepsy can be categorized into those who are treatment responsive or treatment resistant. In fact, approximately two thirds of patients will become seizure free with the first or second drug administered. In recent studies, these treatment-responsive patients responded to low doses of essentially all the AEDs studied, both old and new. Although this information can be interpreted as an indication that no new drugs are needed in this patient group, another completely different conclusion can be arrived at. Because these patients will remain on the initial or second therapy for several years, and because they will respond to most drugs, the burden is on the treating physician to select the AED that is the most tolerable, has the lowest potential for harm, and has the least likelihood of negatively impacting quality of life. At the same time, there must be evidence from valid, well-controlled trials that the drugs are equally as effective as the older medications. The older AEDs have an advantage of broad familiarity, lower cost, known efficacy, wide availability via coverage by third party payers, and long-term experience. This parameter will review the available evidence on efficacy, tolerability, and safety profiles of the new AEDs in newly diagnosed adults and children with epilepsy. The AEDs are discussed in the order in which they received approval by the FDA. Among these seven new AEDs, the FDA has so far approved oxcarbazepine for the treatment of new-onset partial epilepsy.

Description of the analytical process. 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

Table 1 Serious and nonserious adverse events associated with the new AEDs

AED	Serious adverse events	Nonserious adverse events
Gabapentin	None	Weight gain, peripheral edema, behavioral changes*
Lamotrigine	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, DIC, and arthritis	Tics* and insomnia
Levetiracetam	None	Irritability/behavior change
Oxcarbazepine	Hyponatremia (more common in elderly), rash	None
Tiagabine	Stupor or spike wave stupor	Weakness
Topiramate	Nephrolithiasis, open angle glaucoma, hypohidrosis*	Metabolic acidosis, weight loss, language dysfunction
Zonisamide	Rash, renal calculi, hypohidrosis*	Irritability, photosensitivity, weight loss

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.

* Predominantly children.

AED = antiepileptic drug; DIC = disseminated intravascular coagulation.

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 AEDs unless they describe relevant idiosyncratic reactions or safety concerns, and articles on basic AED mechanisms.

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.

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 trials and case reports.

Data for each AED were reviewed by three panel members, with a different group assembled for each drug. These three panelists classified each article as class I through IV (table 5). 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 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 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).

Newly diagnosed epilepsy in adults and adolescents. Most studies of newly diagnosed epilepsy are conducted in patients with both partial and generalized seizures, and therefore these will not be discussed separately unless there are specific data on the individual groups. The majority of these studies defined newly diagnosed epilepsy as two or more untreated seizures. Many compared a new AED with an older AED. This is the only available comparative evidence of new AEDs versus old. Studies of new AED efficacy in the newly diagnosed epilepsy population are typically performed as active-control comparison studies, due to the potential risk to subjects inherent in a placebo-controlled monotherapy trial. These studies differ in their methodology; some study newly diagnosed patients, some focus on newly

Table 2 Common drug-drug interactions associated with the new AEDs⁴

AED	Oral contraceptives	Warfarin	Other agents	Enzyme inducer?	Enzyme inhibitor?	Clinical notes
Gabapentin	(-)	(-)	Modest decrease in gabapentin bioavailability with Maalox-TC	(-)	(-)	No known interactions with other AEDs
Lamotrigine	(+) Decrease in lamotrigine serum concentrations by oral contraceptives	(-)		(+/-)	(-)	Modest induction of glucuronidation with slight decrease in valproic acid plasma levels (25%) noted; interactions with cytochrome p450 isozymes not seen
Levetiracetam	(-)	(-)		(-)	(-)	No known interactions with other AEDs
Topiramate	(+) Dose dependent (>200 mg/d) decrease in ethinyl estradiol serum concentrations	(-)	Modest increase in haloperidol serum concentrations; modest decrease in lithium serum concentrations; modest decrease in digoxin serum concentrations	(+/-)	(+)	Modest, dose-dependent induction of CYP 3A4 may reduce effectiveness of oral contraceptives; inhibition of CYP 2C19 may result in increases in phenytoin plasma concentrations
Tiagabine	(-)	(-)	No interaction seen with erythromycin	(-)	(-)	Potential for protein binding displacement (clinical relevance unclear)
Oxcarbazepine	(+) Decrease in ethinyl estradiol serum concentrations	(-)	Modest decrease in felodipine serum concentration; modest decrease in MHD concentrations following verapamil administration; no interaction seen with erythromycin	(+/-)	(+)	Modest, dose-dependent induction of CYP 3A4; possible induction of glucuronidation, with reduced plasma concentrations of lamotrigine noted; inhibition of CYP 2C19 may result in increased phenytoin or phenobarbital plasma concentrations
Zonisamide	(-)	(-)		(-)	(-)	Clearance may be increased by enzyme-inducing AEDs

