# A COMPARISON OF VALPROATE WITH CARBAMAZEPINE FOR THE TREATMENT OF COMPLEX PARTIAL SEIZURES AND SECONDARILY GENERALIZED TONIC–CLONIC SEIZURES IN ADULTS

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**Abstract** *Background.* Valproate is approved for use primarily in patients with absence seizures, but the drug has a broad spectrum of activity against seizures of all types. Partial or secondarily generalized tonic–clonic seizures are often difficult to control adequately with standard treatment, usually carbamazepine or phenytoin.

*Methods.* We conducted a multicenter, double-blind trial that compared valproate with carbamazepine in the treatment of 480 adults with complex partial seizures (206 patients) or secondarily generalized tonic–clonic seizures (274 patients). The patients were randomly assigned to treatment with carbamazepine or divalproex sodium (valproate) at doses adjusted to achieve blood levels in the middle of the therapeutic range. Patients were followed for one to five years or until seizures became uncontrollable, treatment had unacceptable adverse effects, or both these events occurred.

*Results.* For the control of secondarily generalized tonic–clonic seizures, carbamazepine and valproate were comparably effective (in 136 patients and 138 patients, respectively). For complex partial seizures, four of five outcome measures favored carbamazepine (100 patients) over valproate (106 patients): the total number of seizures (2.7 vs. 7.6, $P=0.05$), the number of seizures per month (0.9 vs. 2.2, $P=0.01$), the time to the first seizure ($P<0.02$), and the seizure-rating score ($P=0.04$). Carbamazepine was also superior according to a composite score that combined scores for the control of seizures and for adverse effects ($P<0.001$). Valproate was associated more frequently than carbamazepine with a weight gain of more than 5.5 kg (12 lb) (20 percent vs. 8 percent, $P<0.001$), with hair loss or change in texture (12 percent vs. 6 percent, $P=0.02$), and with tremor (45 percent vs. 22 percent, $P<0.001$). Rash was more often associated with carbamazepine (11 percent vs. 1 percent, $P<0.001$).

*Conclusions.* Valproate is as effective as carbamazepine for the treatment of generalized tonic–clonic seizures, but carbamazepine provides better control of complex partial seizures and has fewer long-term adverse effects. (N Engl J Med 1992;327:765-71.)

EACH year symptomatic localization-related (partial) epilepsy with partial or secondarily generalized tonic–clonic seizures develops in 70,000 to 130,000 adults.[1] If such seizures are not controlled, major compromises in the quality of life result. Adverse effects of drugs add to the disabling consequences of the disorder.[2,3] Although several medications are used to treat such seizures, in approximately one third of patients they cannot be adequately controlled with any single drug or combination of drugs. On the basis of many clinical trials, carbamazepine and phenytoin are considered to have the best overall combination of efficacy and freedom from adverse effects during treatment of symptomatic localization-related (partial) epilepsy.[4-7]

Valproate (divalproex sodium), one of the newest antiepileptic drugs, was approved by the Food and Drug Administration in 1978 for "use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures." Over the past decade, considerable evidence has accrued to indicate that valproate used alone is also effective for tonic–clonic seizures associated with absence seizures and for myoclonic seizures in patients with idiopathic generalized epilepsy.[6-14] Valproate is the only drug capable of controlling all types of seizures associated with the idiopathic generalized epilepsies and is considered by many to be the drug of choice for these conditions.[5]

In experimental models of seizures and epilepsy, valproate has a broad spectrum of antiepileptic properties, leading to the expectation that it may have some efficacy against all types of seizures.[15] A number of clinical studies indicate that valproate is comparable to carbamazepine or phenytoin in the treatment of complex partial seizures and secondarily generalized seizures associated with symptomatic localization-related (partial) epilepsy.[6,7,16-18]

To address the need for additional drugs to treat complex partial and secondarily generalized tonic–clonic seizures and to assess the potential role of valproate for this purpose, a multicenter trial was designed to study the efficacy and toxicity of valproate as compared with carbamazepine.

