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Monotherapy Trials of New Antiepileptic Drugs

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Summary: A number of clinical trials that test the efficacy and safety of the newer antiepileptic drugs (AEDs) have recently been concluded. Two dose–response trials in inpatients with refractory partial seizures and outpatients with newly diagnosed partial epilepsy established the efficacy of gabapentin as monotherapy. Lamotrigine was found to have efficacy similar to that of phenytoin and carbamazepine (CBZ) and to be better tolerated than CBZ in patients with newly diagnosed epilepsy. It was also shown to have efficacy as monotherapy in partial seizures, based on the results of an active controlled trial, and in the treatment of absence seizures, based on the results of a responder-enriched study. Topiramate as monotherapy was found to be efficacious for treatment of partial-onset seizures, based on the results of a single-center dose–response trial. A dose–response trial that tested the efficacy of tiagabine monotherapy in patients with refractory partial epilepsy was uninformative. Oxcarbazepine was found to be safe and efficacious in four comparative trials in patients with newly diagnosed epilepsy as well as in one placebo-controlled inpatient trial in patients with refractory partial seizures. **Key Words:** Epilepsy—Clinical trials—Monotherapy—Antiepileptic drugs—Double-blind trials.

Antiepileptic drugs (AEDs) administered as monotherapy are the preferred treatment regimen for most patients with epilepsy. Monotherapy offers several advantages over polytherapy, including avoidance of drug interactions, fewer adverse effects, greater ease of administration, and decreased cost. The more recently available AEDs, such as gabapentin (GBP), lamotrigine (LTG), and topiramate (TPM), are presently approved by the Food and Drug Administration (FDA) as add-on therapy for treatment of partial-onset seizures. Compared with the standard AEDs, these newer AEDs offer more favorable pharmacokinetic profiles, better tolerability, or both, and may prove useful when used as monotherapy. This article reviews the results of completed randomized, double-blind monotherapy trials with the newer AEDs, on the basis of published and as yet unpublished data.

ADJUNCTIVE CLINICAL TRIAL DESIGNS

The safety and efficacy of the newer AEDs were assessed initially in add-on clinical trials of relatively uniform design. The typical protocol includes a baseline evaluation period of 8–12 weeks, followed by randomization of patients with refractory partial seizures in double-blind fashion to add-on treatment with either the study drug or placebo in addition to normal dosages of their baseline AEDs. The duration of the double-blind phase is 8–12 weeks and the primary efficacy variable is the reduction in seizure frequency, relative to baseline, demonstrated by the study drug and placebo.

Although add-on trials offer some advantages, they also have a number of drawbacks. On the positive side, they have demonstrated efficacy for GBP, LTG, TPM (1), tiagabine (TGB), felbamate, and vigabatrin (2). Add-on trials are also considered ethical trial designs, in that participants who are randomized to the placebo arm continue to take the same dosage of their baseline drugs. On the negative side is the tendency to overestimate adverse events (AEs) and to underdose the study drug. In addition, there is always the concern of potential pharmacokinetic interactions between the study drug and the baseline AEDs. For example, if an add-on study drug causes an *increase* in the serum levels of baseline AEDs, determining how much of the change in seizure frequency could be attributed to the study drug (as opposed to the contribution from elevated baseline AED serum levels) would be difficult. Conversely, the efficacy of a study drug that *decreases* the serum levels of baseline AEDs would tend to be underestimated in such a trial design (3). It is understandably difficult to predict from add-on trials the utility of the study drug in monotherapy because, even in the absence of pharmacokinetic interac-

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tions, the possibility of pharmacodynamic interactions between the study drug and the baseline AEDs always exists. For this reason, such trials support approval only for adjunctive indications.

MONOTHERAPY TRIALS

To obtain a monotherapy indication, a study drug should have demonstrated safety and efficacy in a monotherapy trial. The requirements of regulatory agencies often dictate the designs of such clinical trials. As discussed by Chadwick elsewhere in this supplement (4), the FDA and European regulatory agencies differ philosophically over the design and interpretation of monotherapy trials. In Europe, the most common monotherapy design is a comparative trial in which the safety and efficacy of a study drug is compared with that of a standard AED that is believed to be effective for treating the seizure type(s) under evaluation. Although these trials most often fail to show a significant difference in efficacy between the study drug and the standard AED, European regulatory agencies accept the results of such trials as proof of efficacy of the study drug. The FDA, however, is suspicious of the validity of equivalence trials and doubts the efficacy of the study drug in such trial designs. Its rationale is often misunderstood and misrepresented. The fundamental reason behind the FDA's position is that to accept the results of equivalence trials as proof of a study drug's efficacy, it must assume that the comparative standard AED has efficacy in *every* patient population in which it is being tested and in all designs and dosages chosen (5,6). That is a precarious assumption, mainly because the efficacy of most standard AEDs as monotherapy has never been established in placebo-controlled clinical trials. To satisfy the FDA requirements for efficacy, it is therefore necessary to demonstrate the statistical superiority of the study drug in one arm of a trial against another. A number of designs, known as therapeutic failure designs (4), have been advocated to satisfy these requirements for efficacy while maintaining patient safety. Although it is true that the designs and efficacy variables evaluated in these clinical trials do not provide much in terms of clinically relevant data, they are the only trials that can definitely prove the efficacy of the study drug when it is used as monotherapy. The results of specific studies involving the newer AEDs are summarized here.

GBP MONOTHERAPY TRIALS

GBP is presently indicated for adjunctive treatment of partial seizures in patients ≥12 years of age, on the basis of three double-blind, multicenter, placebo-controlled trials. These studies showed that addition of GBP to standard AEDs at daily dosages of 600–1,800 mg significantly reduced the frequency of partial seizures (7–9). The efficacy and safety of GBP as monotherapy have been evaluated in three randomized, double-blind clinical trials conducted in the United States, Canada, and Europe. The North American trials consisted of outpatient and inpatient dose–response therapeutic failure designs in patients with refractory localization-related epilepsy. The European trial was an outpatient dose–response study of patients with newly diagnosed epilepsy (Table 1).

