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# Results of a Nationwide Veterans Administration Cooperative Study Comparing the Efficacy and Toxicity of Carbamazepine, Phenobarbital, Phenytoin, and Primidone

Dennis B. Smith, *Richard H. Mattson, †Joyce A. Cramer, ‡Joseph F. Collins, §Robert A. Novelly, ‖Bruce Craft, and the ¶Veterans Administration Epilepsy Cooperative Study Group

*Good Samaritan Hospital & Medical Center, Portland Oregon; *Yale University School of Medicine, New Haven, Connecticut; ‡Veterans Administration Cooperative Studies Program, Perry Point, Maryland; *†§Veterans Administration Hospital, West Haven, Connecticut; and ‖Neurology Service, Veterans Administration Medical Center, Augusta, Georgia, U.S.A.*

**Summary:** In 1985 a 5-year multicenter Veterans Administration Cooperative Study was completed that compared the efficacy and toxicity of phenobarbital, carbamazepine, phenytoin, and primidone in a double-blind prospective study design. A total of 622 patients, either previously untreated or undertreated, were entered into the study. Strict exclusion criteria limited confounding factors such as drug or alcohol abuse. Results showed that each of the four drugs used as monotherapy were similarly effective in the treatment of generalized tonic–clonic seizures, but carbamazepine was significantly more effective in the treatment of complex partial seizures as measured by 100% control. When the results for all four drugs were combined, the data showed that approximately 80% of the patients were adequately managed on monotherapy. Differences in toxicity were the most significant factor that discriminated between these four drugs. Both carbamazepine and phenytoin were associated with significantly lower incidences of intolerable side effects than were primidone or phenobarbital. A behavioral toxicity battery was performed whenever possible prior to administration of any antiepileptic drug and at 1, 3, 6, and 12 months after initiation of monotherapy. Significant differences in performance on all subtests of the battery were found between patients with epilepsy and a control group matched by age, sex, and education. When the differential effects of all four drugs on behavioral toxicity were compared, few statistically significant differences emerged. However, carbamazepine consistently produced fewer adverse effects on tests of attention/concentration and motor performance than did the other three antiepileptic drugs. **Key Words:** Epilepsy—Seizures—Therapy—Anticonvulsants—Controlled clinical trials—Drug-induced abnormalities—Carbamazepine—Phenobarbital—Phenytoin—Primidone.

In 1985 a nationwide multicenter study sponsored by the Veterans Administration (V.A.) was completed. The study was a 5-year prospective, double-blind trial comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone in adults with partial or secondarily generalized seizures (Mattson et al., 1985). The study was initiated in order to overcome shortcomings of previous studies of the comparative efficacy and toxicity of antiepileptic drugs.

Coatsworth (1971) reviewed the literature from 1920 through 1971 reporting on studies of the clinical efficacy of marketed antiepileptic drugs and found that a total of 250 case reports on the efficacy and toxicity of these agents had been published. In addition, results of 110 clinical trials were published during this same reporting period. Of the clinical trials, only three involved a single- or double-blind protocol, 25 included an electroencephalogram (EEG) profile, five included a psycho-

Address correspondence and reprint requests to Dr. D. B. Smith at Good Samaritan Hospital & Medical Center, 1015 N.W. 22nd Avenue, Suite 400, Portland, OR 97210, U.S.A.

¶ Includes Antonio V. Delgado-Escueta, Thomas R. Browne, Peter D. Williamson, David M. Treiman, James O. McNamara, Charlotte B. McCutchen, Richard W. Homan, Wayne E. Crill, Michael F. Lubozynski, N. Paul Rosenthal, and Assa Mayersdorf.

TABLE 1. *Studies comparing major antiepileptic drugs for partial and generalized tonic–clonic seizures (1966–1979)*