## METHODS

The trial was initiated in 1985 at 13 Veterans Affairs medical centers. The design of the study was similar to the previous study of antiepileptic drugs by the Department of Veterans Affairs.[4,19,20] All patients were fully informed about the trial and the fact that valproate was not approved by the Food and Drug Administration for treatment of partial or secondarily generalized tonic–clonic seizures. Adult patients with previously untreated or undertreated complex partial seizures, secondarily generalized tonic–clonic sei-

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Supported by the Department of Veterans Affairs Medical Research Service, Cooperative Studies Program (CS no. 264), with additional support from Abbott Laboratories Pharmaceutical and Diagnostic Divisions and Ciba–Geigy Pharmaceuticals.

*Participants in the Epilepsy Cooperative Study No. 264 are listed in the Appendix.

zures, or both were randomly assigned to therapy with carbamazepine or valproate. A different randomization scheme was used for each of the two seizure groups, which were based on the type of seizure predominant in each patient.

Evaluations were performed at 1 and 2 weeks and at 1, 2, 3, 4, 6, 9, and 12 months during the first study year, quarterly during the second year, semiannually thereafter, and at unscheduled visits when clinically appropriate. Patients continued to take the original study drug until the end of the trial unless the drug failed to control their seizures or had unacceptable side effects. Thus, all patients entered were eligible for follow-up lasting at least one year, but those entering the study early were followed for as long as five years.

### Criteria for Entry

We studied men and women 18 to 70 years of age with a diagnosis of symptomatic localization-related (partial) epilepsy with complex partial seizures (psychomotor) or secondarily generalized tonic–clonic seizures (grand mal) as defined in the International Classification of Epileptic Seizures[21] and the International Classification of Epilepsies and Epileptic Syndromes.[22] Patients were included if they had no documented failure of treatment with either of the study drugs or hypersensitivity to them, no history of alcohol or drug abuse, no record of noncompliance with treatment programs, no severe psychiatric problems, and no progressive neurologic disorder or serious, unstable medical condition; in addition, they had to be of normal intelligence (IQ above 85 according to the Wechsler Adult Intelligence Scale). Patients with alcohol-related seizures were excluded.

### Drug Treatment

The study protocol was designed to conform as closely as possible to standards of optimal clinical practice, except that treatment was double-blinded. Patients were randomly assigned to receive one of the two active preparations — carbamazepine (Tegretol; 200-mg scored tablets) or valproate (divalproex sodium, Depakote; 250-mg or 500-mg tablets). The active medications and matching placebos were provided by Ciba–Geigy Pharmaceuticals and Abbott Laboratories (Pharmaceutical Division). Doses were adjusted on an individual basis to achieve serum concentrations in the middle of the target ranges (carbamazepine, 7 to 8 $\mu$g per milliliter; valproate, 80 to 100 $\mu$g per milliliter).

If the initial use of a drug had dose-related adverse effects, the medication was withheld or the dosage was decreased temporarily. If seizures were not controlled, the dose was increased. If adverse effects occurred, the dose was reduced to resolve the problem. If seizures of unacceptable frequency or severity occurred when the dose was lowered to a tolerable level, the drug treatment was considered to have failed. Thus, treatment failure was defined as the result of a combination of adverse effects and seizures, a definition that would be accepted in standard clinical practice.

Compliance was monitored by measuring serum concentrations of the drug, interviewing the patients, and recording their adherence to scheduled appointments.

### Assessment of Outcome

The measures of the frequency and severity of seizures used in this trial, as well as those of systemic toxicity and neurotoxicity, were adapted from scales designed for a previous trial[20] in anticipation of somewhat different adverse effects (details are available from the authors). The rating-scale scores, determined at each visit, served as a quantitative assessment of the overall adequacy of management.

The total of each type of seizure (generalized tonic–clonic, complex partial, and simple partial) was tabulated at each visit. In addition, seizures were scored according to a rating scale that assigned a value to each type, combining the frequency and severity of seizures and other factors.