Outpatient trial in patients with refractory partial seizures

A 26-week, multicenter, double-blind, parallel-group, dose-controlled trial (Study No. 945-82) was undertaken to evaluate the safety and efficacy of GBP monotherapy in patients with medically refractory partial epilepsy (10). The patients recruited for the study were ≥12 years of age and had experienced at least two complex partial or secondarily generalized tonic–clonic seizures ("study seizures") per month while maintained on constant dosages of one or two standard AEDs. After an 8-week baseline period, qualified patients were randomized to treatment with GBP at 600, 1,200, or 2,400 mg daily, administered in three equally divided doses. Titration to the targeted dosage was carried out over 2 weeks, followed by an 8-week period during which the baseline AED(s) was tapered and discontinued (Fig. 1). Patients were then maintained on GBP monotherapy for a total of 16 weeks or until they met one or more of the following protocol-defined exit events: a doubling of the 28-day or highest 2-day study seizure rate during baseline; a secondarily generalized tonic–clonic seizure if none was experienced in the previous 2 years; an episode of status epilepticus; or a clinically significant intensification in seizure frequency or duration. The primary efficacy variable was time to exit from the double-blind phase.

A total of 274 patients were randomized at 25 centers in the United States and Canada. Mean time to exit was

TABLE 1. *Number of completed trials with newer antiepileptic drugs*

		Therapeutic failure		
			Outpatient	
Drug	Comparative	Inpatient	Refractory	New onset
GBP		1	1	1
LTG[a]	2		1	
OCBZ	4	1		
TGB			1	
TPM			1	

GBP, gabapentin; LTG, lamotrigine; OCBZ, oxcarbazepine; TGB, tiagabine; TPM, topiramate.

[a] Also evaluated for treatment of new-onset absence seizures in one placebo-controlled trial.

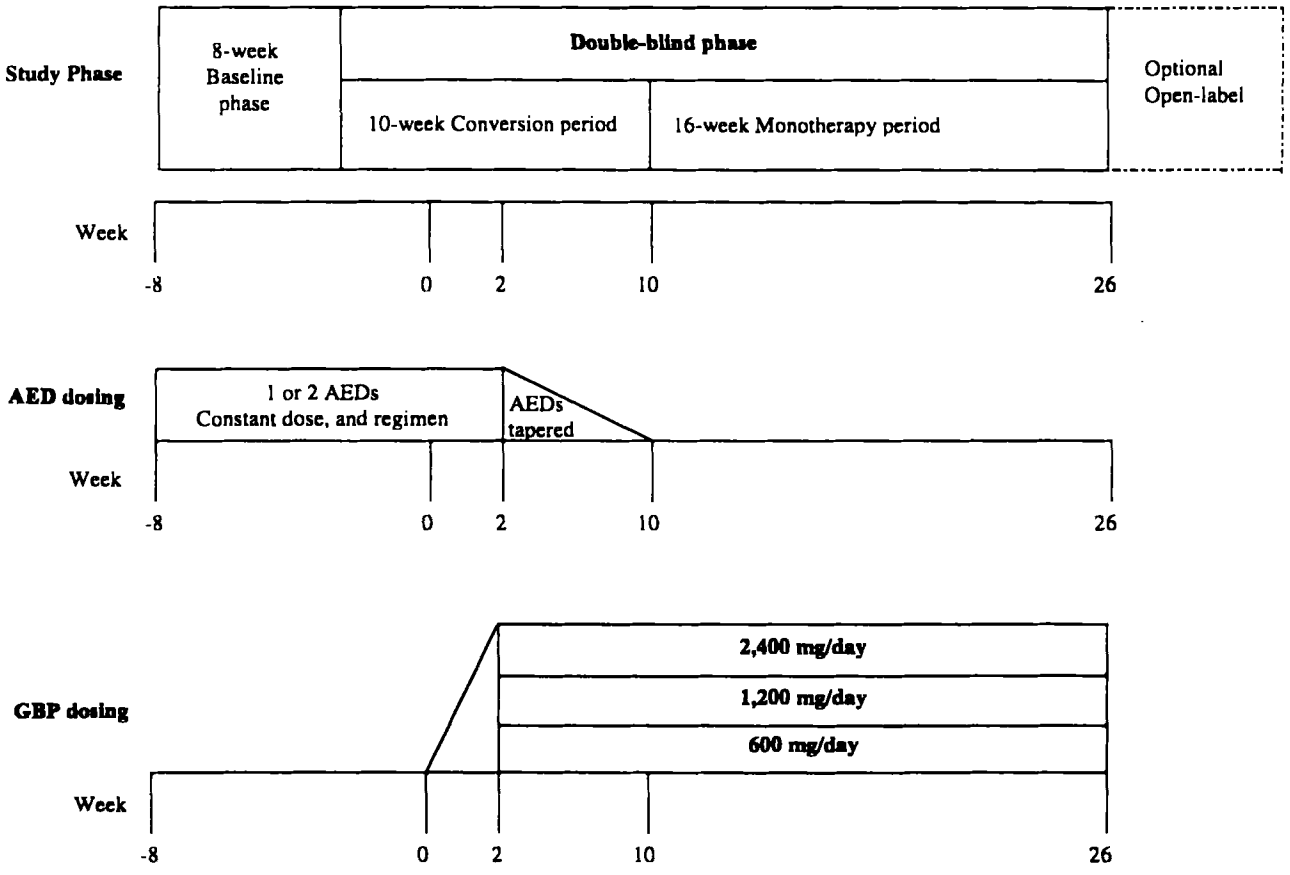

FIG. 1. Gabapentin (GBP) monotherapy outpatient study design. AED, antiepileptic drug.