| Study | Goal | Comparison of drug toxicity | Relative efficacy of seizure control | Comments (duration; patients) |
|---|---|---|---|---|
| White et al., 1966 | Show PRM equals PHT or PB | All drugs equal | All drugs equal | 2 weeks; 20 institutionalized patients |
| Millichap and Aymat, 1968 | Compare PRM with PHT | PHT more toxic than PRM | Both drugs equal | 8 months; 20 outpatient children; no drug levels |
| Cereghino et al., 1974 | Show CBZ equals PHT or PB | CBZ more toxic than PHT or PB (equal behavior for all drugs) | All drugs equal | 3 weeks; 45 institutionalized patients |
| Troupin et al., 1975 | Show CBZ equals PHT | All drugs equal | Both drugs equal | 4 weeks; 20 outpatients |
| Cereghino et al., 1975 | Best combination of two or three drugs (PHT, PB, CBZ) | Combinations including CBZ more toxic than PB and PHT | PHT + PB combination is best | 3 weeks; 41 institutionalized patients |
| Rodin et al., 1976 | Best drug (PRM or CBZ) to add to PHT if PB fails | CBZ more toxic than PRM; CBZ fewer behavioral deficits than PRM | All combinations equal | 3 months; 45 outpatients; behavioral testing; no drug levels |
| Kosteljanetz et al., 1979 | Show CBZ equals PHT | All drugs equal, but PHT more difficult to adjust dose | Both drugs equal | 6 months; 19 outpatients; triple-blind |

CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone.

logical evaluation, and only three included any kind of statistical analysis. From 1972 to 1979, results of an additional seven clinical trials were reported, but because of a variety of shortcomings (failure to use a double-blind randomized protocol, failure to compare all four drugs and to monitor serum concentration of the drugs, inclusion of institutionalized refractory patients and patients with mixed seizure types, and insufficient sample size for statistical analysis), these studies failed to reveal any clear differences in the clinical effectiveness or relative toxicities of carbamazepine, phenobarbital, phenytoin, and primidone (Table 1).

It was thus apparent that despite a wealth of literature dating back nearly 50 years, no convincing scientific evidence had been developed that could be used to justify the selection of any single antiepileptic drug for any specific seizure type (with the exception of generalized absence seizures) in adults. Despite the inconclusiveness of these studies, there was no dearth of dogmatic statements recommending one drug over another, as exemplified by the following quotations from three commonly used textbooks in neurology.

> For the treatment of major and focal epilepsy, "it is usual to begin in an adult with phenobarbitone. . . ." (Brain's *Diseases of the nervous system,* 8th ed. Oxford University Press, 1977.)
>
> "The treatment of grand mal seizures in adults always begins with phenytoin. . . ." (*Modern practical neurology.* Raven Press, 1977.)
>
> "Carbamazepine is a major antiepileptic drug for the treatment of complex partial, elementary partial, and generalized tonic clonic seizures." (*Antiepileptic drugs,* 2nd ed. Raven Press, 1982.)

These conflicting recommendations emphasize the problems that existed in interpreting the comparative literature on antiepileptic drugs. It was against that background that the V.A. Cooperative Study was conceived. The study was designed to overcome shortcomings in previous trials by (1) studying newly diagnosed patients with epilepsy not currently receiving antiepileptic drug therapy, (2) utilizing a homogeneous, noninstitutionalized population that would be representative of a typical outpatient seizure population, (3) documenting etiology by EEG and imaging studies, (4) quantifying the frequency and severity of seizures, (5) monitoring serum concentrations of the antiepileptic drugs, (6) comparing all four drugs simultaneously by a randomized, double-blind study design, (7) using each drug singly as monotherapy until proven unsatisfactory, and (8) using a sufficiently large population base to allow meaningful statistical analysis on completion.

These objectives were achieved, and the results of that study for the first time provide a scientific rationale for recommending specific antiepileptic drugs for specific seizure types. In this paper, some of the results of that study are summarized.

## METHODS

Enrolled in the study were 622 patients newly diagnosed as having simple or complex seizures or primarily or secondarily generalized tonic–clonic

seizures. All patients were previously untreated or undertreated. A double-blind prospective study design was used. Patients were followed for as long as 6 years (average, 3 years) at 10 V.A. medical centers (Augusta, GA; Boston, MA; Dallas, TX; Durham, NC; Los Angeles, CA; Minneapolis, MN; San Diego, CA; Seattle, WA; Sepulveda, CA; and West Haven, CT, U.S.A.). The study population included men and women (age range, 18 to 70 years). Nonveterans were also entered into the study. Exclusion criteria were strict (Table 2).

### Study design

Details of the study design have been described elsewhere (Delgado-Escueta et al., 1983; Mattson et al., 1983; Cramer et al., 1983). Figure 1 schematically summarizes the principles of the study design. Patients were randomly assigned to receive therapy with carbamazepine, phenobarbital, phenytoin, or primidone. Inadequate seizure control with the initially assigned drug was counted as a drug failure and the patient was randomly assigned to a second study drug. (Patients with generalized tonic–clonic seizures were randomly assigned to two study drugs.) If drug treatment resulted in unacceptable toxicity, this was also counted as a drug failure, and the patient received a second single study drug by random assignment. Patient compliance was monitored throughout the study by measurement of antiepileptic drug levels and by pill counts at each follow-up visit.