Changes in physical status after drug administration started were recorded after evaluation of the gastrointestinal, hematopoietic, renal, hepatic, and dermatologic systems and the occurrence of sexual dysfunction, weight gain, or hair loss. In addition, these variables were scored on a toxicity-rating scale that reflected their clinical importance.[20]

Changes in neurologic status were recorded at each visit after drug administration started. The changes recorded were any problems with vision, speech, or motor functions (including tremor), sedation, headache, dizziness, lightheadedness, and changes in affect, mood or cognitive function. These variables were also scored in proportion to their severity.[20]

The total seizure-rating score (representing all types of seizures) was combined with the scores for systemic toxicity and neurotoxicity to produce a composite score. The rating scales were designed so that a composite score of 0 to 20 points represented a good clinical response; a score of 21 to 35 points, an acceptable but suboptimal response; a score of 36 to 49 points, a fair-to-poor but not clearly unacceptable outcome; and a score of 50 points or more, an unacceptable outcome that would correspond to a change in therapy. A difference of approximately 10 points was considered clinically important.

### Statistical Analysis

The primary outcome measures determined at the start of the study were efficacy (seizure control), adverse effects, treatment-success rate (represented by the length of time that patients continued to take the study drug without its being withdrawn because of lack of seizure control or adverse effects), and the composite score (a measure of the overall efficacy and adverse effects of the study drugs at 12 months). Efficacy was determined by analyzing five measures of seizure control: the total number of seizures during 12 or 24 months, the seizure rate, the percentage of patients whose seizures were completely controlled, the time to the first seizure, and the seizure-rating score at 12 and 24 months. All analyses of seizures were performed twice: first with inclusion of the results of the first month of treatment, and then with exclusion of the first month to allow for stabilization of the drug dosage and the serum levels of antiepileptic drug.

Recruitment goals were based on the largest sample required for assessing any of the primary end points and were determined separately for the patients with secondarily generalized tonic–clonic seizures and those with complex partial seizures. The sizes of the samples for all end points were calculated so that important clinical differences in the outcome measures at 12 months could be detected with a power of at least 0.80 and a significance level of 0.05, with expected dropout rates of less than 30 percent in the group with tonic–clonic seizures and less than 20 percent in the group with complex partial seizures. All statistical tests were two-sided. The group with predominantly secondarily generalized seizures contained 274 patients, allowing the detection of a difference of 16 percent in the percentage of patients who were seizure-free in the two drug-treatment groups, 20 percent in the treatment-failure rate and the incidence of adverse effects, and 10 points in the composite score. The group with predominantly complex partial seizures contained 206 patients, allowing the detection of a difference of at least 20 percent in the percentage of patients who were seizure-free and in the incidence of adverse effects, 25 percent in the treatment-failure rate, and 10 points in the composite score.

Treatment failure and the time to the first seizure were analyzed with the actuarial life-table method.[23] This method was preferred to the Kaplan–Meier method because withdrawal from the study or a seizure was recorded when the patient made a scheduled visit rather than when the event occurred. The generalized Wilcoxon statistic[24] was used to determine statistical significance in the life-table analyses. The Wilcoxon rank-sum test with correction for continuity was used to analyze composite, seizure, and toxicity-rating scores, seizure rates, and total numbers of seizures, to take into account the abnormal distribution of values for these variables and outlier values. Chi-square techniques were used to analyze the rate of complete control of seizures and the incidence of adverse effects. Analyses were performed separately for each seizure group as well as for both seizure groups combined.

The first set of analyses of the treatment-failure rate included the data recorded on patients who were withdrawn early for reasons not related to the study treatment, up to the time of withdrawal; these data were censored as of the date when these patients left the trial. The second set of analyses included these patients among those with treatment failure. These latter analyses addressed the possibility that an unrecognized, drug-related difference in the dropout rate existed but was not specifically detected.

