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Efficacy and Tolerability of the New Antiepileptic Drugs, II: Treatment of Refractory Epilepsy: Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society

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Summary: *Purpose:* To assess the evidence demonstrating efficacy, tolerability, and safety of seven new antiepileptic drugs (AEDs) [gabapentin (GBP), lamotrigine (LTG), topiramate (TPM), tiagabine (TGB), oxcarbazepine (OXC), levetiracetam (LEV), and zonisamide (ZNS)] 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 to March 2003.

Results: All of the new AEDs were found to be appropriate for adjunctive treatment of refractory partial seizures in adults. GBP can be effective for the treatment of mixed seizure disorders, and GBP, LTG, OXC, and TPM for the treatment of refractory partial seizures in children. Limited evidence suggests that LTG and TPM also are effective for adjunctive treatment of idiopathic generalized epilepsy in adults and children, as well as treatment of the Lennox–Gastaut syndrome.

Conclusions: The choice of AED depends on seizure and/or syndrome type, patient age, concomitant medications, and AED tolerability, safety, and efficacy. The results of this evidence-based assessment provide guidelines for the prescription of AEDs for patients with refractory epilepsy and identify those seizure types and syndromes for which more evidence is necessary.

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MISSION STATEMENT

The Quality Standards and the Therapeutics and Technology 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" (AEDs) in the management of refractory epilepsy. They are gabapentin (GBP; Neurontin), lamotrigine (LTG; Lamictal), topiramate (TPM; Topamax), tiagabine (TGB; Gabitril), oxcarbazepine (OXC; Trileptal), levetiracetam (LEV; Keppra), and zonisamide (ZNS; Zonegran). These AEDs were approved by the Food and Drug Administration (FDA) in the last 10 years. We recognize that these drugs are not antiepileptic but antiseizure drugs. However, we chose to use the term AED, 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 >20 AEDs 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 (FBM) and the seven AEDs cited earlier 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 refractory partial seizure disorders, primary generalized epilepsy, and the Lennox–Gastaut syndrome in adults and children.

The working group has elected to address seven of the eight new AEDs approved after 1990, as FBM was addressed in a previous parameter (3). Of the several reasons for this decision, first, we thought that the newer AEDs, less familiar to the practicing physician, were the cause of the most practice variance and confusion. Second, 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 AEDs was developed in the era of randomized clinical trials, and development was guided by more rigorous FDA requirements. We believed 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 chronologic order in which they were approved by the FDA. Unfortunately, no class I evidence compares the new AEDs with the old, or the new AEDs with 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.

No unifying definition of refractory epilepsy exists. Often, patients are referred to as refractory or treatment resistant when three or more AEDs have "failed." Studies of AEDs are performed in more limited populations, usually for issues related to clinical-trial conduct. Each section includes 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 ANALYTIC 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 through 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 papers that included the terms *epilepsy* and one of the following: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide (a) relevant to the clinical questions of efficacy, safety, tolerability, mode of use; (b) human subjects only; (c) types of studies: randomized controlled trials, cohort, case–control, observational, and case series; and (d) all languages for randomized controlled trials not available in English.

Exclusion criteria: (a) reviews and meta-analyses; (b) articles related to nonepilepsy uses of AEDs unless they describe relevant idiosyncratic reactions or safety concerns; and (c) articles on basic AED mechanisms.

A total of 1,462 articles was identified: 240 of GBP, 433 of LTG, 244 of TPM, 17 of LEV, 212 of OXC, 177 of TGB, and 146 of ZNS. Among these, data were extracted for classification of evidence class from 353 articles: 91 of GBP, 63 of LTG, 65 of TPM, 46 of TGB, 45 of OXC,

33 of ZNS, and 11 of LEV. 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 patients. Safety data also were derived from open 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 (see Appendix 1). Disagreements on article classification were resolved by discussion and consensus.

Panel selection

The panel comprised a group of general neurologists, pediatric neurologists, epileptologists, and doctors in pharmacy (Pharm.D.) 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 (stocks, ownership).

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 (GTCCs). It can begin in childhood or in adult years.