Details of drug administration and statistical considerations are given by Mattson et al. (1985).

### Evaluations

A primary end point for evaluating the efficacy and toxicity of the study drugs was patient retention (i.e., the length of time that the patient continued to take the randomly assigned drug). Additional assessments included rating scales of seizure frequency, systemic toxicity, and neurotoxicity that were designed specifically for this study (Cramer et al., 1983). These scales were designed to reflect the effects of seizures and drug toxicity on the quality of life of the patient. A composite score was completed by the evaluating physician at every clinic visit. A score of 0–20 points corresponded with a good clinical response, a score of 20–35 represented a satisfactory but suboptimal response, and a score of 35–49 represented a fair to poor but not clearly unacceptable outcome; a score of 50 or more represented an unacceptable outcome requiring a change in therapy (Cramer et al., 1983).

TABLE 2. *Exclusions*

1. Under age 18 years
2. Diagnosis of epilepsy not confirmed
3. Classification of specific seizure type not possible
4. Etiology of seizure is neoplastic, progressive degenerative, metabolic, demyelinating, or active infection (a patient with a previously resected tumor that is not recurrent is acceptable)
5. Patient has generalized seizures but not tonic–clonic (e.g., only absence)
6. Patient is abuser of alcohol (≥4 drinks per day)
7. Patient is abuser of other drugs (e.g., narcotics)
8. Patient has progressive neurologic disorder
9. Patient has serious medical disorder (unstable or requiring intervention or both) or active infection
10. Patient is psychotic, grossly organic, or severely depressed
11. Patient's intelligence quotient (WAIS) full-scale is less than 85
12. Patient is a willful noncomplier
13. Repeated seizures may occur under a variety of circumstances related to acute medical disorders such as uremia, hypoglycemia, etc., and are not considered epilepsy for the purpose of this study

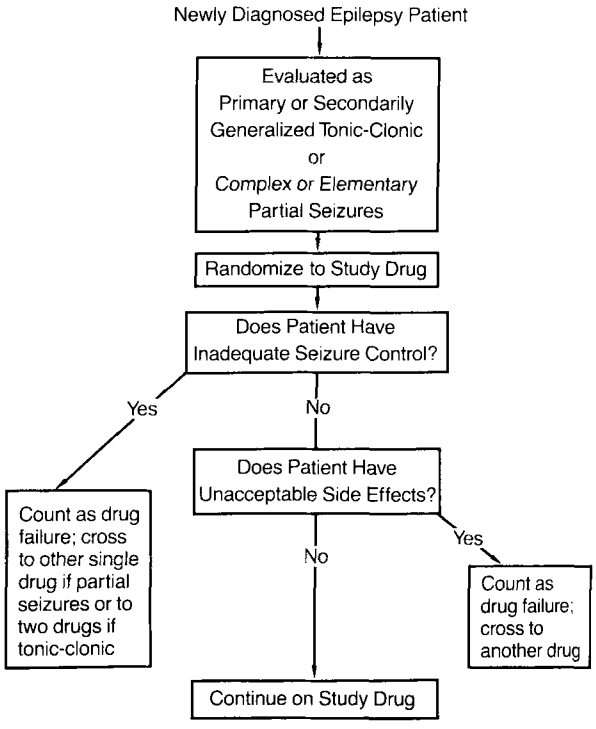


**FIG. 1.** Flow chart of study design.

### Behavioral toxicity battery

All patients had extensive neuropsychological evaluation before administration of any antiepileptic drug and at 1, 3, 6, and 12 months after initiation of monotherapy with one of the study drugs. Seventy-five control subjects representing all 10 study sites were selected to match the epilepsy patient group closely in terms of age, education, sex, and absence of significant medical problems. This group of controls was administered the same battery of neuropsychological tests on two occasions 30 days apart.