This is not meant to be a comprehensive list but represents the most common interactions, based on consensus of panel. There are no data on the interactions of new AEDs with many of the non-AED drugs. Future research may identify pharmacokinetic or pharmacodynamic interactions between new AEDs that are metabolized and non-AED drugs, that could result in adverse events.

AED = antiepileptic drug; MHD = monohydroxy derivative (metabolite of oxcarbazepine).

treated patients, and the number of seizures prior to entry may differ. Primary outcome variables differ as well and include endpoints such as time to exit, time to first seizure, and percentage of patients rendered seizure free. All of these factors can influence response to monotherapy and complicate comparison between studies. Therefore, while it appears valid to accept comparisons within a given trial, it is not valid to compare percent completers in one trial versus another to determine the most effective drug in newly diagnosed patients. The studies in general are not powered to rule out superiority of one drug over the other. In order to determine equivalence, very large studies enrolling 500 to 1,000 patients would be required, whereas the studies that were performed typically recruited only 200 to 300 patients. This smaller sample size would lead to confidence intervals that would not exclude a small difference. Furthermore, among all the studies on new onset epilepsy, there was no study that compared the efficacy and safety of the new AEDs among each other.

Question 1: How does the efficacy and tolerability of the new AEDs compare with that of older AEDs in patients with newly diagnosed epilepsy?

Gabapentin. One study with class I evidence⁹ compared the safety and efficacy of three different blinded doses of gabapentin (300 mg/day, 900 mg/day, and 1,800 mg/day) in monotherapy to that of an open label fixed dose of immediate release carbamazepine (600 mg/day) in the treatment of 275 adolescents and adults newly diagnosed with partial or generalized epilepsy. Gabapentin was titrated to its maximal dose in 1 week and carbamazepine in 3 weeks. Patients exited the study if they experienced a total of three simple or complex partial seizures, one generalized tonic-clonic seizure, or status epilepticus. Time to exit was longer for gabapentin at 1,800 mg/day than at the 300 mg/day dose. There was no difference in the percentage of patients that completed the study among the gabapentin 900 mg/day and 1,800 mg/day groups and the carbamazepine group. Discontinuation rate due to adverse events

Table 3 Comparative pharmacokinetic parameters for new AEDs⁴

AED	Protein binding, %	Elimination T _{1/2} , h	Site of elimination	Clinical notes
Gabapentin	0	4–6	Renal, 100%	Displays dose dependent absorption
Lamotrigine	55	15–30	Hepatic, 90%	Clearance (via glucuronidation) increased by enzyme-inducing AEDs, reduced by VPA; metabolites inactive
Topiramate	9–17	15–23	Renal, 40–70%	Fraction hepatically metabolized; increased by enzyme-inducing AEDs; metabolites inactive
Levetiracetam	0	6–8	Renal, 66%; hydrolysis of acetamide group, 34%	Metabolism is nonhepatic; metabolites inactive
Oxcarbazepine	40	4–9	Hepatic, 70%	Based upon 10 hydroxy carbamazepine (MHD), the major, active metabolite
Tiagabine	96	4–7	Hepatic, 98%	Oxidative metabolism to inactive metabolites
Zonisamide	40–60	24–60	Hepatic, 70%	Clearance increased by enzyme-inducing AEDs

AED = antiepileptic drug; VPA = valproic acid; MHD = monohydroxy derivative.

was higher among patients on carbamazepine (24%) than those on the higher dose of gabapentin (13.5%). Dizziness, fatigue, and somnolence were significantly more frequent among patients on carbamazepine than gabapentin.