## Results

### Description of the Study Groups

A total of 480 patients qualified for entry, gave written informed consent, and were randomly assigned to a treatment group on the basis of their predominant type of seizure; in the group with secondarily generalized tonic–clonic seizures 136 patients received carbamazepine and 138 received valproate, and in the group with complex partial seizures 100 received carbamazepine and 106 received valproate. Recruitment of patients started in February 1985; there were 100 patients in the group with tonic–clonic seizures and 65 in the group with partial seizures by the end of the first year; 159 and 95, respectively, by the end of the second year; 204 and 130, respectively, by the end of the third year; 247 and 175, respectively, by the end of the fourth year; and 274 and 206, respectively, by the end of the fifth year (February 1990). All patients who entered in the fifth year were eligible for follow-up for 12 months. The average length of follow-up treatment of the patients who remained in the study until its conclusion was 40 months; some patients were followed for as long as 5 years. Among the 130 patients unable to complete 12 months of follow-up for reasons unrelated to the study, there were no significant differences according to treatment or seizure group (47 carbamazepine recipients and 45 valproate recipients in the group with tonic–clonic seizures; 21 carbamazepine recipients and 17 valproate recipients in the group with complex partial seizures). The number of patients who withdrew early for reasons unrelated to the study treatment was the number anticipated on the basis of the previous trial.[4] Data on these patients recorded while they participated in the trial were included in the analyses. Four percent of these patients left the study because they moved, 6 percent because they had other medical problems, 5 percent because they did not comply with the protocol, 5 percent because they chose to leave, and 10 percent because they discontinued contact with study investigators (none of these reasons were related to epilepsy or the use of antiepileptic drugs); an additional 3 percent died. The treatment groups did not differ significantly in mean age (47 years), IQ according to the Wechsler Adult Intelligence Scale (99), number of years of education (11.2), age at first seizure (39 years), or cause of seizures (trauma in 31 percent, stroke in 14 percent, other reasons in 21 percent, and unknown factors in 33 percent). Overall, 93 percent of the patients were men, and 90 percent were veterans.

Serum drug concentrations were maintained within the therapeutic range throughout the study, indicating continuing good compliance. The mean levels (±SD) of both antiepileptic drugs at 12 months were in the middle of the target range (carbamazepine, 7.8±7.1 μg per milliliter; valproate, 89.6±35.2 μg per milliliter). The mean daily doses at 12 months were 722±230 mg of carbamazepine and 2099±824 mg of valproate.

Fifty percent of the patients had never received antiepileptic drugs before the study, 24 percent had taken them at some time but had discontinued treatment, and 26 percent were receiving them (in doses producing subtherapeutic serum levels) but discontinued treatment before they entered the trial.

### Measures of Efficacy

All patients were eligible for at least 12 months of follow-up, the interval planned for the primary assessment (Table 1). Five measures of efficacy were assessed.

#### *Seizure Count*

The total number of each type of seizure was significantly lower among the carbamazepine-treated patients with complex partial seizures, but not among the carbamazepine recipients with tonic–clonic seizures (Table 1).

#### *Seizure Rate*

The analysis of the seizure rate included the data recorded on all patients for as long as they remained in the trial, whereas the analysis of the seizure count (see above) included only the data recorded on patients who remained in the trial for 12 months. In the group

Table 1. Measures of the Efficacy of Carbamazepine and Valproate at 12 Months.

| Seizure Group | Carbamazepine | Valproate | P Value |
|---|---|---|---|
| | *mean ±SD (no. of patients)* | | |
| Generalized tonic–clonic (n = 274)* | | | |
| Seizure count/12 mo† | 0.6±1.3 (73) | 2.1±7.3 (78) | 0.09 |
| Seizure rate/mo | 0.2±1.0 (133) | 0.2±0.6 (134) | 0.06 |
| Seizure control — % of patients† | 35±59 (75) | 31±46 (80) | 0.65 |
| Seizure-rating score‡ | 4.0±11.2 (71) | 4.2±10.9 (75) | 0.79 |
| Complex partial (n = 206)§ | | | |
| Seizure count† | 2.7±4.0 (60) | 7.6±16.1 (65) | 0.05 |
| Seizure rate/mo | 0.9±3.0 (96) | 2.2±8.2 (105) | 0.01 |
| Seizure control — % of patients† | 34±45 (62) | 29±40 (65) | 0.57 |
| Seizure-rating score‡ | 2.0±4.4 (57) | 6.2±12.3 (61) | 0.04 |
| Both groups | | | |
| Seizure control — % of patients† | 34 (137) | 30 (175) | 0.48 |
| Seizure-rating score‡ | 3.1±8.9 (128) | 5.1±11.5 (136) | 0.11 |

*Only seizures of the predominant type were counted — i.e., tonic–clonic seizures.

†Seizures occurring in the first month were excluded.

