CLINICAL TRIALS IN NEW-ONSET EPILEPSY

James W. Wheless, MD*

ABSTRACT

Although a number of new antiepileptic drugs (AEDs) have entered clinical practice during the last decade, only 2 first-line agents (lamotrigine and oxcarbazepine) have been specifically approved for epilepsy monotherapy, and a third agent (topiramate) has received preliminary monotherapy approval from the US Food and Drug Administration. Older agents are often used for epilepsy monotherapy, although these drugs were approved before rigorous monotherapy testing was required. Large randomized double-blind clinical trials have shown that the newer AEDs lamotrigine, oxcarbazepine, and topiramate are at least as effective as older agents such as carbamazepine and valproate for monotherapy in patients with newly diagnosed epilepsy, but with better tolerability and long-term adherence to therapy. Initial clinical trials have suggested that these agents are also well suited for special patient populations, including elderly or pediatric patients. The results of a recent large, randomized, double-blind clinical trial demonstrate that topiramate at a dose of 100 mg once daily is effective and well tolerated for the control of seizures in adult and pediatric patients with newly diagnosed epilepsy. (Adv Stud Med. 2005;5(3B):S180-S184)

Monotherapy for patients with newly diagnosed epilepsy has several potential advantages over polytherapy, including fewer side effects and drug interactions, better patient adherence to treatment, and lower treatment cost. Although several of the older antiepileptic drugs (AEDs) are commonly used for epilepsy monotherapy, many of the medications that are most familiar to physicians, including carbamazepine, phenytoin, and valproate, were approved for use before the US Food and Drug Administration (FDA) began licensing AEDs with a specific monotherapy indication. As a consequence, they were never required to undergo specific evaluation and approval for epilepsy monotherapy. Only one of the currently available first-line agents (oxcarbazepine) has been specifically approved by the FDA for monotherapy in newly diagnosed patients (adults and children 4 years of age and older). Lamotrigine is approved for conversion to monotherapy in adult patients taking carbamazepine, phenytoin, phenobarbital, primidone, or valproate. A third AED, felbamate, is approved for monotherapy but is not widely used because of concerns about toxicity. Topiramate, the newest AED to undergo evaluation for a monotherapy indication, has received preliminary approval for monotherapy of newly diagnosed epilepsy from the FDA, and it may soon receive final approval for epilepsy monotherapy.

This article reviews the clinical trial evidence supporting the use of newer AEDs as monotherapy for patients with newly diagnosed epilepsy. It also describes some of the methodological and ethical challenges that are inherent in the design and interpretation of monotherapy trials, how these challenges have been addressed in recent studies, and some considerations for the design of future monotherapy trials.

Efficacy and Safety of Newer AEDs as Epilepsy Monotherapy

The efficacy and safety of lamotrigine as monotherapy in newly diagnosed patients with epilepsy and no prior AED treatment were examined in a multicenter, randomized, double-blind clinical trial of 260 patients 13 years of age or older. Patients were randomized to receive either lamotrigine (titrated up to a daily dose of 150 mg) or carbamazepine (titrated up to a daily dose of 600 mg) for 48 weeks. The median number of seizures before treatment was 4 in the lam...
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Monotherapy with oxcarbazepine was compared with valproate in a double-blind clinical trial of 249 patients between 15 and 65 years of age with newly diagnosed partial seizures or generalized tonic-clonic seizures and no prior AED use (except for short-term emergency use for up to 3 weeks). During an 8-week dose titration phase, patients received double-blind treatment with either oxcarbazepine or valproate at a flexible, individualized dose, beginning at 300 mg once daily and increasing at biweekly intervals to attain a final dose of 900 to 2400 mg (in 3 divided doses). Double-blind treatment was then continued for another 48 weeks, with dose adjustment permitted as needed. The time from first seizure to enrollment in the study was 178 weeks for patients in the oxcarbazepine group, and 181 weeks in the valproate group. The median number of seizures before treatment was 5 (mean, 26.3) in the oxcarbazepine group and 9 (mean, 157.9) in the valproate group. Twenty-three patients in the valproate group and 10 patients in the oxcarbazepine group had more than 100 seizures before enrollment into the study, and the seizure frequency at baseline was greater with valproate (1.09 seizures per week) than with oxcarbazepine (0.58 seizures per week). The seizure-free rate during the 48-week maintenance phase (the primary efficacy endpoint) was similar for the 2 treatments (56.6% of patients with oxcarbazepine, 53.8% with valproate; P = .50). The rate of treatment discontinuation due to adverse events was also similar for the 2 groups: 15 patients discontinued with oxcarbazepine (most commonly due to allergic skin reactions) and 10 patients with valproate (most commonly due to hair loss; P = .33). Some adverse events tended to be less common among patients who received oxcarbazepine, including alopecia, tremor, weight gain, increased appetite, and headache, although these comparisons were not analyzed statistically. Similar results were observed in a randomized, double-blind clinical trial that compared oxcarbazepine with phenytoin in 287 adult patients with newly diagnosed partial or generalized tonic-clonic seizures. After 48 weeks of maintenance therapy, the proportion of patients who were seizure-free was similar with oxcarbazepine (59.3%) and phenytoin (58%), although patients who received phenytoin were more likely to discontinue treatment because of poor tolerance for the drug. The results of these 2 trials suggest that oxcarbazepine is similar to valproate and phenytoin in efficacy for the treatment of partial or generalized tonic-clonic seizures, but with a more favorable tolerability profile.