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 require only that three or more AEDs have failed in the patient, and the patient has three to four seizures/month, the average number of failed AEDs is often eight or more, and the median baseline seizure frequency is typically eight to 10/month. Accordingly, in these patients, efficacy is established by a "significantly" greater reduction in seizure frequency, compared with 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 percentage 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

Four studies had class I evidence evaluating the efficacy of GBP 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 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 with placebo) at a GBP dose of 1,200 mg/day (7). The discontinuation rate of GBP 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 was 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 movements such 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 GBP and other AEDs. Blood levels of GBP were measured, but no therapeutic range was identified.

Lamotrigine

Three studies with class I evidence were identified (14–16). In two of these studies, LTG or placebo was added to a drug regimen with only enzyme-inducing AEDs (14,15). In the third study, patients taking an enzyme-inducing AED and valproic acid (VPA) also were included, although the maximal dose for patients taking VPA was titrated to 50% of the dose taken by patients taking enzyme-inducing AEDs only (16). One study (14) compared placebo with two doses of LTG: 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 taking placebo and 4.2% and 14% for patients taking 300 and 500 mg/day, respectively.

The other two studies compared placebo with 300 mg/day (or 150 mg/day if also taking VPA) (16) and 400 mg/day (15). The 50% responder rate ranged between 20 and 22% (vs. none in the placebo arms). In one of these studies (15), the discontinuation rate due to adverse events was 1% for patients taking placebo and 5% for those taking LTG. 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 taking CBZ. The incidence of rash ranged between 6 and 10% among patients taking placebo and 10 and 17% for patients taking LTG.

TABLE 1. *Summary of AAN evidence-based guidelines level A or B recommendation for use*

	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[a]	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

[a]Not FDA approved for this indication.

Patients randomized to LTG 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

Eight articles had class I evidence that assessed the efficacy of TPM for refractory partial seizures as add-on therapy (17–24). The target doses in these studies ranged between 200 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 TPM. One study (19) that compared placebo with 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 from 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 with placebo (22), the 50% responder rate of patients taking TPM was 47.8% (vs. 13% for placebo). In general, doses of $\geq$400 mg/day did not appear to yield significant differences in 50% responder rate in these studies. A study with class I evidence (25) demonstrated that fewer dose-related side effects occurred 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 TPM arm versus none to 7% in the placebo arm. In one of the two studies that compared efficacy and tolerance at three different doses of TPM (200, 400, 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 with 600, 800, and 1,000 mg/day, discontinuation rates were higher than those 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

Two studies had class I evidence (26,27), and one study had class II evidence (28) that evaluated the efficacy of TGB 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. Although the half-life of TGB ranges from 4 to 8 h, one study (26) showed no difference in responder rates between patients taking doses on b.i.d. and q.i.d. regimens. In these three studies, the discontinuation rate related to adverse events ranged between 8 and 20% among patients taking 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 TGB regimens were not associated with changes in cognitive functions.

Oxcarbazepine

To date, one large study with class I evidence evaluated the efficacy of OXC as add-on therapy in adults with refractory partial epilepsy (30). In this study, the efficacy of three doses of OXC (600, 1,200, and 2,400 mg/day) were compared among themselves and with a placebo

arm in 694 patients aged 15 to 65 years. The 50% responder rate was 12.7% for the placebo group versus 26.8% for patients taking 600 mg/day, 41.2% for patients taking 1,200 mg/day, and 50% for those taking 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 taking placebo, 12% among patients taking 1,200 mg, 36% among patients taking 1,200 mg/day, and 67% among those taking 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) with placebo (31), and the second study compared efficacies of three different doses of ZNS (100, 200, and 400 mg/d) with placebo (32). In the first study, the 50% responder rate to ZNS was 30%, and that to placebo was 9.4%. In the second study, the 50% responder rate at both 100 and 200 mg/day was 25% (vs. 9.8 and 11.3% for placebo), and at 400 mg/day, the responder rate was 43% (vs. 9% for placebo). The discontinuation rates of placebo and ZNS were 10% each. The ZNS 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

Three studies had class I evidence evaluating the efficacy of add-on LEV in refractory partial epilepsy (33–35). One of these also evaluated the impact of add-on LEV 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 with a range of 10–17% in placebo groups from different studies. Seizure-free rates 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 taking active drug, and 5 to 8% with placebo. No relation was found between discontinuation rate and dose. In one study in which patients were initiated with 2,000 or 4,000 mg without a titration, a significantly higher rate of somnolence and asthenia were found 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 demonstrated efficacy as add-on therapy in patients with refractory partial epilepsy. Even though the methods were 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 maximal doses, whereas others appear to have been administered above the 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 in which two different titration rates were compared, the slower titration was better tolerated. Therefore it would seem advisable to start low and go slow, by using increasing doses until side effects occur (in other words, push to maximal tolerated dose).