The tests selected were designed to reflect neuro-

psychological functioning in four major areas: (a) general intellect, (b) attention/concentration/mental flexibility, (c) motor/motor manipulation, and (d) emotional/mood states. Intellectual ability was measured by the Wechsler Adult Intelligence Scale (WAIS), a well-standardized measure of general cognitive function based on 11 verbal and nonverbal subtest activities. The behavioral test battery consisted of the following tests: Digit Symbol, Digit Span, Critical Flicker Discrimination, Discriminative Reaction Time, Word Finding, Index Finger Tapping, Lafayette Pegboard, and Color Naming. Mood and emotional states were measured by the profile of mood states (POMS) (Lorr et al., 1971). A complete description of this test battery and the procedure for its administration has been previously detailed (Smith et al., 1986; Novelly et al., 1986).

## RESULTS

### Seizure control

Of the several measures employed in this study for assessment of the comparative efficacy of the study drugs in seizure control, the most straightforward and simple analysis was examination of the percentage of patients seizure free after 1 year. Combined results for all four drugs showed that the percentage of patients with fully controlled seizures remaining in the study for 1 year after drug levels reached the therapeutic range was significantly higher for patients whose primary seizure type was tonic–clonic seizures than for those whose primary seizure type was either simple or complex partial seizures (56% versus 39% of patients seizure-free). For both groups, seizure control was similar at 6 months and 1 year, with most seizure breakthroughs occurring within the first 1 to 3 months (Homan et al., in press). Complete control of tonic–clonic seizures for 12 months was not significantly different among the study drugs: 55% of patients were seizure free in the carbamazepine group, 58% in the phenobarbital group, 48% in the phenytoin group, and 63% in the primidone group. In contrast, control of partial seizures was significantly better with carbamazepine than with the other three study drugs after 18 months of follow-up ($p < 0.05$) (Table 3). Partial seizures were controlled in 65% of the patients receiving carbamazepine as opposed to 33% taking phenobarbital, 34% taking phenytoin, and 26% taking primidone.

TABLE 3. *Percent of patients by drug group free of all seizures*

| Drug group | Seizure type: Generalized Tonic–clonic (12 mos) | Seizure type: PTL (18 mos) |
|---|---|---|
| Phenobarbital | 58 | 33 |
| Phenytoin | 48 | 34 |
| Primidone | 63 | 26 |
| Carbamazepine | 55 | 65* |
| All | 55 | 42 |

* $p < 0.05$.

Another method of comparing the efficacy of these four drugs was to examine the number of patients on each drug remaining active in the study over time. A decreasing retention of patients over time represents an inability of the drug to manage seizures, whether because of poor seizure control, unacceptable toxicity, or both. Figure 2 shows the number of patients successfully managed with each drug during 36 months of follow-up. This analysis combines data for all seizure types (53% of all the patients had more than one seizure type). Retention rates were significantly better among patients receiving carbamazepine or phenytoin than among

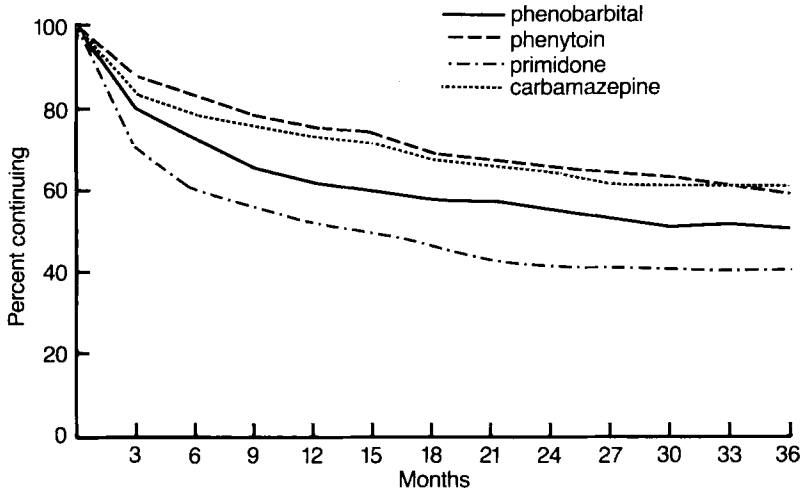


**FIG. 2.** Number of patients, by treatment group, remaining active in the study for 36 months. (Reprinted by permission of *The New England Journal of Medicine.*)

TABLE 4. *Reasons for drug failure in the four treatment groups*

| Reason | Treatment group | | | | All patients (n = 421) |
|---|---|---|---|---|---|
| | CBZ (n = 101) | PB (n = 101) | PHT (n = 110) | PRM (n = 109) | |
| Toxicity alone | 12 | 19 | 18 | 36 | 85 |
| Toxicity plus seizures | 30 | 33 | 29 | 35 | 127 |
| Seizures alone | 3 | 4 | 1 | 3 | 11 |
| Total failures | 45 | 56 | 48 | 74 | 233 |

CBZ, carbamazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone.

those receiving primidone ($p < 0.001$). Phenobarbital also had a better retention rate than primidone ($p < 0.05$). Retention rates were better for carbamazepine or phenytoin than for phenobarbital, but this difference did not reach statistical significance.