The most recent large, randomized, double-blind trial to compare a newer AED with conventional treatments examined the efficacy and safety of topiramate, carbamazepine, and valproate in patients with newly diagnosed epilepsy. Patients at least 6 years of age who had not previously been treated for epilepsy (except for urgent treatment for up to 6 weeks with no more than one AED, if required) were enrolled at a total of 115 study centers around the world. In order to examine the broadest spectrum of activity possible, all patients with newly diagnosed epilepsy were eligible for enrollment, regardless of specific seizure type or epilepsy syndrome. Patients with nonepileptic seizures were excluded. The design of the study is shown in Figure 2 on page S197. Before the initiation of treatment, each patient’s physician determined whether the patient would best be treated using carbamazepine or valproate, and the patient was assigned to one of the 2 treatment tracks shown on page S197. The patients were then randomized within each track to double-blind treatment with either the physician’s selected therapy (carbamazepine 600 mg once daily or valproate 1250 mg once daily) or one of 2 doses of topiramate (100 or 200 mg once daily). The study continued until 6 months after the last patient was randomized: 62% of the patients were treated for at least 6 months, and 29% were treated for at least 1 year. A total of 621 patients were enrolled in the study, and efficacy data were available for 613 patients. Investigators selected valproate as preferred therapy for 223 patients (primarily with generalized seizures), and carbamazepine as preferred therapy for 390 patients (primarily with partial-onset seizures). The median time from the first seizure to enrollment in the study was similar for the 3 treatments (4.0, 5.5, and 5.5 months for patients who received topiramate, carbamazepine, and valproate, respectively); the median time from diagnosis of epilepsy to enrollment in the study was 1.0 months for all 3 groups.
Within each of the 3 study tracks, treatment outcomes were similar for patients randomized to topiramate 100 or 200 mg once daily, and the topiramate groups within each track were therefore combined. The time to study exit for any reason (including lack of efficacy, adverse events, or patient choice) was not significantly different between topiramate and valproate (in the valproate branch of the study; $P = .53$) or between topiramate and carbamazepine (in the carbamazepine branch; $P = .53$). When all of the topiramate-treated patients were combined across both study branches, no differences were observed between topiramate and either carbamazepine or valproate in the time to study exit for any reason. The study was designed with sufficient statistical power to exclude the possibility that topiramate was inferior to either of the standard therapies. Topiramate was equivalent to both carbamazepine and valproate for several secondary outcomes, including retention in the trial at 90 days and time to first seizure. The overall rate of study exit due to adverse events was similar for topiramate, carbamazepine, and valproate, although patients who received the topiramate 100-mg dose had a lower rate of treatment-limiting adverse events (19% of patients) than patients who received topiramate 200 mg (28%), carbamazepine (25%), or valproate (23%). The most common treatment-limiting adverse events were fatigue, paresthesia, somnolence, and decreased appetite with topiramate; rash and fatigue with carbamazepine; and alopecia, tremor, fatigue, weight gain, somnolence, memory difficulty, and thrombocytopenia with valproate. Cognitive side effects with topiramate were dose-related; occurred with similar frequency in the topiramate 100 mg, carbamazepine, and valproate groups; and were less common with topiramate 100 mg in this study than in clinical trials in which patients have undergone rapid topiramate dose escalation while taking other AEDs.4 The results of this study demonstrated that topiramate at a dose of 100 mg once daily is at least as effective as valproate or carbamazepine for patients with a broad spectrum of epileptic seizure types. A possible limitation of this trial is the fact that patients who were seizure-free with carbamazepine required doses of 800 mg or less once daily, and 91% of patients seizure-free with valproate required doses of 1500 mg or less once daily.5 The most common dose ranges used in seizure-free patients were 400 to 600 mg of carbamazepine once daily and 600 to 1000 mg for valproate once daily. These doses are very similar to the doses of the comparator agents used in the topiramate monotherapy clinical trial (600 mg once-daily carbamazepine, 1250 mg once-daily valproate), suggesting that the comparator dose ranges were adequate to provide seizure control for most patients.