Summary of evidence (Table 1)

Partial seizures in adults

GBP (600–1,800 mg), LTG (300–500 mg in enzyme-induced patients, and 150 mg/day in patients receiving enzyme inducers and VPA), LEV (1,000–3,000 mg), OXC (600–2,400 mg), TGB (16–56 mg), TPM (300–1,000 mg), and ZNS (100–400 mg) are effective in reducing seizure frequency as adjunctive therapy in patients with refractory partial seizures.

GBP, LTG, TGB, TPM, OXC, and ZNS are more effective at higher doses. The evidence for a dose response for LEV is less clear, but more patients were seizure free at 3,000 than at 1,000 mg. Side effects and dropouts due to side effects also increase in a dose-dependent manner for all these drugs.

OXC, 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 GBP and TPM. This may be true for the other AEDs as well, but no class I or II evidence is available to support this.

Recommendation

It is appropriate to use GBP, LTG, TPM, OXC, LEV, and ZNS as add-on therapy in patients with refractory epilepsy (level A).

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 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 VPA 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 seizure ("failures") or have completed the trial without that exit criterion having occurred ("completers"). Analysis is based on how many completers are found in the placebo/pseudoplacebo group compared with the treatment group. These trials can be performed on either inpatients undergoing presurgical evaluation or outpatients. Presurgical studies are very short (8–10 days). Outpatient studies last $\leq$6 months, but questions are raised 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 $>$80%) exit the "pseudoplacebo" arm because of worsening, a drug can be determined to be "effective" even if more than 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, because of either 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

Two studies had class I evidence evaluating the efficacy of GBP monotherapy for intractable partial-seizure disorders (38,39). One study (38) compared 300 with 3,600 mg/day. The study included inpatients with intractable seizures undergoing video-EEG monitoring who were off other AEDs. Time to exit in the course of an 8-day period was the outcome variable. The median time to exit was longer (151 vs. 85 h) for the higher GBP dose ($p = 0.0001$). The percentage of completers also was higher in the 3,600-mg group ($p = 0.002$).

In the second study (39), 275 outpatients were randomized to one of three GBP monotherapy regimens at doses of 600, 1,200, and 2,400 mg/day, as part of a conversion from polytherapy to monotherapy GBP. Only 20% of patients completed the study. No difference in time to exit was noted between 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 LTG with low-dose VPA. Patients taking PHT or immediate-release formulation of CBZ monotherapy were randomly switched to either LTG (500-mg/day dose) or VPA (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 taking LTG completed the study versus 20% of patients taking VPA, but in an intent-to-treat analysis, only 37% of the LTG cohort completed the trial. The time to escape was significantly longer for patients taking LTG (median, 168 days) than taking VPA (median, 57 days). The discontinuation rate due to adverse events was 5% for patients taking VPA and 11% for patients taking LTG. Rash was reported by 8% of patients taking VPA and 11% for patients taking LTG, 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 LTG 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. Because only patients taking enzyme-inducing AED regimens were enrolled, no evidence-based data are available on conversion from VPA or regimens including non–enzyme-inducing AEDs.

Topiramate

One single-center study had class I evidence (41) that evaluated the efficacy of TPM monotherapy for refractory partial seizures at two doses, 100 and 1,000 mg/day, in 48 patients. Patients were required to convert to TPM 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 TPM had 100% seizure reduction versus none of the 100-mg group. Furthermore, 62% of patients taking 1,000 mg/day completed the study compared with only 25% of those taking 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 taking 1,000 mg/day, and none for patients taking 100 mg/day.

The adverse events with monotherapy were similar but less frequent than those reported in add-on trials.