89–101 days, with no statistically significant difference across the three dosage groups. Kaplan–Meier estimates of time to exit showed that patients who were maintained on one AED during baseline and those whose baseline AEDs did not include carbamazepine (CBZ) remained longer in the study. The trough GBP plasma concentration averaged approximately 2.5 mg/L in the 600-mg/day and 6 mg/L in the 2,400-mg/day dosage groups. GBP was well tolerated, with only 3% of patients exiting because of significant side effects. The most common adverse events were dizziness (13–25%), somnolence (7–16%), headache (10–13%), ataxia (7–13%), and fatigue (6–14%).

Inpatient trial in patients with refractory partial seizures

This multicenter, double-blind, dose-response trial (Study No. 945-88) was performed in an inpatient setting. Patients who were enrolled had medically refractory partial epilepsy, were admitted for EEG monitoring via closed-circuit television, and had discontinued their baseline AEDs as part of their surgical workup (11). Qualifying patients were randomized to treatment with GBP at 300 mg/day or 3,600 mg/day, with the full daily dosage administered on day 1 on a t.i.d. schedule (Fig. 2). Patients remained in the trial for a total of 8 days or until they satisfied one of the following exit criteria: four complex partial or secondarily generalized tonic–clonic seizures; a single generalized tonic–clonic seizure if none had occurred during the previous 6 months; an episode of status epilepticus; or a significant prolongation in the duration or intensity of the seizures. The primary efficacy variable was time to exit between the two groups, and the secondary efficacy parameter was the percentage of patients in each group who completed the 8-day trial without satisfying any of the study-defined exit criteria.

A total of 82 patients were randomized in the trial. The mean time to exit was significantly longer for patients receiving 3,600 mg/day (151 h) than for patients receiving 300 mg/day (85 h) ($p = 0.0001$). Similarly, 53% of patients randomized to the high-dosage group completed the trial, compared with 17% of those randomized to the low-dosage group ($p = 0.002$). The mean trough GBP level in patients randomized to the 300-mg/day group was 1 mg/L compared with 9 mg/L for those in the 3,600-mg/day group. Despite administration of the full dose on day 1, none of the patients exited the trial because of AEs. The most common AEs for patients in the 3,600-mg/day group were ataxia (20%), dizziness (18%),

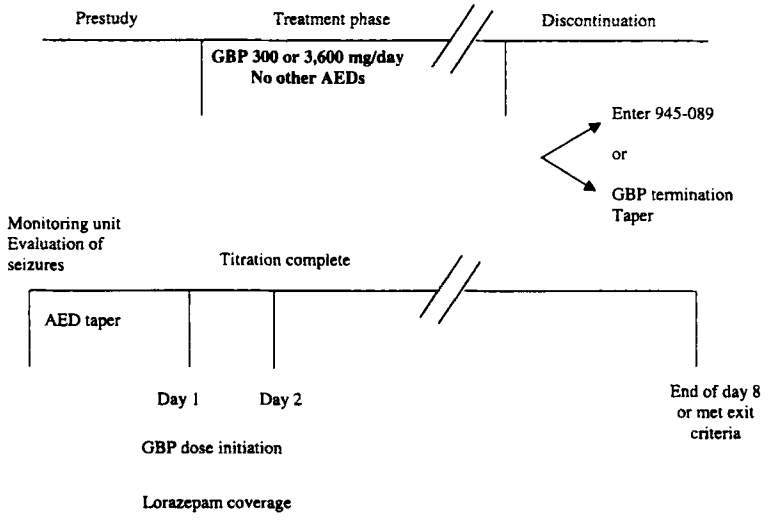

FIG. 2. Gabapentin (GBP) monotherapy inpatient study design. AED, antiepileptic drug.

somnolence (15%), nystagmus (13%), paresthesia (10%), and fatigue (10%).

Outpatient trial in patients with new-onset seizures

In a multicenter, randomized, double-blind, dose–response clinical trial, 292 patients with newly diagnosed epilepsy who had experienced at least two partial or generalized tonic–clonic seizures were randomized to blinded dosages of GBP (300, 900, or 1,800 mg/day) or to open-label treatment with CBZ at 600 mg/day (Fig. 3). After a titration period (1 week for GBP, 3 weeks for CBZ), patients were maintained on randomized dosages for 24 weeks or until they experienced one or more exit events, defined as one generalized tonic–clonic seizure, three partial seizures, status epilepticus, or other lack of efficacy. The primary efficacy variable was time to exit across the three blinded GBP dosage groups.

Mean time to exit was significantly longer for patients who received GBP 900 mg/day ($p = 0.02$) or 1,800 mg/day ($p = 0.04$) than for patients who received 300 mg/day. The exit rate was significantly higher for the GBP group receiving 300 mg/day than for those in the 900-mg/day ($p = 0.01$) or 1,800-mg/day ($p = 0.02$) dosage groups. No significant difference was found in time to exit or exit rate between the GBP 900-mg/day and 1,800-mg/day groups. The withdrawal rate attributable to AEs was significantly higher for the GBP 1,800 mg/day group than for the GBP 300-mg/day group ($p = 0.003$). Time to exit and completer rates were comparable for patients treated with CBZ and for those treated with GBP at 900 mg/day or 1,800 mg/day. The exit rates were 30, 40, and 43% in the CBZ, GBP 900-mg/day, and GBP 1,800-mg/day groups, respectively, whereas the withdrawal rates attributable to AEs were 24, 4, and 14% in the same groups, respectively.