Lamotrigine. Three studies with class I evidence evaluated patients with newly diagnosed idiopathic generalized and partial epilepsy.^{10–12}

One study¹¹ compared the efficacy and safety of lamotrigine and immediate release formulation of carbamazepine in 146 patients with new onset partial seizure disorders and in 122 patients with idiopathic generalized epilepsy. Age range was 13 to 81 years. Seventy-three patients with partial seizure disorders were randomized to lamotrigine and 73 to carbamazepine. Among the patients with idiopathic generalized epilepsy, 60 were randomized to lamotrigine and 62 to carbamazepine. Lamotrigine was started at a dose of 50 mg/day and was titrated up to 150 mg/day over 4 weeks, while carbamazepine was started at 200 mg/day and titrated up to 600 mg/day during the same period. During the last 24 weeks of therapy the doses of lamotrigine and carbamazepine

could be increased by 50 mg and 200 mg, respectively, in case of persistent seizures. Among patients with partial seizure disorders, 48% of patients on lamotrigine and 51% of those on carbamazepine remained seizure-free during the last 24 weeks of therapy. Among patients with idiopathic generalized epilepsy, 78% of those on lamotrigine and 76% of those on carbamazepine remained seizure-free. The discontinuation rate was significantly higher among patients on carbamazepine (21%) than lamotrigine (11.5%). The incidence of rash was higher among patients on carbamazepine (13%) than lamotrigine (9%), but this difference did not reach significance.

In a second study,¹⁰ the efficacy and safety of lamotrigine were compared among 150 elderly patients (mean age 77 years) with newly diagnosed epilepsy. In this study, lamotrigine was started at a dose of 25 mg/day for the first 2 weeks and immediate release formulation of carbamazepine at a dose of 100 mg/day. By the end of the sixth week, patients on lamotrigine took 100 mg/day and those on carbamazepine were treated with 400 mg/day. From week 7 to 24, the doses could be adjusted to maximal doses of 500 mg/day of lamotrigine and 2,000 mg/day of carbamazepine. There was no difference in seizure efficacy between the two drugs. However, a significantly higher number of patients on carbamazepine (42%) had to be discontinued from the study because of adverse events (versus 18% for lamotrigine). Furthermore, more patients on carbamazepine were discontinued from the study because of rash (19%) than those on lamotrigine (3%).

In the third study,¹² 86 patients were randomized to lamotrigine and 95 to phenytoin. Seizure freedom during the last 24 weeks of therapy was the outcome variable. There was no difference in seizure control between these two drugs, with 43% of patients on lamotrigine and 36% on phenytoin remaining seizure free. Among patients with newly diagnosed partial epilepsy, 44 were randomized to lamotrigine and 46 to phenytoin. There was no difference in seizure-free rate during the last 24 weeks of therapy between

Table 4 Effect of comorbid condition or its treatment on the adverse effects or pharmacokinetics of AEDs

Effects	Older AED	Newer AED
Metabolic disorder may increase risk of hepatotoxicity	VPA	—
Increased risk of hyponatremia	CBZ	OXC
Measurable increase in free fraction with hypoalbuminemia	PHT VPA	—
Metabolism affected by renal disease	PB	GBP, LEV, TPM
Metabolism affected by liver disease	CBZ, PHT, VPA	LTG, ZNS, OXC, TGB

AED = antiepileptic drug; VPA = valproic acid; CBZ = carbamazepine; OXC = oxcarbazepine; PHT = phenytoin; PB = phenobarbital; GBP = gabapentin; LEV = levetiracetam; TPM = topiramate; ZNS = zonisamide; TGB = tiagabine.

Table 5 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 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
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	
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.

the two drugs (45% for lamotrigine and 46% for phenytoin). The discontinuation rate related to adverse events, 15% for lamotrigine and 19% for phenytoin, did not differ either. However, rash accounted for 12% of the patients on lamotrigine discontinued from the study, while only 5% of patients on phenytoin discontinued because of rash. Altogether, 14% of patients on lamotrigine and 9% of those on phenytoin had a rash. The starting dose of lamotrigine in this study was 100 mg/day, which is four times higher than the recommended starting dose today. Patients on phenytoin had a significantly higher incidence of asthenia (29% versus 16%), somnolence (28% versus 7%), and ataxia (11% versus 0).