Oxcarbazepine

Three studies had class I evidence (42–44) that evaluated the efficacy of OXC monotherapy in patients with refractory partial epilepsy. In one study (42), OXC was compared with placebo in patients who had their AEDs discontinued for presurgical evaluation. Eighty-four percent of the placebo patients exited the study versus 47% of those taking OXC during the 10-day trial. This trial was too short to demonstrate sustained efficacy in monotherapy. In the second study (43), two doses of OXC, 300 and 2,400 mg/day, were compared. Among the patients taking the lower dose, 93.3% of patients exited the 126-day study compared with 41.2% taking the higher dose. Twelve percent of the patients in the OXC 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 OXC, 300 and 2,400 mg/day, were compared. Patients taking the lower dose had a median time to exit of 28 days, whereas those taking the higher dose had a 68-day time to exit. The five most common adverse events were dizziness, sedation, nausea, diplopia, and fatigue. In the presurgical study (42), in 21.6% of patients, hyponatremia developed versus in 2% taking placebo.

Levetiracetam

One study (35) evaluated the efficacy of LEV 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 LEV or placebo from an earlier phase of the study. Responders continued to receive LEV, 1,500 mg, or placebo in a blinded fashion twice daily for 12 weeks, or until they exited because of prespecified criteria based on worsening. Significantly more LEV than placebo patients completed the monotherapy phase, 42.1% versus 16.7%, respectively ($p < 0.001$). However, only 49 patients were treated with sustained monotherapy in the study. Because of 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 important, 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 (Table 1)

Monotherapy for refractory partial epilepsy

LTG: 500 mg/day superior to 1,000 mg/day of VPA (acting as a "pseudoplacebo"), and is therefore effective in monotherapy for refractory partial epilepsy.

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

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

Insufficient evidence exists to determine the efficacy of LEV, TGB, or ZNS in this population.

In one trial, GBP was 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 GBP in monotherapy for refractory partial epilepsy in these patients.

Recommendations

1. OXC and TPM can be used as monotherapy in patients with refractory partial epilepsy (level A).
2. LTG can be used as monotherapy in patients with refractory partial epilepsy (level B, downgraded because of dropouts).
3. Insufficient evidence exists to recommend use of GBP, LEV, TGB, or ZNS in monotherapy for refractory partial epilepsy (level U).

GENERALIZED EPILEPSY

Generalized epilepsy syndromes are categorized as idiopathic or symptomatic. Idiopathic epilepsy, also called 1^0 generalized epilepsy, occurs on a presumed genetic basis, in the setting of normal brain structural architecture. Seizure types are limited to myoclonic seizures, GTCCs, 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 VPA, are effective in >80% of patients, whereas others, even those that are effective in partial seizures, may be ineffective. In contrast, symptomatic epilepsy, also called 2^0 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 AEDs in the generalized epilepsy syndromes is not so readily available as is evidence in the partial syndromes. Many of the available data are for 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

One article has class I evidence assessing the efficacy of GBP in refractory GTCCs in patients with primary or secondarily generalized epilepsy (45). Patients aged 12 and older with refractory GTCCs were randomized to placebo or 1,200 mg of GBP. No significant difference was found. In retrospect, it is possible that the dose was too low. In addition, one article has class I evidence and four have class IV evidence assessing efficacy in a "mixed" group of ≤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

One class I article (51) was found. In this small crossover study, 50% of the participants, aged 15 to 50 years, had >50% decrease in GTCCs, whereas 33% had >50% decrease for absence seizures. The discontinuation rate among patients taking LTG was 8% versus none for those taking placebo. A rash was reported in 27% of patients taking LTG, 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

One study had class I evidence (37) that evaluated the tolerability and efficacy of two doses of LEV, 2,000 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

One study had class II evidence (56), in which 48 patients were crossed over from immediate-release formulation of CBZ to OXC. Nine patients had only generalized epilepsy, and 29 had partial and generalized epilepsy. Twenty-five patients had a "decrease" in all seizures with OXC, compared with CBZ, whereas 17 had an increase. The adverse events with OXC were similar to those described in previously cited studies.