LTG MONOTHERAPY TRIALS

In the United States, LTG has been approved as an add-on agent for treatment of partial seizures in patients

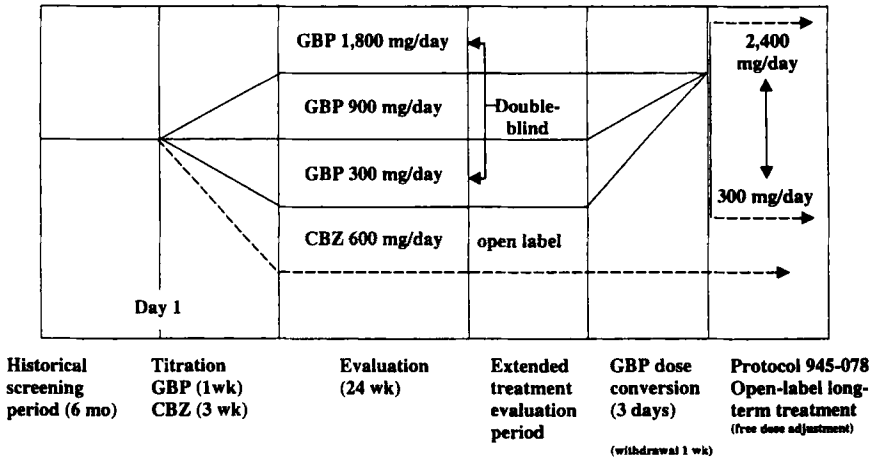

FIG. 3. Gabapentin (GBP) monotherapy new-onset epilepsy study design. CBZ, carbamazepine.

aged ≥16 years on the basis of results of clinical trials in which daily dosages of 300–500 mg were used (13,14). The efficacy and safety of LTG as monotherapy have been evaluated in two European comparative trials in patients with newly diagnosed epilepsy and in one North American active-control, therapeutic failure design trial in patients with medically refractory partial seizures (Table 1).

Comparative trial of LTG vs. CBZ

This 48-week study was a multicenter, double-blind, parallel-group design clinical trial that compared the efficacy and safety of LTG with that of CBZ in patients ≥13 years of age who had newly diagnosed, untreated epilepsy and were naive to AED treatment (15). LTG and CBZ were titrated over a 4-week period to a total daily dosage of 150 mg for LTG and 600 mg for CBZ on a b.i.d. schedule. During weeks 6–24, dosage adjustments were permitted on the basis of seizure occurrence, AEs, and serum levels. Between weeks 25 and 48, the daily dosage remained constant except when adverse events required decreasing the dose. Efficacy variables were time to first seizure after 6 weeks of treatment, time to withdrawal, and proportion of seizure-free patients during the last 24 and last 40 weeks of the trial.

A total of 260 patients were randomized at eight centers throughout the United Kingdom. Approximately 55% of patients in each group had partial seizures with or without secondary generalization, whereas the rest had primary generalized epilepsy with tonic–clonic seizures. No statistically significant difference was found between the two groups (or according to seizure types in each group) either in time to first seizure after 6 weeks of treatment or in the percentage of seizure-free patients during the last 24 weeks (39% LTG, 38% CBZ) or 40 weeks (26% LTG, 29% CBZ) of treatment. The median daily dosage of LTG was 150 mg (range 100–300 mg), with median serum levels ranging between 2.6 and 3.2 mg/L. The median daily dosage of CBZ was 600 mg (range 300–1,400 mg), with median serum levels ranging between 7.4 and 8.3 mg/L. Time to withdrawal analysis, a measure of both efficacy and tolerability, showed that significantly more patients in the LTG group completed the trial compared with the CBZ-treated group (65% vs. 51%; $p = 0.018$). A total of 35 CBZ-treated patients (27%) exited the trial because of AEs, compared with 19 patients (15%) who had been treated with LTG. Rash was the most common AE leading to withdrawal from the study in both groups. Sleepiness or ataxia led eight CBZ-treated patients to exit the trial, compared with none in the LTG-treated group. Overall, the most common AEs were headache (LTG group 30%; CBZ group 25%), asthenia (LTG group 21%; CBZ group 29%), and rash (19% in each group). No statistically significant differences were found between the two groups with respect to frequency of AEs except for sleepiness, which was seen in 22% of CBZ-treated patients compared with 12% of LTG-treated patients ($p < 0.05$).

Comparative trial of LTG vs. phenytoin (PHT) in newly diagnosed epilepsy

In a multicenter, double-blind, parallel-group, concentration-controlled clinical trial, 181 patients aged 14–75 years with newly diagnosed untreated epilepsy were randomized to treatment with LTG or PHT (16). Efficacy variables were time to first seizure after 6 weeks of treatment, time to withdrawal, and proportion of patients who were seizure-free during the last 24 weeks of the trial.

No significant difference was found between the two groups in time to first seizure after 6 weeks of treatment, percentage of seizure-free patients during the last 24 weeks of treatment (43% LTG and 36% PHT), or in time to exit from the study. Modal dosages during the study were 150 mg/day for LTG- and 300 mg/day for PHT-treated patients.

Outpatient trial in patients with medically refractory epilepsy

A 156-patient, multicenter, double-blind, parallel-group, active-control study was conducted at 36 centers across the United States (17). The participants were medically refractory patients ≥13 years of age who had experienced eight or more partial seizures during an 8-week baseline period while maintained on PHT or CBZ monotherapy, and were randomized to treatment with LTG 500 mg/day or valproate (VPA) 1,000 mg/day. Conversion took place over a period of 8 weeks, after which the patients were maintained on randomized doses as monotherapy for 12 weeks or until they satisfied one or more of the following exit criteria: a doubling of the 28-day or highest 2-day seizure frequency during baseline; emergence of a new and more severe seizure type; or significant prolongation of generalized tonic–clonic seizures (Fig. 4). The primary efficacy variable was the proportion of patients who met exit criteria, and the secondary outcome parameter was time to exit across the two treatment groups.

The proportion of treatment failures in the LTG group was 63%, compared with 84% for patients randomized to the VPA group ($p < 0.007$). The median time to treatment failure was significantly longer in the LTG-treated patients (80 days) vs. the VPA-treated patients (58 days) ($p = 0.027$). Overall, LTG was well tolerated in this trial.