‡The higher the score, the worse the seizure control.

§Only seizures of the predominant type were counted — i.e., complex partial seizures.

with complex partial seizures, seizure rates were significantly lower among the patients treated with carbamazepine than among those treated with valproate ($P<0.01$).

### *Seizure Control*

Analysis of the proportion of patients whose seizures were completely controlled after therapy began revealed no significant differences between the carbamazepine and valproate recipients in either seizure group after 12 or 24 months of follow-up.

### *Seizure-Rating Score*

The seizure-rating scale was used to assign scores for generalized tonic–clonic, complex partial, and simple partial seizures, which were combined into a total score. This score was significantly lower (i.e., denoted improvement) among carbamazepine recipients in the group with complex partial seizures, but not in the group with tonic–clonic seizures.

### *Time to the First Seizure*

The percentage of patients remaining seizure-free, as well as the time to the first seizure after an appropriate dose had been established, was analyzed with life-table methods. Seizures recurred significantly sooner among valproate-treated patients in the group with complex partial seizures or in both seizure groups combined, despite the similar outcome in those groups after 12 months (Fig. 1).

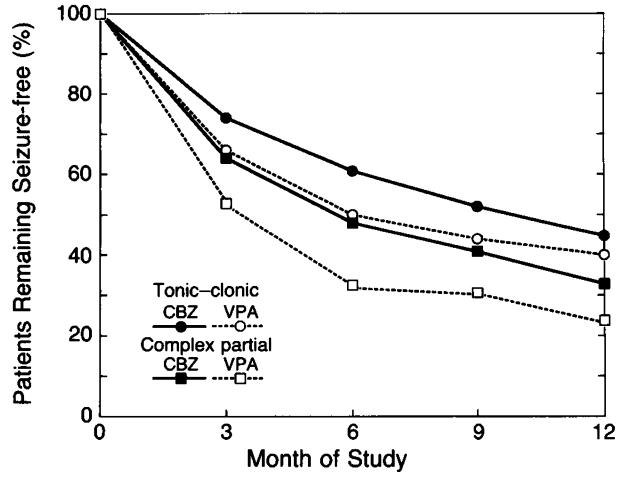


Figure 1. Percentage of Patients Remaining Seizure-free (Time to the First Seizure).

During the 12-month period, patients in the group with complex partial seizures who were taking valproate (VPA) had recurrences earlier than those who were taking carbamazepine (CBZ) ($P<0.02$). When the patients in both seizure groups were combined, seizures of any type were still found to recur significantly earlier in those taking valproate ($P<0.03$). There were no significant differences between the valproate and the carbamazepine recipients in the group with generalized tonic–clonic seizures, according to the life-table analysis. A total of 395 patients could be evaluated at 3 months, 235 at 6 months, 162 at 9 months, and 74 at 12 months.

## Adverse Effects

### *Potentially Serious Effects*

Although some potentially serious adverse effects occurred, all problems resolved when the study drugs were discontinued. An idiosyncratic hypersensitivity reaction (rash) was associated with carbamazepine (10.9 percent) but rarely with valproate (0.8 percent; $P<0.001$). Occasional subnormal leukocyte counts were noted in each drug-treatment group, but severe granulocytopenia did not develop. Platelet counts below 100,000 per cubic millimeter ($100\times10^9$ per liter) were observed in one patient taking carbamazepine and eight patients taking valproate; the count fell to 8000 per cubic millimeter ($8\times10^9$ per liter) in one patient taking valproate, with no symptoms. Hyponatremia in which the serum sodium levels were below 120 meq (mmol) per liter developed in four patients taking carbamazepine. Transient pancreatitis with pain, nausea, and vomiting occurred in two patients taking valproate after 18 and 36 months and required hospitalization. Third-degree heart block developed in one patient taking carbamazepine within four days after the drug was started in a low dose. Hepatic enzyme activity as reflected by serum aspartate aminotransferase levels in patients whose levels were ≤50 U per liter before entry rose above the normal range during the first year in 31 patients (15 percent) taking carbamazepine and 47 (22 percent) taking valproate. Elevations in the range of 100 to 300 U per liter led to the discontinuation of the study drug in three patients taking carbamazepine and two taking valproate.