Topiramate. There are two class I studies on the use of topiramate in new or recently diagnosed partial or generalized epilepsy.^{13,14} The first compared the safety and efficacy of 50 mg of topiramate (25 mg if weight < 50 kg) versus 500 mg (200 mg if weight < 50 kg) in 252 patients aged 3 to 65 with new or recently diagnosed partial epilepsy.¹³ Patients had to have experienced one to six partial onset seizures in the 3-month baseline period. Patients exited the study if they experienced two partial onset seizures, a generalized tonic-clonic seizure if they had no his-

tory of that seizure type, or status epilepticus. The two treatment arms did not differ on the primary outcome variable, which was time to exit, although there was a significant difference in time to second seizure when time to first seizure was used as a simultaneous variable. The second study¹⁴ compared the safety and efficacy of topiramate at doses of 100 mg/day and 200 mg/day, valproate at 1,250 mg/day, and carbamazepine at 600 mg/day in 613 adult and pediatric patients, aged 6 years or older, with newly diagnosed partial and primary generalized epilepsy. Outcome variables included time to first seizure after randomization, time to exit due to lack of efficacy or adverse events, and proportion of seizure-free patients for the last 6 months of treatment. There were no statistical differences in any of the outcome variables between the four treatment groups. The discontinuation rates due to adverse events were 19% and 28% for patients in the 100 mg/day and 200 mg/day topiramate arms, respectively, 23% for those on valproate, and 25% for those on carbamazepine.

Oxcarbazepine. Three studies have class I and one has class II evidence that compared the efficacy and safety of oxcarbazepine to that of an older AED (phenytoin, immediate release formulation of car-

bamazepine, or valproic acid) in adolescents and adults with newly diagnosed partial seizures and idiopathic generalized epilepsy.¹⁵⁻¹⁸

The first study¹⁵ randomized 287 patients to oxcarbazepine or phenytoin. An 8-week flexible titration period yielded oxcarbazepine doses from 600 to 2,100 mg/day (n = 143) and phenytoin at doses ranging between 100 and 560 mg/day (n = 144). A total of 182 patients had a partial seizure disorder and 104 had primary generalized tonic-clonic seizures. There were no differences in seizure control between the treatment groups, with 59.3% and 58% remaining seizure-free, respectively, during a 48-week maintenance period. The rate of discontinuation because of adverse events was significantly higher among patients on phenytoin.

The second study¹⁶ compared the efficacy of oxcarbazepine (600 mg to 2,400 mg/day) and valproic acid (600 to 2,700 mg/day) in 154 patients with partial seizures and 95 patients with primary generalized tonic-clonic seizures. The variable doses were reached during an 8-week flexible titration period. A total of 56.6% in the oxcarbazepine group and 53.8% in the valproic acid group remained seizure free during the maintenance period. There were no differences between the two drugs with respect to early discontinuation from the study because of adverse events.

The third study¹⁷ compared the efficacy of oxcarbazepine to that of immediate release formulation of carbamazepine in 190 patients with primary generalized tonic-clonic seizures or with secondarily generalized tonic-clonic seizures. A 4 to 8 week flexible titration period yielded oxcarbazepine doses ranging from 300 to 1,800 mg/day and carbamazepine doses ranging from 300 to 1,400 mg/day. Sixty percent of patients on carbamazepine and 52% on oxcarbazepine remained seizure free. The discontinuation rate due to adverse events was significantly higher among patients on carbamazepine (26%) than oxcarbazepine (14%).

The last study¹⁸ compared the efficacy of oxcarbazepine to phenytoin in 193 children and adolescents aged 5 to 18 years with newly diagnosed partial seizures (n = 151) or primary generalized tonic-clonic seizures (n = 39). An 8-week flexible titration period yielded oxcarbazepine doses ranging from 100 to 1,350 mg/day and phenytoin doses ranging from 100 to 400 mg/day. As in the other studies, the two drugs failed to differ in efficacy, with 61% and 60% of patients on oxcarbazepine and phenytoin, respectively, remaining seizure free during the maintenance period. The discontinuation rate was significantly higher for patients on phenytoin (14.5% versus 2%).

Conclusion. Many of these studies resulted in the finding that two drugs were "equivalent" in their ability to control seizures. There is a great deal of controversy surrounding this outcome. The FDA does not accept such a finding as proof of efficacy, due to the possibility that two ineffective drugs might also exhibit no difference in effect when compared

against one another. For the purpose of this parameter, we accepted the demonstration of equivalence between an established AED such as carbamazepine or phenytoin and a new drug as confirmation of effectiveness.