LTG monotherapy and absence seizures

The safety and efficacy of LTG monotherapy for absence seizures were evaluated in a multicenter, double-

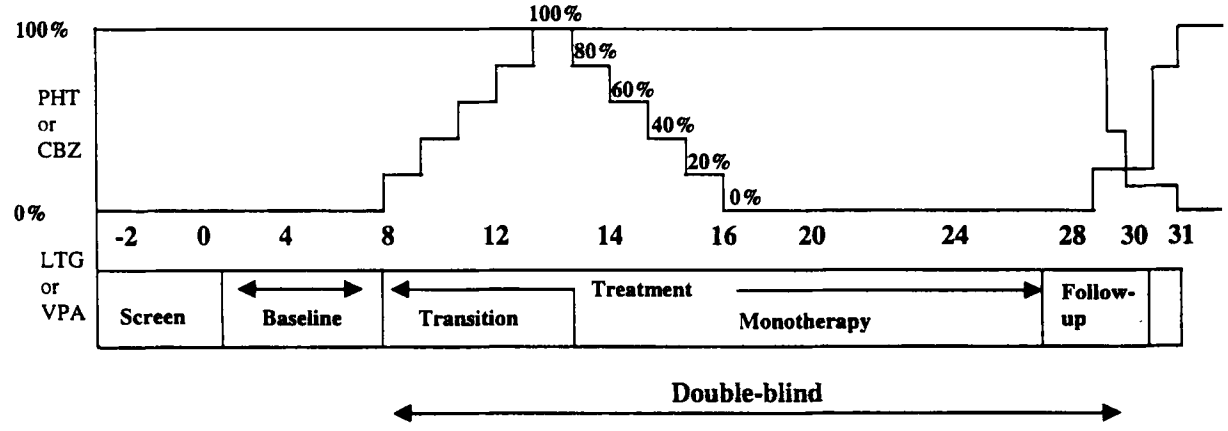

FIG. 4. Lamotrigine (LTG) monotherapy active-control study design. CBZ, carbamazepine; PHT, phenytoin; VPA, valproate.

blind, responder-enriched study in children and adolescents aged 2–16 years with newly diagnosed typical absence seizures who were naive to AED treatment (18). The diagnosis of absence seizures was confirmed by EEG recording during hyperventilation. After enrollment in the trial, all patients received LTG during a 4- to 18-week open-label treatment phase. The initial LTG dosage, 0.5 mg/kg/day for the first 2 weeks, was progressively increased (by 0.5 mg/kg/day for the subsequent 2 weeks, then by 1 mg/kg/day at weekly intervals) until the patients became seizure-free or reached the maximal allowable LTG dose: the lesser of 7 mg/kg/day or 700 mg/day for the first 20 patients, and the lesser of 15 mg/kg/day or 1,000 mg/day for the subsequent 25 patients (Fig. 5). Patients who became seizure-free were assigned in a 1:1 ratio during the double-blind phase to either placebo treatment after LTG taper or continuation of the LTG dose determined to be effective during the open-label phase. If patients developed seizures at any time during the 4-week double-blind phase, they were considered to have completed the study. The primary efficacy variable was the proportion of patients in each treatment group who remained seizure-free throughout the double-blind treatment phase.

Of the 45 patients enrolled in the open-label treatment phase, 28 patients were randomized in the double-blind phase. Significantly more patients in the LTG group remained seizure-free throughout the double-blind phase (64%) compared with patients in the placebo group (36%) ($p < 0.05$). In the open-label treatment phase, 71% became seizure-free receiving a mean LTG dose of 6 mg/kg/day (range 2–15 mg/kg/day). LTG was well tolerated in this trial; no patient exited because of AEs.

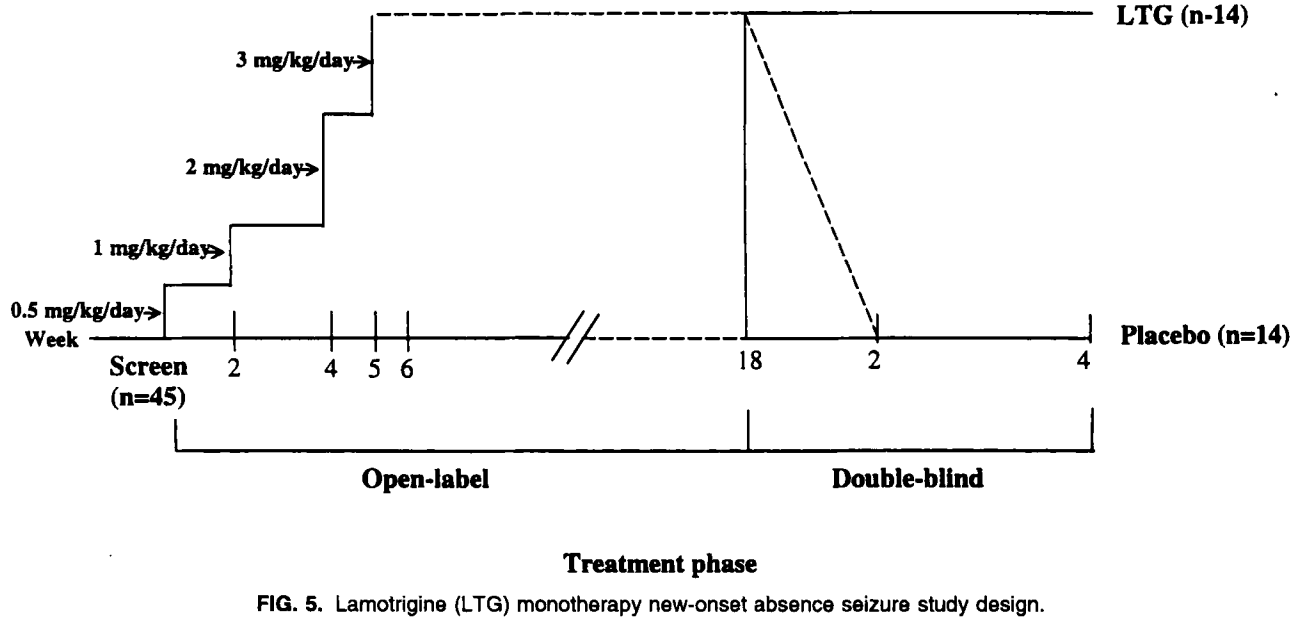

FIG. 5. Lamotrigine (LTG) monotherapy new-onset absence seizure study design.