### *Other Systemic Effects*

Other systemic adverse effects of a less serious nature also occurred (Table 2). Weight gain, assessed during the first and subsequent examinations, was associated with both drugs, but more often with valproate, particularly a gain of more than 5.5 kg (12 lb) ($P<0.001$). Loss of hair or changes in its texture were more common during valproate therapy (12 percent vs. 6 percent, $P=0.02$). Gastrointestinal symptoms

Table 2. Incidence of Systemic Adverse Effects.

| Effect | % of Patients* | | P Value | % at 12-Mo Visit† | | P Value |
|---|---|---|---|---|---|---|
| | Carbamazepine | Valproate | | Carbamazepine | Valproate | |
| Gastrointestinal symptoms | 29 | 33 | 0.36 | 6 | 2 | 0.11 |
| Rash | 11 | 1 | <0.001 | 1 | 0 | 0.31 |
| Hepatic toxicity | 4 | 3 | 0.56 | 0 | 0 | 1.00 |
| Weight gain | 32 | 43 | 0.02 | 9 | 20 | 0.01 |
| Large weight gain‡ | 8 | 20 | <0.001 | 3 | 13 | 0.01 |
| Hair change or loss | 6 | 12 | 0.02 | 1 | 4 | 0.06 |
| Impotence | 7 | 10 | 0.30 | 2 | 1 | 0.29 |
| No. of patients | 231 | 240 | | 130 | 136 | |

*Percentage of patients in whom each type of adverse effect occurred at any time during the trial.

†Percentage of patients in whom each type of adverse effect was noted at the 12-month visit.

‡Defined as a gain of 12 lb (5.5 kg) or more.

were common, especially at the start of therapy, but were infrequent overall, as were drug-related symptoms of decreased potency and libido.

### *Neurologic Effects*

The neurologic adverse effects of both drugs were similar except that tremor was significantly more frequent with the use of valproate ($P<0.001$) (Table 3). At the 12-month visit, mild intermittent tremor was present in 5 percent of patients taking carbamazepine and 32 percent of those taking valproate. Moderate tremor (i.e., tremor readily evident to the patient or physician) was reported or found in 6 percent of valproate recipients, and marked (dysfunctional) tremor in another 3 percent, but no tremors were attributed to carbamazepine therapy.

### Treatment Failure

Drug therapy was considered a failure if seizures of unacceptable severity or frequency persisted despite an increase in the dose to a level that produced unacceptable side effects. Overall, treatment failure was more commonly due to seizures in the patients taking valproate and to adverse effects alone in those taking carbamazepine. The duration of participation in the trial was considered to represent the overall success of drug therapy in preventing seizures with tolerable adverse effects. Life-table analyses showed no significant differences between the results of the two treatments in either seizure group or in both seizure groups combined, with or without the inclusion of data on patients whose withdrawal was not related to drug treatment (Fig. 2).

### Composite Score (Overall Status)

At 12 months, composite scores were significantly higher (indicating worse overall status) in the valproate recipients, in the group with complex partial seizures and in both seizure groups combined, but not in the group with tonic–clonic seizures (Table 4).

## Discussion

This clinical trial was designed to assess the usefulness of valproate for the treatment of complex partial and secondarily generalized tonic–clonic seizures associated with symptomatic localization-related (partial) epilepsy. Carbamazepine and valproate were comparable in efficacy for the treatment of secondarily generalized tonic–clonic seizures, but carbamazepine gave significantly better results on four of five outcome measures in the patients with complex partial seizures — the total number of seizures, the seizure rate, the seizure-rating score, and the time to the first seizure — at the primary end point (12 months) and at other end points throughout longer follow-up (Table 1).

Over the past decade, numerous investigators have assessed the use of valproate for the treatment of symptomatic localization-related (partial) epilepsy.