These results, however, do not indicate the reasons for a patient failing to remain on therapy with a single anticonvulsant (see Table 4). Very few patients failed to remain on their original antiepileptic drug because of a lack of seizure control alone; most failures occurred because of both toxicity and lack of seizure control.

Patients receiving primidone experienced the highest incidence of toxicity. Most of these patients experienced unacceptable toxicity within the first 1 to 3 months of therapy. The side effects included nausea, vomiting, dizziness, ataxia, and somnolence, and caused early discontinuation of the drug. Patients tolerating the initiation of therapy with primidone, however, experienced no more toxicity with chronic therapy than did patients taking any of the other three antiepileptic drugs.

## Monotherapy

Analysis of the percentage of patients remaining in the study on monotherapy for 1 year showed clearly that the majority of patients remained adequately managed with monotherapy regardless of drug (Fig. 3). Sixty percent of patients were adequately managed by monotherapy with the first drug they received by random assignment. Of those who had treatment failure with the first drug and who were switched to a second drug (either because of toxicity, lack of seizure control, or both), 55% were successfully treated with the second randomly assigned drug also used as monotherapy. In this selected patient group, 20% could *not* be adequately managed on monotherapy. Of this 20%, 49% could be adequately managed by treatment with two drugs in combination.

## Behavioral effects

Of the 622 patients entered into the study, 618 received the full battery of neuropsychological tests at the initiation of the study. All 75 control subjects completed the full battery of tests. Table 5 compares the demographic characteristics of the control subjects and the patients with epilepsy.

The two groups match closely for age, sex, and education. Educational level was coded from 1 through 9, with the highest level of education (Ph.D.) represented by a 1 and the lowest level of education (grade school or less) represented by a 9. The general intellectual ability, as measured by the WAIS score, represents a normal range of function for patients with epilepsy, and the wide variability

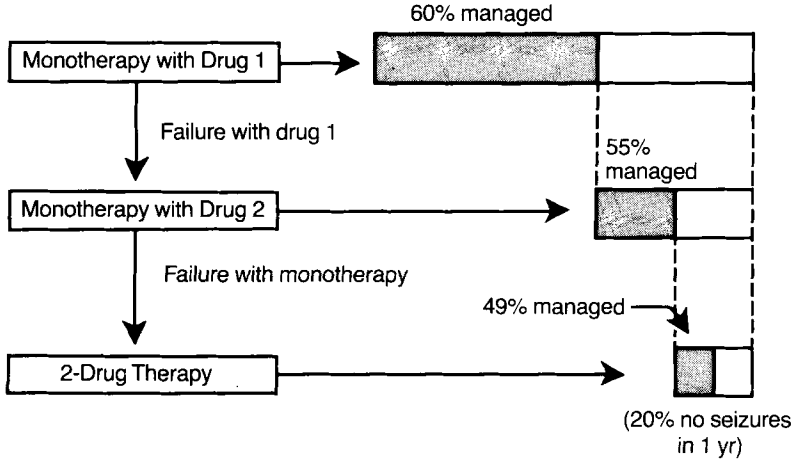


**FIG. 3.** Percent of patients successfully managed on monotherapy with first or second drug randomly assigned (combined data for all drug groups).