TPM MONOTHERAPY TRIAL

TPM monotherapy for medically refractory partial seizures was evaluated in a single-center, double-blind, dose–response, therapeutic-failure design clinical trial (19). The patients enrolled in the trial had four or more partial-onset seizures per month while maintained on constant doses of one or two AEDs during a 56-day baseline phase. After 1 week of open-label add-on TPM at 100 mg/day, study participants were randomized to receive either 100 mg/day or 1,000 mg/day of TPM taken on a b.i.d. schedule (Fig. 6). The conversion to monotherapy took place over 5 weeks, after which patients were maintained in randomized TPM dosage groups for 11 weeks or until they satisfied one or more of the following exit criteria: a doubling of the 28-day or highest 2-day seizure frequency during baseline; a secondarily generalized tonic–clonic seizure (if none was noted during baseline); serial seizures or status epilepticus; or more prolonged duration of generalized seizures. The primary efficacy variable was time to exit between the two groups, and the secondary efficacy parameter was the percent completers across the two dosage groups.

A total of 48 patients were randomized in this trial. Time to exit was significantly longer for patients receiving 1,000 mg/day than for those receiving 100 mg/day ($p = 0.002$). Similarly, 54% of patients randomized to the high-dosage group completed the trial, compared with 17% randomized to the lower dosage group ($p = 0.02$). Only one patient discontinued the trial during the double-blind phase because of AEs. The most frequently reported AEs were paresthesias (56–63%), fatigue (33–46%), dizziness (25%), headache (25%), and nausea (17–25%), with similar incidence between the two groups except for anorexia, which was more common in the TPM 1,000 mg/day group.

TGB MONOTHERAPY TRIAL

The safety and efficacy of TGB as monotherapy were evaluated in patients with medically refractory partial seizures in a multicenter, double-blind, parallel-group, dose-response, therapeutic-failure-design clinical trial (20). Recruited patients ranged in age from 10 to 85 years, and had experienced at least four complex partial seizures, with or without secondary generalization, over an 8-week period while maintained on constant doses of one AED. After an 8-week baseline period, patients were randomly assigned to treatment with TGB 6 mg/day or TGB 36 mg/day (Fig. 7). Patients were titrated to the target dosage over a 2-week period that was followed by a 4-week taper and discontinuation of the baseline AED. They were subsequently maintained in randomized dosage groups for a total of 12 weeks or were eligible to exit if any of the following criteria were met: a secondarily generalized tonic–clonic seizure in patients if no previous history of this seizure type had been noted; two generalized tonic–clonic seizures if none had occurred during baseline; and doubling of the highest 2-day seizure frequency during baseline. The primary efficacy variable was the median 4-week complex–partial seizure rates between the two dosage groups.

A total of 198 patients from 22 centers across the United States were randomized in the trial. No statistically significant difference was observed between the two groups in the median 4-week complex partial seizure rates, nor in time to exit. Trial completion was achieved by 34 patients (33%) in the 6-mg/day group and 23

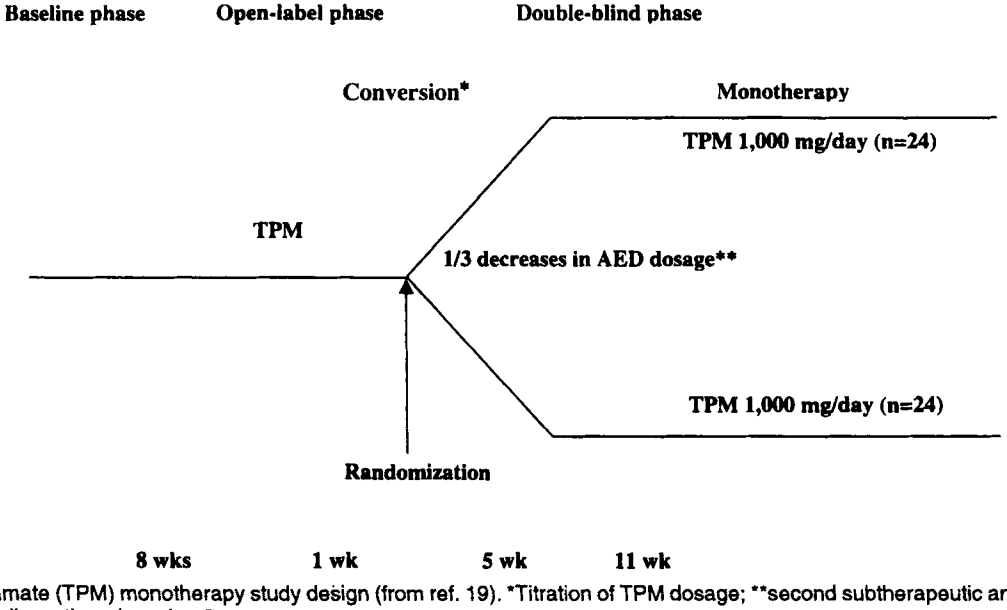

FIG. 6. Topiramate (TPM) monotherapy study design (from ref. 19). *Titration of TPM dosage; **second subtherapeutic antiepileptic drug (AED), if any, discontinued on day 8.