Topiramate

One study had class I evidence (57) in adults and children older than 3 years with refractory GTCCs with or without other seizure types. Patients were randomized to a target dose of ~6 mg/kg/day versus placebo. The 50% responder rate was 56% for TPM compared with 20% for placebo. An open-label class IV follow-up of the randomized trial demonstrated continued effectiveness of TPM. Discontinuation rate due to adverse events was similar for TPM (2.6%) and placebo (2.4%). The adverse events in this study were similar to those of the TPM studies already cited.

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.

No studies were found of efficacy of TGB or ZNS in idiopathic generalized epilepsy.

Conclusion

Trials for refractory generalized epilepsy have been criticized because 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 secondarily GTCCs.

Because the seizures of 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 (Table 1)

Refractory Primary Generalized Epilepsy

TPM: 6 mg/kg/day is effective for the treatment of refractory GTCCs with or without other seizure types.

GBP:1,200 mg is not effective in refractory GTCCs in patients with primary or secondarily generalized epilepsy.

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

Recommendations

1. TPM may be used for the treatment of refractory GTCCs in adults and children (level A).
2. Insufficient evidence exists to recommend GBP, LTG, OXC, TGB, LEV, or ZNS for the treatment of refractory GTCCs in adults and children (level U).

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

One study has class I evidence (68) that evaluated the efficacy of GBP in 247 children whose ages ranged between 3 and 12 years in a 12-week double-blind placebo-controlled trial. GBP 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 GTCCs. Children randomized to GBP had a median decrease of 35% of complex partial and 28% of secondarily GTCCs, whereas those taking placebo had a 12% median reduction and 13% increase, respectively. The discontinuation rate was 5% for children taking GBP and 2% for those taking placebo. The five most frequent adverse events were viral infection, fever, hostility, fatigue, and weight gain.

Lamotrigine

One study (69) has class I evidence evaluating the efficacy of LTG versus placebo in 199 children aged from 2 to 16 years. The LTG target doses varied according to the type of AEDs the child was taking at the time of randomization: 1 to 3 mg/kg, in the presence of VPA only, 1 to 5 mg/kg if an enzyme-inducing AED (PHT, CBZ, PB) was taken in combination with VPA, and 5 to 15 mg/kg if the child was taking enzyme-inducing AEDs only. The responder rate was 45% among children randomized to LTG and 25% for those taking placebo. Children taking LTG had a significantly higher decrease in weekly seizure frequency (44%) compared with those taking placebo (12.8%). The discontinuation rate caused by adverse events was 5% for children taking LTG and 6% for those taking placebo. The five most frequent adverse events included ataxia, dizziness, tremor, nausea, and asthenia. One patient had a severe rash, seen as Stevens–Johnson syndrome.

Topiramate

One study with class I evidence evaluated the efficacy of TPM versus placebo in 86 children aged 2 to 16 years during a 16-week trial (70). The TPM 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 taking TPM, and 20% for those taking placebo. Children taking TPM had a median reduction in seizures of 33% versus 10.5% for those taking placebo. No child taking TPM and two children taking placebo were discontinued from the study. The five most frequent adverse events included emotional lability, difficulty concentrating, fatigue and memory deficits, and weight loss. No cases of hypohidrosis were found in clinical trials. A case series reported three children, aged 17 months, 9 years, and 16 years, in whom hypohidrosis developed while receiving TPM monotherapy (71).

Oxcarbazepine

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

Levetiracetam

One study with class IV evidence (73) evaluated the efficacy of LEV 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 was 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 specifically studied the efficacy of ZNS in pediatric patients with partial seizures. A single case was reported of hypohidrosis caused by ZNS (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

A National Institutes of Health (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). Each AED tested as adjunctive therapy in children older than 2 years with refractory partial seizures 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 seizures 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 in other pediatric-specific epilepsy syndromes, to evaluate efficacy in children younger than 2 years, 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 must be evaluated.

Summary of evidence (Table 1)

Refractory partial seizures, pediatric

GBP (23–35 mg/kg/d), LTG (1–5 mg/kg/day with enzyme inducers; 1–3 mg/kg/day in regimens including VPA), OXC (30–46 mg/kg/day), and TPM (125–400 mg/day) are effective in reducing seizure frequency as adjunctive therapy in children with refractory partial seizures. No class I or II evidence exists regarding the efficacy of LEV, TGB, or ZNS. Based on class III and IV evidence, specific safety concerns are present in children with these drugs, specifically serious rash with LTG, and hypohidrosis with ZNS and TPM.