Table 3. Incidence of Neurologic Adverse Effects.

| Effect | % of Patients* | | P Value | % at 12-Mo Visit† | | P Value |
|---|---|---|---|---|---|---|
| | Carbamazepine | Valproate | | Carbamazepine | Valproate | |
| Diplopia | 10 | 6 | 0.10 | 0 | 0 | 1.00 |
| Nystagmus | 30 | 26 | 0.33 | 6 | 9 | 0.42 |
| Dizziness | 29 | 23 | 0.09 | 2 | 5 | 0.23 |
| Gait problems | 25 | 23 | 0.65 | 4 | 7 | 0.22 |
| Tremor | 22 | 45 | <0.001 | 5 | 32 | <0.001 |
| Sedation | 42 | 42 | 0.98 | 8 | 8 | 0.92 |
| Change in affect or mood | 24 | 25 | 0.69 | 4 | 2 | 0.43 |
| Cognitive disturbance | 18 | 18 | 0.97 | 3 | 4 | 0.80 |
| Headache | 20 | 15 | 0.20 | 1 | 5 | 0.11 |
| No. of patients | 231 | 240 | | 129 | 136 | |

*Percentage of patients in whom each type of adverse effect occurred at any time during the trial.

†Percentage of patients in whom each type of adverse effect was noted at the 12-month visit.

Most previous trials failed to show differences in efficacy among carbamazepine, phenytoin, and valproate in treating this type of epilepsy in either adults or children.[6,7,12,14,16,18,25,26] Callaghan et al.[7,26] randomly assigned 181 previously untreated patients to treatment with valproate, carbamazepine, or phenytoin and assessed seizure control as excellent, good, or poor. When control of complex partial seizures with or without secondary generalization was used as a measure of efficacy, the three drugs gave similar results. In a similar trial, Turnbull et al.[6] evaluated 140 patients

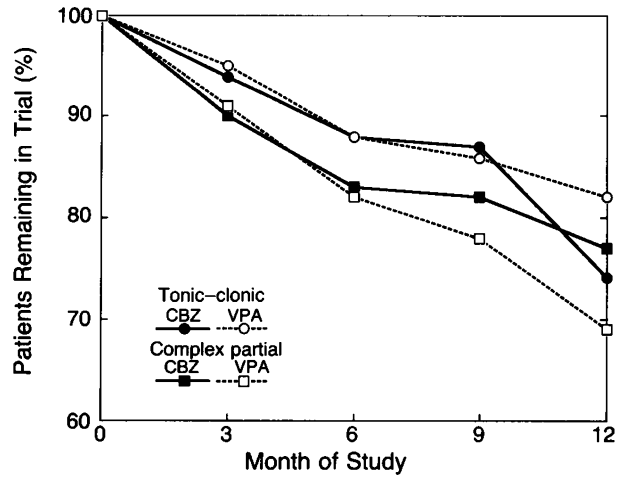


Figure 2. Percentage of Patients Remaining in the Trial.

The life-table analysis of continuing successful treatment showed no significant differences during the 12-month period between the patients taking valproate (VPA) and those taking carbamazepine (CBZ), whether they had complex partial seizures or generalized tonic–clonic seizures. In this analysis patients who dropped out were considered lost to follow-up. When they were included as patients with treatment failure, however, analysis also showed no significant difference in the results of treatment in either seizure group or both seizure groups combined. There were 480 patients at entry, 438 at 3 months, 351 at 6 months, 302 at 9 months, and 150 at 12 months.

Table 4. Composite Rating Scores.*

| SEIZURE GROUP | CARBAMAZEPINE | VALPROATE | P VALUE |
|---|---|---|---|
| | *mean ±SD (no. of patients)* | | |
| Generalized tonic–clonic | | | |
| 12 mo | 9.4±14.0 (71) | 13.8±17.9 (75) | 0.39 |
| 24 mo | 6.1±9.6 (50) | 10.7±16.1 (52) | 0.37 |
| Complex partial | | | |
| 12 mo | 6.8±10.0 (57) | 16.0±15.7 (61) | <0.001 |
| 24 mo | 8.2±11.4 (39) | 13.6±16.2 (36) | 0.14 |
| Both groups | | | |
| 12 mo | 8.3±12.4 (128) | 14.8±16.9 (133) | 0.002 |
| 24 mo | 7.0±10.4 (89) | 11.9±16.1 (88) | 0.11 |

*The composite score was based on the total seizure-rating score and the scores for systemic toxicity and neurotoxicity. The lower the score, the better the outcome.

with new-onset partial epilepsy in three age groups and found no differences between valproate and phenytoin therapy in the number of patients in remission for two years or in the time to the first seizure. In contrast to these earlier investigators, we found that carbamazepine was more efficacious than valproate according to several measures in patients with predominantly complex partial seizures. Although there are many differences in the design of these studies, the most probable explanation for the differences in efficacy is the large size of our study group.