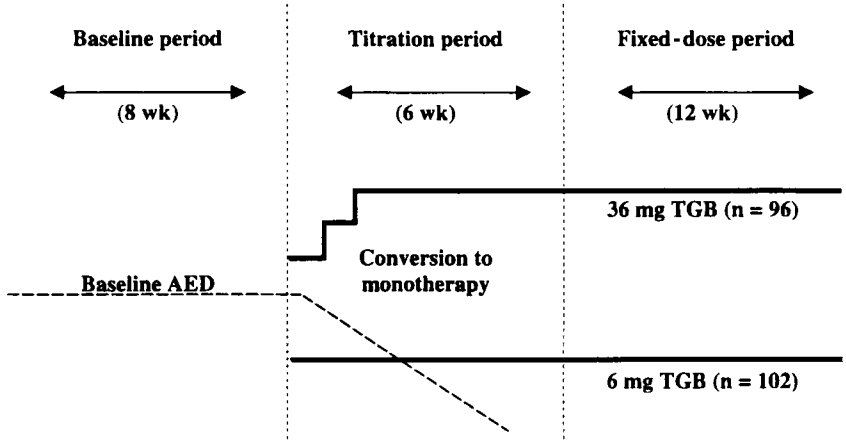

FIG. 7. Tiagabine (TGB) monotherapy study design. AED, antiepileptic drug.

patients (24%) in the 36-mg/day group. A statistically significantly higher percentage of patients in the TGB 36-mg/day group experienced amblyopia, dizziness, incoordination, nervousness, paresthesias, somnolence, speech disorder, abnormal thinking, and tremor compared with patients in the TGB 6-mg/day group.

OXCARBAZEPINE (OCBZ) MONOTHERAPY TRIALS

The safety and efficacy of OCBZ monotherapy have been evaluated in four European comparative trials in patients with newly diagnosed epilepsy and in one North American inpatient therapeutic-failure–design trial in patients with medically refractory partial epilepsy.

Comparative trials

All four European trials had similar designs. Patients with partial seizures or with idiopathic generalized epilepsy with tonic–clonic seizures were randomized in a double-blind fashion to treatment with OCBZ or one of the standard AEDs. The trial consisted of an 8-week titration phase followed by a 48-week maintenance period. Efficacy variables consisted of the mean seizure frequency per week and the percentage of seizure-free patients during the maintenance phase.

OCBZ was compared with PHT in adults aged 15–91 years and in children and adolescents aged 5–17 years. In both trials, PHT and OCBZ had similar efficacy, with 57–65 of patients remaining seizure-free during the maintenance phase. However, OCBZ was significantly better tolerated than PHT in both trials, with withdrawal because of AEs being significantly less frequent in OCBZ-treated patients (2–4%) compared with PHT-treated patients (11–15%). The daily dosage of OCBZ averaged 672 mg in children and adolescents (range 300–1,350 mg) and 1,028 mg (range 600–2,100 mg) in adults. The average daily PHT dosage was 226 mg (range 100–400 mg) in children and adolescents and 313 mg (range 100–650 mg) in adults.

A comparative trial between OCBZ and VPA in 424 patients aged 15–65 years found them to be of similar efficacy and tolerability, with 60% of patients randomized to OCBZ remaining seizure-free during the maintenance phase compared with 57% of VPA-treated patients. AEs led to withdrawal rates of 13% and 7% in OCBZ- and VPA-treated patients, respectively. The average daily dosage of OCBZ was 1,052 mg (range 600–2,400 mg) and that of VPA was 1,146 mg (range 600–2,700 mg).

Inpatient trial in patients with refractory partial seizures

The efficacy and safety of OCBZ in monotherapy were evaluated in a multicenter, double-blind, randomized, placebo-controlled inpatient trial whose study population consisted of patients undergoing evaluation for epilepsy surgery (21). Eligible patients were randomized to receive OCBZ (1,200 mg b.i.d.) or placebo (Fig. 8). Patients remained in the trial for 10 days or until they experienced one of the following study-defined exit criteria: a total of four seizures; two new-onset secondarily generalized seizures; serial seizures; or status epilepticus. The primary efficacy variable was time to exit between the two groups, and the secondary efficacy parameter was the percentage of patients who met one or more of the exit criteria.

A total of 102 patients were randomized in this trial, with time to exit being significantly longer in OCBZ-treated patients compared with placebo ($p = 0.001$). Of the OCBZ-treated patients, 44% met an exit criterion compared with the placebo-treated patients, 88% of whom met an exit criterion ($p < 0.001$).

THERAPEUTIC FAILURE DESIGN TRIALS

The design of monotherapy trials in the United States is in an evolutionary stage, and much can be learned from the results of the concluded trials. For example, inpatient trials appear to be very useful for demonstrating

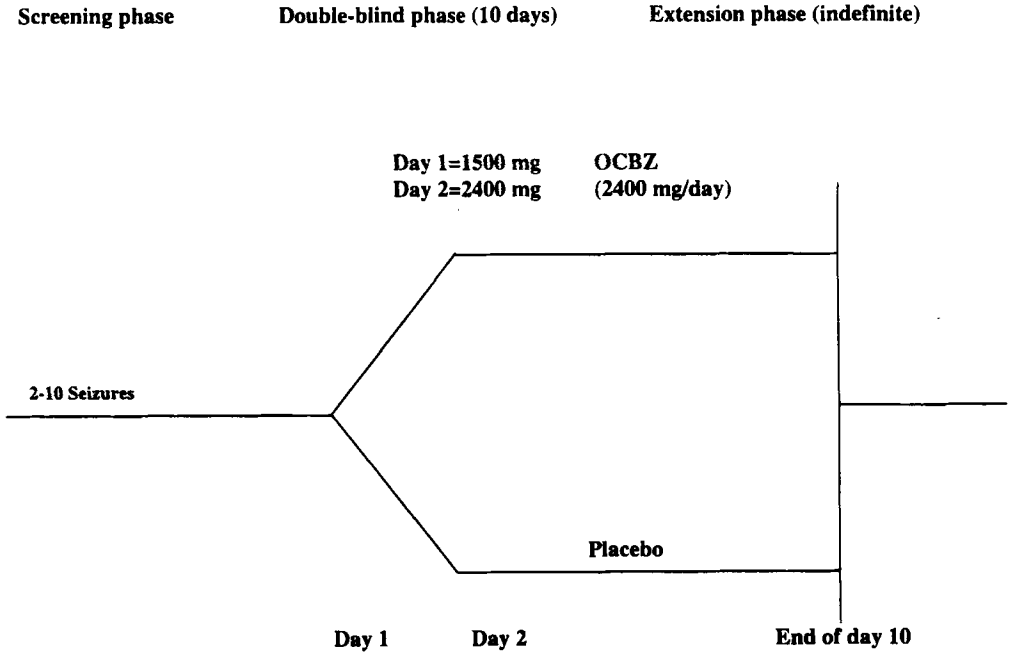

FIG. 8. Oxcarbazepine (OCBZ) monotherapy inpatient study design.