These studies are able to demonstrate that the new AEDs may be better tolerated than the standard, with equivalent efficacy. However, they cannot speak to the importance of other differences between old and new AEDs, such as simpler pharmacokinetics, absence of apparent disturbance of the hormonal milieu, better safety, and the need for less laboratory monitoring. It is difficult to make such comparisons in an evidence-based fashion. The new drugs are all substantially more expensive than the old. There is no literature that addresses the cost-benefit related to these issues.

Summary of findings. Efficacy in newly diagnosed patients. Gabapentin is effective in the treatment of newly diagnosed partial epilepsy. Lamotrigine, topiramate, and oxcarbazepine are effective in a mixed population of newly diagnosed partial and generalized tonic-clonic seizures. There are insufficient data to make a recommendation for the syndromes individually.

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

Comparison to standard AED. Oxcarbazepine is equivalent to carbamazepine and phenytoin in efficacy, but superior in dose-related tolerability, at individually determined doses. Oxcarbazepine is equivalent in efficacy and tolerability to valproic acid. Topiramate at doses of 100 and 200 mg/day was equivalent in efficacy and safety to 600 mg fixed dose carbamazepine and 1,250 mg/day valproic acid, both in children aged 6 years and older and adults. Lamotrigine is equivalent in efficacy to carbamazepine and phenytoin and superior in tolerability to carbamazepine, both in adults and elderly individuals. Topiramate at 100 mg and 200 mg is equivalent in efficacy and safety to 600 mg of fixed-dose, immediate-release carbamazepine administered in a BID regimen for partial seizures and to 1,250 mg of fixed-dose valproic acid for idiopathic generalized seizures.

Gabapentin is effective in monotherapy at 900 and 1,800 mg and is equivalent in efficacy to a 600 mg fixed dose of carbamazepine. Nine hundred milligrams of gabapentin is better tolerated than 600 mg fixed-dose, short-acting carbamazepine administered in a BID schedule.

Recommendation. 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).

Question 2: What is the evidence that the new AEDs are effective in adults or children with primary or secondary generalized epilepsy?

Lamotrigine. There was one study with class II evidence¹⁹ that evaluated the efficacy of lamotrigine under double-blind, placebo-controlled conditions in 45 children with newly diagnosed absence seizures. Following an open phase trial with lamotrigine (up to 2 to 15 mg/kg/day), 29 patients became seizure free. These 29 patients were then randomized to remain on lamotrigine or placebo. During the 4-week study, 64% of children on lamotrigine remained seizure free versus 21% of children on placebo. None of the children on lamotrigine or placebo were discontinued from the study. One child on lamotrigine had a mild rash. The most frequent adverse events included abdominal pain, headache, nausea, anorexia, and dizziness.

Gabapentin. There is one study with class I evidence²⁰ that evaluated the efficacy of gabapentin monotherapy in 33 children aged 4 to 12 years with newly diagnosed absence seizures in a double-blind, placebo-controlled study of 4 weeks' duration. Children were randomized to gabapentin at doses of 19 mg/kg/day (achieved in 2 days) or placebo. There was no difference in seizure frequency between children on gabapentin and placebo. None of the children were discontinued from the study. Somnolence and dizziness were the two most frequent adverse events.

There are no studies in newly diagnosed patients that assess the efficacy of oxcarbazepine, topiramate, tiagabine, levetiracetam, or zonisamide in children with exclusively idiopathic or symptomatic generalized epilepsy.

There are no studies of any new AED that assess efficacy/tolerability in adults with newly diagnosed epilepsy with exclusively idiopathic or symptomatic generalized epilepsy.

Conclusions. Lamotrigine is effective in children with newly diagnosed absence seizures.

Summary of findings. Lamotrigine is effective in the treatment of children with newly diagnosed absence seizures. At present, there is insufficient evidence to determine effectiveness in newly diagnosed primary or secondary generalized epilepsy for topiramate, oxcarbazepine, tiagabine, zonisamide, or levetiracetam.