Recommendations

1. GBP, LTG, OXC, and TPM may be used as adjunctive treatment of children with refractory partial seizures (level A).
2. Insufficient evidence exists to recommend LEV, TGB, or ZNS as adjunctive treatment of children with refractory partial seizures (level U).

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 TPM and GBP in idiopathic GTCCs already discussed included children as well.

Secondarily generalized epilepsy or Lennox–Gastaut syndrome

Patients with the Lennox–Gastaut syndrome have many seizures each 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

No studies were found. One case series and one case report identified worsening of myoclonic seizures in this population when they were treated with GBP (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 VPA use, and ranged from 50 to 100 mg for patients <25 kg taking VPA, to 300 to 400 mg for patients >25 kg not receiving VPA. These studies demonstrated 50% reduction in seizures in 33% of patients, compared with 16% taking placebo. Discontinuation rates because of adverse events were comparable (5% for patients taking LTG and 6% for those taking placebo). The incidence of rash was similar (16% among patients taking LTG and 18% in those taking placebo). However, in one pediatric patient in this study, Stevens–Johnson syndrome developed. 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 taking LTG and placebo, respectively. Rash was reported in 9% of patients taking LTG (in two patients, it was considered serious) and 7% in patients taking placebo.

One class IV study demonstrated efficacy in Lennox–Gastaut syndrome (79). One case report was found of worsening of myoclonic jerks in a patient with 2^0 generalized epilepsy treated with LTG (80).

Topiramate

One study had class I evidence (81) and one class IV study (82) evaluated the efficacy of TPM as adjunctive therapy in the treatment of Lennox–Gastaut syndrome. The class I study (81) used a dose of 6 mg/kg/day. The TPM group had a 14% reduction in drop attacks compared with 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.

No studies had class I or II evidence that evaluated the efficacy of LEV, OXC, TGB, or ZNS.

Conclusions

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

Summary of evidence (Table 1)

Secondarily generalized epilepsy

LTG at doses adjusted for weight and VPA use, ranging from 50 to 400 mg/day, reduces seizures associated with the Lennox–Gastaut syndrome.

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

To date, no class I or II evidence is found that GBP, TGB, OXC, LEV, or ZNS is effective.

In case reports, LTG and GBP both worsened myoclonic seizures in some patients.

Recommendations

Lennox–Gastaut syndrome

TPM and LTG may be used to treat drop attacks associated with the Lennox–Gastaut syndrome in adults and children (level A).

WHAT IS THE RISK OF TERATOGENICITY WITH THE NEW AEDS COMPARED WITH 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, PHT, CBZ, and VPA are category D. Category D drugs are those drugs related to teratogenicity in both animal and human pregnancies. In both categories, the recommendation remains the same: selection of an AED in pregnancy should be decided on the risk–benefit ratio for seizure control.

RECOMMENDATIONS FOR FUTURE RESEARCH

The only attempt at comparing the efficacy of new drugs in patients with refractory epilepsy has been performed through 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., TPM and OXC), whereas efficacy may appear lower for drugs studied at low doses (e.g., GBP). 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. A need is evident for studies that compare the new drugs in a head-to-head fashion.

Add-on trials in patients with refractory partial seizures 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 important, 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 Veterans Administration cooperative studies of the 1980s that randomized newly diagnosed patients to one of four available drugs, titrated to optimal doses, and monitored 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. A simple seizure count may not capture improvements in seizure severity or pattern (such as conversion from diurnal to nocturnal events). 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 in 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 regard to new AEDs. Several questions remain unanswered, including, 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 in patients with both refractory and newly diagnosed epilepsy? Which is more clinically and scientifically valid, a study comparing a drug with a "pseudo-placebo" or an active control comparison design?

Disclaimer

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methods. 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 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 (RCT) with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or appropriate statistical adjustment is made 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 an RCT in a representative population that lacks one criterion from a to 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

APPENDIX 2. *Members of the American Academy of Neurology Subcommittees*

Members of the American Academy of Neurology Quality Standards Subcommittee
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