the efficacy of a study drug as monotherapy in a relatively short period of time and with a relatively small number of patients. Thus far, all concluded trials that use this design (either dose–response or placebo-controlled) have resulted in "positive" trials (11,21,22). These studies are conducted in a controlled environment, the seizure count is well documented, and the risk to patients is minimized by the inclusion of strict exit criteria. However, this type of design does not provide any information about the long-term safety of the study drug as monotherapy or about its efficacy over time because of the development of tolerance. In addition, drugs that cannot be titrated quickly, such as LTG or TPM, cannot be tested in such a study design. On the other hand, monotherapy trials in outpatients with medically refractory partial seizures are proving to be very difficult designs. Despite differences in the duration of the double-blind and conversion phases and in the allowed number of baseline AEDs, the completer rates have been uniformly low across all such concluded trials (Table 2). Although two of the four trials were "positive" and two were "uninformative" (5), the only study with a completer rate of greater than 50% was the single-center dose–response trial with TPM. Various factors that lead to a high failure rate may play a role in this type of design, including the refractory nature of the patient population being tested, the occurrence of withdrawal seizures, the duration of the trial, the dosages of the study drug chosen, and perhaps an incentive for some patients to be in the open-label phase of the trial. The trend toward this type of design is likely to continue and may prompt a shift toward testing of the efficacy of study drugs as

TABLE 2. *Outpatient therapeutic-failure-design trials in patients with medically refractory partial epilepsy*

Drug	Dosage (mg/day)	Patients (%)	Duration of double-blind phase (wk)	Duration of conversion phase (wk)	Baseline AEDs (*n*)	Completer rate (%)
GBP	600	93	26	10	1 or 2	15
	1,200	90	26		1 or 2	26
	2,400	91	26	(2 + 8)	1 or 2	19
LTG	LTG 500	76	20	8	1	37
	VPA 1,000	80	20	(4 + 4)	1	16
TPM	100	24	16	5	1 or 2	17
	1,000	24	16	5	1 or 2	54
TGB	6	102	18	6	1	33
	36	96	18	(2 + 4)	1	24

AEDs, antiepileptic drugs; other abbreviations as in Table 1.

monotherapy in patients with less refractory seizures or in those with newly diagnosed epilepsy in future clinical trials.

EFFICACY OF THE NEWER AEDs AS MONOTHERAPY

Thus far, evaluation of GBP as monotherapy has consisted of three clinical trials: two "positive" and one uninformative (Table 3). Their results have been submitted to the FDA to satisfy requirements for efficacy. A supplemental new drug application for a monotherapy indication in patients with partial-onset seizures was filed in September of 1996, with a decision expected in the fall of 1997. The efficacy of LTG monotherapy was shown in one active-control trial in patients with medically refractory partial epilepsy. In addition, its efficacy was found to be similar to that of PHT and CBZ and significantly better tolerated than CBZ (Table 2). On the basis of these trials, a supplemental new drug application for monotherapy indication was filed with the FDA in early 1997. It is likely that approval will be granted based on that one "positive" trial alone, because divalproex sodium was recently approved for monotherapy indications based on the "positive" results of a single therapeutic-failure-design clinical trial (23). OCBZ was found to have equivalent efficacy to and comparable or superior tolerability than the standard AEDs. It was also shown to have short-term anticonvulsant properties as monotherapy in an inpatient trial (Table 3). The "positive" results from the inpatient trial alone are unlikely to satisfy the FDA's requirements, because information obtained solely from one or more short inpatient trials makes it difficult to approve a drug for an outpatient population. An interesting point for discussion would be whether the results of one or more "positive" inpatient trials, in conjunction with one or more comparative trials showing equivalence between the study drug and a standard AED, should be enough to satisfy the FDA's requirements for efficacy. TPM was found to have efficacy as monotherapy in a single-center, dose–response trial (Table 3) (24). Although these results are encouraging, more data are needed to establish the efficacy of TPM as monotherapy. The TGB trial yielded uninformative results, and more studies are needed to evaluate its efficacy as monotherapy (Table 3) (25).

TABLE 3. *Therapeutic failure designs*

	Comparative equivalence	Presurgical	Active control	Dose–response
GBP		+		+
LTG	Yes		+	
TPM				+
OCBZ	Yes	+		
TGB				

Abbreviations as in Table 1.

CONCLUSIONS

Although therapeutic-failure-design trials are the only types of trials that can unequivocally prove the efficacy of the study drug as monotherapy, they do not necessarily address the concerns of physicians about how the study drugs compare with more familiar standard AEDs, or how best to use them as monotherapy. It is unlikely that pharmaceutical companies will be willing to invest large sums of money to answer these questions once FDA approval has been granted for some indication. We are therefore left with trials that show statistical evidence of efficacy but whose clinical utility, especially when compared with the standard AEDs, remains largely undetermined. Concerns regarding the statistical validity of equivalence trials and the clinical relevance of therapeutic-failure-design trials remain unresolved.

The answer need not be an either/or phenomenon. The design of statistically sound and clinically relevant monotherapy trials will require input from regulatory agencies, statisticians, pharmaceutical companies, clinicians, and insurance company representatives. In addition, much can be learned from the results of completed monotherapy trials to design future studies that not only are statistically sound but are also safe and clinically relevant.

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