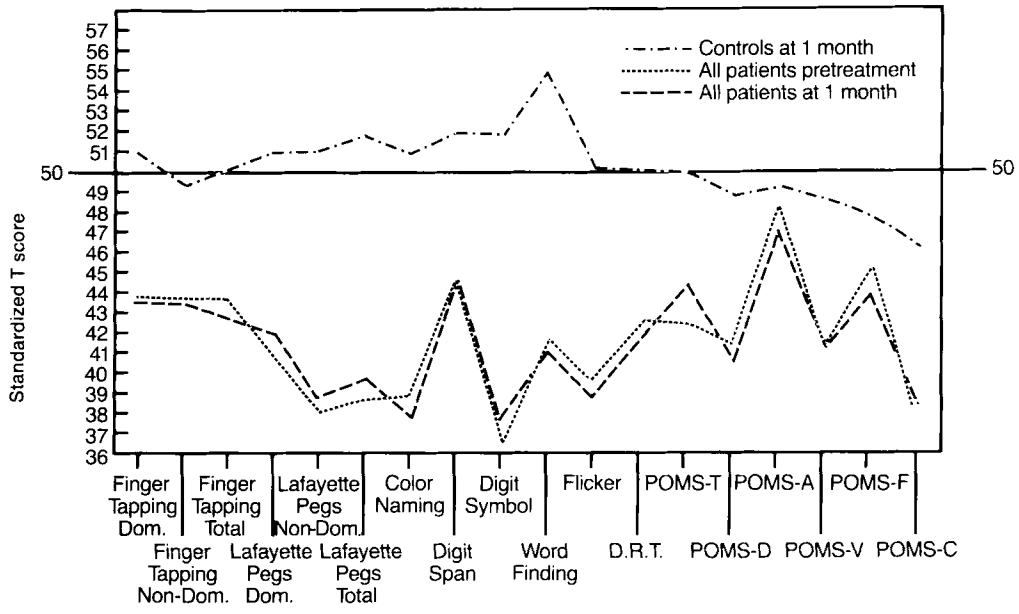


**FIG. 4.** Behavior toxicity battery data showing comparisons between control and epilepsy groups. Data were transformed into standardized T score values (higher score indicates better performance). The level of performance of the control group at trial I was scaled to 50 and used as the basis for comparison for controls at trial II and for epilepsy subjects at trials I and II. (Adapted with permission from Smith et al., 1986.)

shown in the study population is no more than would be expected in such a large sample. WAIS scores were not obtained for the control subjects, but the two groups were comparable with regard to educational level, and the correlation between education and I.Q. is high (Smith et al., 1986).

The mean performances of both the control group and the patients with seizures for each of the behavioral measures are compared in Fig. 4. The results are shown for both the initial (trial I) and 30-day (trial II) performances. For the epilepsy subjects, trial I performances were obtained under a relatively drug-free condition, whereas at trial II, all epilepsy patients had been receiving monotherapy with one of the four anticonvulsant medications for approximately 30 days.

TABLE 5. *Patient characteristics*

| Characteristic | Control | Epilepsy |
|---|---|---|
| Number | 75 | 618 |
| Age (years, mean) | 38.6 (±13.1) | 40.4 (±15.3) |
| Range (years) | 17–72 | 18–82 |
| Sex (males) | 72% | 85% |
| Education (coded) | 4.1 | 4.9 |
| Education range | 1–8 | 1–8 |
| Verbal I.Q. | | 100.5 (±14.5) |
| Range | | 55–142 |
| Performance I.Q. | | 99.2 (±13.6) |
| Range | | 52–134 |
| Full-scale I.Q. | | 100.0 (±13.5) |
| Range | | 52–135 |

Adapted with permission from Smith et al., 1986.
Numbers in parentheses are standard deviation.

The control group differed significantly from the epilepsy group on all but three behavioral measures at trial I and on all but two measures at trial II. A most important observation was that a practice effect appeared to occur for selected performances in the control group. Virtually no practice effect was seen between trial I and trial II in the epilepsy group. These patients tended to show only slight improvement at trial II for Pegboard, Digit Symbol, and Word Fluency tests.

The total behavioral toxicity score was derived by combining the scores of the individual subtests transformed into weighted ordinal units of change based upon published norms. The higher the score on the behavioral toxicity battery, the more deterioration from baseline performance is indicated. A negative score indicates an improvement in performance compared with baseline predrug test scores.