The interpretation of monotherapy studies is often complicated by the requirement that patients in the comparator groups receive treatment with an established AED at an effective dose. In general, it is no longer considered ethical to randomize patients to monotherapy with placebo or to ineffective low doses of comparator medications (referred to as a pseudoplacebo). Random assignment to placebo is less of a problem in clinical tri-

**COMMENTARY: MONOTHERAPY CLINICAL TRIALS IN NEWLY DIAGNOSED EPILEPSY**

The topiramate clinical trial described above incorporated a number of design features that were intended to provide the greatest possible clinical relevance to the study's findings. To the extent possible, the study was designed to mimic actual clinical practice, rather than the highly structured setting that is typical of randomized clinical trials in epilepsy. For example, this trial recruited a broad spectrum of patients with many different seizure types and epilepsy syndromes. This is important when extrapolating study results to clinical practice in patients with newly diagnosed epilepsy, because it is often difficult to quickly and precisely identify the type of seizure syndrome in these patients. In addition, patients were assigned to one of 2 treatment tracks based on the treating physician's determination of the best treatment for each individual patient. With more than 600 patients enrolled, this is among the largest comparative monotherapy studies ever performed in patients with epilepsy. The large sample size and relatively long duration reduce the likelihood that unanticipated side effects will emerge during routine clinical use of topiramate. Adequate long-term testing of new medications is especially important in epilepsy because treatment is typically required for a long period of time, and it is important to know that the medication will remain effective and well tolerated by patients with long-term use.

In this study, the investigators ensured that patients in the valproate and carbamazepine groups received adequate doses of comparator agents, so that if a difference was observed in favor of topiramate, it could not be attributed to inadequate dosing with valproate or carbamazepine. In another study in which the investigators performed a retrospective analysis of the dose-response profiles of carbamazepine and valproate monotherapy among patients with newly diagnosed epilepsy, 93% of patients who were seizure-free with carbamazepine required doses of 800 mg or less once daily, and 91% of patients seizure-free with valproate required doses of 1500 mg or less once daily. The most common dose ranges used in seizure-free patients were 400 to 600 mg of carbamazepine once daily and 600 to 1000 mg for valproate once daily. These doses are very similar to the doses of the comparator agents used in the topiramate monotherapy clinical trial (600 mg once-daily carbamazepine, 1250 mg once-daily valproate), suggesting that the comparator dose ranges were adequate to provide seizure control for most patients.

The interpretation of monotherapy studies is often complicated by the requirement that patients in the comparator groups receive treatment with an established AED at an effective dose. In general, it is no longer considered ethical to randomize patients to monotherapy with placebo or to ineffective low doses of comparator medications (referred to as a pseudoplacebo). Random assignment to placebo is less of a problem in clinical tri-
als that examine adjunctive therapies, because all of the patients are receiving an effective dose of standard therapy to which the adjunctive, experimental therapy (or placebo) is added. The absence of a placebo group often complicates the interpretation of monotherapy trials, because there are 3 possible interpretations to a finding of no statistically significant difference between the new and established treatments: that both drugs were effective; that neither drug was effective; or that one drug was superior to the other but that the trial lacked statistical power to detect a real difference between them. This is a particularly important problem in new-onset epilepsy because these patients tend to be much more responsive to treatment than patients with refractory seizures, which can make it very difficult to demonstrate a difference between 2 effective medications. One way to overcome this problem, and the approach that was used in the topiramate study described here, is to enroll a large enough patient population to statistically exclude the possibility that the true difference between the groups is large enough to be clinically important. Although this approach has been used in several recent monotherapy trials, FDA approval for a new indication requires a clear demonstration of superiority with the treatment under investigation. A finding of equivalence between treatments is not regarded as adequate for approval, despite the fact that placebo-controlled trials are not considered ethical in this patient population. In addition, clinicians are usually more interested in knowing how a new treatment compares with established therapies than how it compares with placebo. Thus, it is often the case that clinical trials that are conducted in order to gain approval do not answer questions that clinicians are most concerned about. None of the large, randomized monotherapy trials described previously meet FDA criteria for approval of a new medication or indication, although all of these trials are helpful to clinicians and provide information about how the efficacy and safety of new medications compare with one or more established AEDs.