Adverse effects were observed with both drugs. Drug sensitivity was more frequently associated with the use of carbamazepine than valproate. Previous reports have noted the occurrence of valproate-related thrombocytopenia and pancreatitis, as well as carbamazepine-related heart block and severe arrhythmias.[27-30] Leukopenia was associated with both drugs, but without clinically important granulocytopenia.[27]

Weight gain was a common adverse effect of both carbamazepine and valproate therapy, but an increase of 5.5 kg or more occurred more often with valproate. Dinesen et al.[31] retrospectively reviewed weight gain in 63 patients, 57 percent of whom gained more than 4 kg (9 lb) while taking valproate. Changes in hair texture and hair loss have been reported in 2 to 12 percent of patients taking valproate, particularly those given high doses during long-term therapy.[32,33]

Both drugs caused minimal cognitive or affective disturbances. Although 42 percent of patients reported sedation, its incidence was found to be low (8 percent) at the 12-month visit (Table 3). Tremor of all types, particularly postural tremor, was more frequent among patients taking valproate and was apparent and persistent in 12 percent of all patients in the study at the 12-month visit. This transient, dose-related effect has been reported since the earliest use of the drug.[29,34]

The composite rating reflects the frequency and severity of seizures and of drug-related adverse effects. This measurement gives some indication of the effectiveness of management at specific points and can be considered a quantitative "global measure." In the group with partial seizures, the mean composite scores at 12 months were 9.2 points higher (i.e., denoted a worse outcome) in the patients taking valproate than in those taking carbamazepine (Table 4), a finding we considered clinically important.

In summary, we found that valproate is comparable to carbamazepine in efficacy for the treatment of secondarily generalized tonic–clonic seizures, supporting a major role for the drug in the management of this type of seizure. However, several measures showed that carbamazepine had greater efficacy and fewer persistent adverse effects than valproate in the treatment of complex partial seizures. Because approximately half of patients with symptomatic localization-related (partial) epilepsy will have both partial and secondarily generalized tonic–clonic seizures at some time, we conclude that carbamazepine is preferable to valproate for the management of this epilepsy syndrome. Although we did not include phenytoin in this trial, no studies have indicated that carbamazepine and phenytoin differ in efficacy for either partial or secondarily generalized seizures, and both remain drugs of choice. On the basis of these findings, as well as previously reported data, we regard valproate as a useful medication for complex partial epilepsy that should be considered as an alternative drug if carbamazepine or phenytoin proves suboptimal because of a lack of efficacy or toxicity.

We are indebted to the Data Monitoring Committee (Fritz E. Dreifuss, M.D., Mary A. Foulkes, Ph.D., and J. Kiffin Penry, M.D.) for their careful overview of the progress of the trial.

## APPENDIX

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In addition to the principal investigators, participants included the study coordinators at each site, staff at the Coordinating Center, Central Research Pharmacy, Chairman's Office, Central Laboratory, and neuropsychologists: Y. Arroyo, D. Barnes, E. Brown, B. Calvert, C. Colling, B. Coull, V. Cruz, M. D'Amico, D. Davis, R. Delaney, C. Dougherty, K. Gallagher, E. Hanahan, J. Hochholzer, T. Kaplan, M. Katsma, F. Kelly, C. Kendrick, J. Kress, S. Kreye, P. Marshall, D. McGinnis, O. Mendia, M. Miceli, N. Morgan, K. Nash, R. Ortiz, G. Osby, V. Ouellette, E. Peralta, M. Prevey, E. Ramirez, B. Reisteter, L. Rhame, P. Rickman, G. Roeshsner, M. Schaeffer, T. Sharp, B. Smith, M. Sparrow, M. Vega, N. Walton, P. Warren, and H.-J. Yu.

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