When the effect of each antiepileptic drug on the total behavioral toxicity battery was examined at both 1 and 3 months, significant differences between the drugs were apparent (Fig. 5). None of the groups showed an improvement in performance at either 1 or 3 months when comparisons were made with their predrug test scores. Carbamazepine patients showed the least deterioration, achieving a total battery score of 16 at 1 month and 14 at 3 months. Patients with primidone also showed relatively little deterioration at 1 and 3 months, having a total score of 14 at 1 month and 18 at 3 months. In contrast, patients taking phenobarbital or phe-

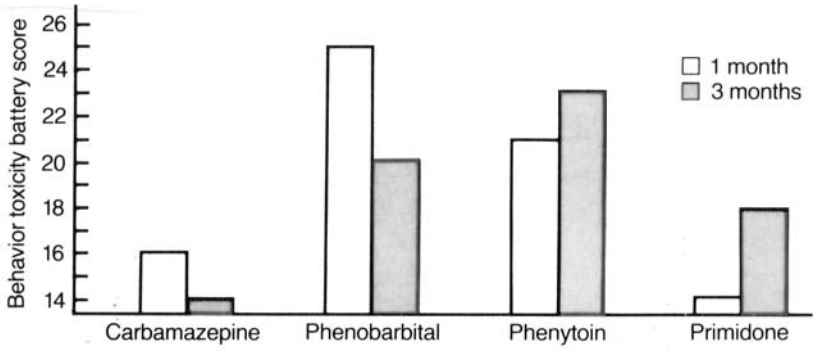


**FIG. 5.** Total behavior toxicity battery scores by drug group at 1 and 3 months. The higher the score, the worse the performance.

nytoin showed significant deterioration in the total behavioral toxicity score at both 1 and 3 months ($p < 0.001$ at 1 month); scores for the phenobarbital, phenytoin, and primidone groups all showed deterioration in total scores at 3 months, while patients taking carbamazepine showed no such deterioration at 3 months ($p < 0.002$ at 3 months). Drug levels for all groups were within the well-accepted therapeutic range. The total behavioral toxicity score for phenobarbital was 25 and 20 at 1 and 3 months, respectively, while for phenytoin the scores were 21 and 23.

Differences between the four drugs for scores on individual subtests of the behavioral toxicity battery occasionally attained statistical significance, but no consistent pattern emerged. For example, on the Word Finding subtest, patients in the carbamazepine group performed significantly better than patients taking phenytoin or phenobarbital ($p < 0.008$) at 3 months, and better than phenytoin patients ($p < 0.06$) at 12 months. Scores for carbamazepine patients were not significantly better than those for patients taking any of the other drugs at either 1 or 6 months. Analysis of covariance using pretreatment score as covariant was used to determine statistical significance in all cases. Although the patients taking carbamazepine had better scores on the Word Finding subtest at 1 and 6 months than did the patients taking the other three drugs, this difference did not reach statistical significance.

Results were further analyzed by counting the number of times that a patient treatment group scored better than two or more other treatment groups with a confidence level of $> 0.05$. Similarly, the number of worst scores for each subtest at each rating period was determined using the same criteria.

Table 6 tabulates the numbers of best and worst scores (combined results from tests at 1, 3, 6, and 12 months) on subtests of the POMS, motor function, and attention/concentration. Subtests of motor function included Index Finger Tapping, Lafayette Pegboard, and Color Naming. Subtests of attention/concentration included Digit Symbol, Digit Span, Critical Flicker Fusion, Word Finding, and Discriminative Reaction Time. Overall, the group taking carbamazepine showed the highest number of "best" scores on subtests of the POMS and on tests measuring attention/concentration. Scores for the individual subtests showed no significant pattern of effect over time among the four anticonvulsants.

## DISCUSSION

In 1978, when planning for the V.A. Cooperative Study was completed, valproate had been approved only for use in generalized absence seizures, and phenobarbital, phenytoin, primidone, and carbamazepine were still the most commonly used antiepileptic drugs in the treatment of adults with epilepsy. All these drugs possess considerable efficacy in the treatment of generalized tonic–clonic seizures (White et al., 1966; Ives, 1951; Cereghino et al., 1974), but selection of one of these drugs over another as the initial therapy for any individual patient was influenced almost entirely by personal

**TABLE 6.** *Total number of best and worst scores on subtests of the behavioral toxicity battery at 1, 3, 6, and 12 months of therapy*

| | POMS | Motor | Attention/ concentration |
|---|---|---|---|
| | Best scores | | |
| Carbamazepine | 11 | 4 | 10 |
| Phenytoin | 2 | 1 | 2 |
| Primidone | 9 | 3 | 1 |
| Phenobarbital | 2 | 1 | 0 |
| | Worst scores | | |
| Carbamazepine | 0 | 0 | 1 |
| Phenytoin | 13 | 4 | 0 |
| Primidone | 2 | 5 | 6 |
| Phenobarbital | 9 | 0 | 5 |

"Best" and "worst" indicate scores that are significantly different from scores attained by two or more of the other groups for the same subtest at the same rating period.
POMS, profile of mood states.

biases and by fragmentary and sometimes conflicting information of relative efficacy from published clinical trials (Tassinari and Roger, 1975). The V.A. Cooperative Study has for the first time provided some comparative data that can be used to justify the selection of the antiepileptic drug that is most likely to be the most successful overall choice.