Another way to address the issue of comparing active medications is to use a high-dose/low-dose design, in which patients are randomized to one of 2 doses of the same medication that are both expected to be effective, yet are also expected to produce a statistically significant difference in outcome. The difficulty with this approach, and the reason that few clinical trials have used this design, is that the drug dose-response characteristics must be well understood before the study is conducted, and the drug must have a wide enough therapeutic window to permit the use of doses that will produce different, but effective, treatment outcomes. These difficulties are illustrated by a dose-response study that examined 3 doses of gabapentin (300, 900, and 1800 mg once daily) and carbamazepine as monotherapy in patients with newly diagnosed partial seizures.10 Although the investigators were able to demonstrate that the number of patients who discontinued treatment either due to lack of efficacy or tolerability was lower with either effective gabapentin dose (900 or 1800 mg once daily) than with an ineffective dose (300 mg once daily), they could not demonstrate a difference in outcomes between the 2 effective gabapentin doses. Only one study in epilepsy monotherapy has successfully used this design. Arroyo and colleagues randomized a total of 470 adults and children (≥25 kg) with newly diagnosed epilepsy or untreated recurrent epilepsy to double-blind treatment with topiramate at a dose of either 50 mg or 400 mg once daily.11 The time to first seizure was significantly greater among patients who received the 400-mg dose (P = .0002), and more patients remained seizure-free at the end of 1 year of treatment with the 400-mg dose (76%) than with the 50-mg dose (59%; P = .005). This was the first randomized, double-blind clinical trial to demonstrate a significant dose-response effect of AED monotherapy in patients with newly diagnosed epilepsy.

**Future Directions in Epilepsy Trials**

The monotherapy trials that have been conducted thus far have all examined the effects of treatment on seizures and medication-related adverse effects. However, none of the available trials have evaluated the effects of treatment on patient quality of life. It is possible that 2 treatments may produce similar seizure control, but that one agent is preferred by patients because it has a more favorable side-effect profile. These differences could be evaluated using standardized quality of life scales. In the past, information about quality of life was not of great importance in clinical trial design because there were relatively few medications from which to choose. However, quality of life differences between treatments may become more important as new medications become available. Other considerations that also may emerge as particularly important are pharmacokinetics, dosing frequency, and the risk of drug interactions.

Future trials may also increasingly emphasize special patient populations. Most of the studies that have been conducted to date have primarily enrolled older adolescents and young adults, patients with epilepsy who are otherwise healthy. However, the fastest-growing group of patients with epilepsy is the geriatric population. These patients often have a number of comorbid conditions and are using a large number of other medications, increasing their risk of medication side effects and significant drug
interactions. Because elderly patients generally do not tolerate medicines as well as younger patients, it is difficult to infer tolerability in the elderly based on studies conducted primarily in healthy young adults. Relatively few studies have specifically examined monotherapy with newer AEDs in elderly patients. One randomized clinical trial compared lamotrigine (titrated up to 75 to 500 mg once daily as needed to control seizures) and carbamazepine (titrated to 200 to 2000 mg once daily) in 150 patients 65 years of age or older with newly diagnosed epilepsy. Lamotrigine was associated with a lower rate of somnolence than carbamazepine (12% vs 29% of patients for the lamotrigine and carbamazepine groups, respectively), and also with a lower rate of discontinuation due to adverse events (18% vs 42% of patients). Patients who received lamotrigine remained in the study and on treatment significantly longer than patients who received carbamazepine. Of the patients who remained in the study, the seizure-free rate was similar for the lamotrigine and carbamazepine groups. Pediatric patients have also not been extensively studied in the clinical trials conducted to date. It is more difficult to study pediatric patients than the elderly because young children have many different seizure types and epilepsy syndromes, with markedly different responses to therapy, whereas older patients tend to be more uniform in seizure type and treatment response. In designing pediatric clinical trials, this heterogeneity of seizure type and response rate requires the selection of specific seizure types to study, which makes it more difficult to enroll patients in a large clinical trial. For this reason, few studies have been performed in young children. In the previously described topiramate monotherapy trial, a subsequent analysis demonstrated the efficacy and safety of topiramate in the 119 children and adolescents enrolled in this study. As in the larger patient population, there were no significant differences in efficacy between the topiramate 100- and 200-mg groups or between topiramate and either carbamazepine or valproate. Discontinuation due to adverse events was noted for 4 of 38 patients (11%) with topiramate 100 mg, 7 of 39 patients with topiramate 200 mg (18%), 1 of 23 patients with carbamazepine (4%), and 6 of 19 patients (32%) with valproate. These results suggest that, as in adults, a topiramate dose of 100 mg once daily is an effective and well-tolerated dose for epilepsy monotherapy in children and adolescents with newly diagnosed epilepsy.

**Summary and Conclusions**

Although older AEDs such as valproate and carbamazepine are often used as monotherapy in patients with newly diagnosed epilepsy, these agents were approved before specific evaluation of efficacy and safety as monotherapy were required. More recent randomized controlled trials have shown that newer AEDs such as lamotrigine, oxcarbazepine, and topiramate are at least as effective as the conventional AEDs for epilepsy monotherapy, but that they may be associated with a lower incidence of side effects and improved long-term adherence to therapy.

**REFERENCES**