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

Recommendations for future research. There is no doubt that the ideal methodology for detecting drug effect in most cases is to use a placebo control comparison. However, because trials in patients with newly diagnosed epilepsy must be performed, by definition, in the monotherapy condition, there are ethical concerns regarding a placebo or substandard control in this population.²¹ Therefore, comparative

Table 6 Summary of 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.

trials, while methodologically difficult, remain the preferred tactic. Clinicians favor this trial design, because it mimics clinical care, and provides useful information. Because patients are appropriately treated in both arms, often with the ability to adjust dose as necessary, trials can be conducted over long periods of time (up to 2 years), and outcome measures can be used that resonate with clinicians, such as percent of patients remaining seizure free. As noted above, these trials are not acceptable for registration purposes in the United States, as the FDA has required demonstration of superiority. In order to demonstrate superiority, often different doses (low versus high) of the test drug are employed, or in some cases placebo has been used as the comparator arm. Because the patients in the low dose/placebo arm may be undertreated, trials tend to be shorter, and outcome measures not as relevant to practice. In addition, by definition, dose adjustment is not possible. Most importantly, the absence of a comparison to a standard drug makes the outcome difficult to interpret. Discussion is ongoing as to how to resolve this conflict between the needs of the clinician and the needs of regulatory bodies. Table 6 includes information regarding the difference between the recommendations in this guideline and FDA approved indications for the drugs addressed in this parameter at the time of its publication.

There is an urgent need for standardization of trial design and inclusion criteria in active control comparison trials in newly diagnosed patients, where selection of a more stable population could increase the likelihood of a “no difference” outcome, even where a difference actually exists. Similarly, selection of different trial durations and outcome variables can increase the impact of dropouts due to side effects, or bias the outcome in other ways. Selection of standardized design would even the playing field for all drugs. Studies should be powered to demonstrate true noninferiority.

No trials have been executed in newly diagnosed patients with any idiopathic generalized syndrome

other than absence epilepsy. Comparative trials should be performed in patients with idiopathic generalized tonic-clonic seizures and juvenile myoclonic epilepsy, who urgently need more AED options.

Whereas new AEDs may have some desirable characteristics, they are much more expensive than standard drugs. Future research using economic decision analysis would help to determine whether the potential benefits are worth the additional cost. This would include studies on the clinical importance of hepatic enzyme induction, changes in hormonal milieu, and long-term side effects. Finally, future studies should use extended release formulations whenever possible.

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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Appendix

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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. Practice parameter: management issues for women with epilepsy (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1998;51:944–948.
4. Patsalos PN, Froscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. *Epilepsia* 2002;43:365–385.
5. Isojarvi I, Rattya J, Myllyla V, et al. Valproate, lamotrigine, and insulin-mediated risks in women with epilepsy. *Ann Neurol* 1998;43:446–451.
6. Morrell MJ, Giudice L, Flynn KL, et al. Predictors of ovulatory failure in women with epilepsy. *Ann Neurol* 2002;52:704–711.
7. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001;42:1255–1260.
8. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
9. Chadwick DW, Anhut H, Greiner MJ, et al. A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945–77. *Neurology* 1998;51:1282–1288.
10. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res* 1999;37:81–87.
11. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet* 1995;345:476–479.
12. Steiner TJ, Dellaportas CL, Findley LJ, et al. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia* 1999;40:601–607.
13. Gilliam FG, Veloso F, Bomhof MAM, et al., and the Topiramate EPMN 104 Study Group. A dose-comparison trial of topiramate as monotherapy in recently diagnosed partial epilepsy. *Neurology* 2003;60:196–201.
14. Privitera MD, Brodie MJ, Mattson RH, Chadwick DW, Neto W, Wang S. Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy. *Acta Neurol Scand* 2003;107:165–175.
15. Bill PA, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997;27:195–204.
16. Christie W, Kramer G, Vigonius U, et al. A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997;26:451–460.
17. Dam M, Ekberg R, Loyning Y, et al. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;3:70–76.
18. Guerreiro MM, Vigonius U, Pohlmann H, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997;27:205–213.
19. Frank LM, Enlow T, Holmes GL, et al. Lamictal (lamotrigine) monotherapy for typical absence seizure in children. *Epilepsia* 1999;40:973–979.
20. Trudeau V, Myers S, LaMoreaux L, et al. Gabapentin in naïve childhood absence epilepsy: results from two double-blind, placebo-controlled, multicenter studies. *J Child Neurol* 1996;11:470–475.
21. Karlawish JHT, French J. Issues in drug study design: the ethical and scientific shortcomings of current monotherapy epilepsy trials in newly diagnosed patients. *Epilepsy Behavior* 2001;2:193–200.

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