Mattson et al. (1985) have pointed out that the results of this study "indicated that carbamazepine and phenytoin are most likely to be successful overall when used as the initial antiepileptic drug in adults with partial seizures or secondarily generalized tonic–clonic seizures or both." It was clear that the choice between these two drugs required consideration of other factors.

Toxicity rather than seizure control proved to be the most significant factor differentiating between the four study drugs. While the highest rate of toxicity was seen in the patients taking primidone, this toxicity occurred almost exclusively within the first 1 to 2 months of therapy. It is clear that if patients tolerate the initiation of therapy with primidone, they may do equally as well as patients taking any of the other three drugs. Results from the behavioral toxicity battery suggest that if patients tolerate the initial side effects of primidone, they perform somewhat better on some subtests of the POMS and perform similar to patients taking phenytoin or carbamazepine on subtests of motor function and of attention/concentration.

Despite the fact that a number of previous studies have pointed out the advantages with monotherapy, the results of this study are the first from a double-blind prospective trial to confirm the effectiveness of initiating therapy with a single drug. In this study, approximately 80% of the patients were successfully managed for 1 year on monotherapy regardless of drug, i.e., they had adequate seizure control and lacked intolerable toxicity. These data show that while some patients may require polytherapy for successful control, the majority can be successfully managed with monotherapy. This study also indicates that most patients who are going to fail to respond to a single antiepileptic drug will do so within the first 3 months of therapy.

One of the unique features of this study was the opportunity to prospectively examine the neurobehavioral effects of each of these four drugs and to compare the drug-treated state with a relatively drug-naive state *in the same patient*. In addition, for the first time, patients with epilepsy who were drug naive or undertreated could be compared with a control group matched for age, sex, and education.

An interesting finding was that the pretreatment intellectual performance for the epilepsy group was generally normal. The distribution of I.Q. scores for the combined epilepsy sample was very similar to that expected in the normal population on the basis of Wechsler's (1955, 1981) normative data. This finding is partly due to the strict exclusion criteria, requiring a full-scale I.Q. of $> 85$. Nonetheless, although the epilepsy group had a normal level of intellectual performance, significant differences were consistently observed between patients with epilepsy and the control group. This finding is particularly significant because the results of all previous studies have been confounded to some extent by drug effect (Dodrill and Troupin, 1974; Geschwind et al., 1980; Giordani et al., 1985; Kløve and Matthews, 1969; Thompson and Trimble, 1982).

The differential behavioral effects of the four anticonvulsant drugs were clearly evident. Again, the importance of these findings is heightened when one considers the study design through which they were obtained, i.e., not only was each drug compared with each other drug used as monotherapy, but, more importantly, results were compared against a predrug baseline, each patient serving as his own control.

Even though the results on individual subtests of the behavioral toxicity battery were not dramatically revealing, the total battery score did show that carbamazepine had fewer behavioral effects than did the other three drugs. None of the drug-treated groups showed any improvement in scores related to practice effects, in contrast to the control group. These results suggest that all four drugs studied have some adverse effect on motor skills, cognition, and mood. Nonetheless, the best performances on subtests of the behavioral toxicity battery were attained by patients taking carbamazepine, and this difference was present at 1, 3, 6, and 12 months of therapy.

On the basis of the results of this long-term prospective comparison of phenobarbital, primidone, carbamazepine, and phenytoin, the most successful drugs when used as initial antiepileptic treatment in adults appear to be carbamazepine and phenytoin. All four drugs demonstrated equal efficacy in patients with secondarily generalized tonic–clonic seizures, but carbamazepine was significantly more effective than either primidone or phenobarbital in controlling partial seizures. The behavioral effects of carbamazepine as measured by the neurotoxicity battery used in this study were less than any of the other three drugs. This finding, coupled with the relatively equal antiepileptic efficacy of all four drugs, indicates that carbamazepine may be the preferred drug for initiation of therapy in some

adults with either generalized tonic–clonic seizures, partial seizures, or both. However, in view of the variability of individual response, other factors may need to be considered when an antiepileptic drug is selected.

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