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Influence of major antiepileptic drugs on neuropsychological function: Results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients on monotherapy

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Abstract

The aim of this study was to assess cognitive effects of anticonvulsants in a way that would yield results that are most directly applicable to epilepsy populations. This was done with a placebo-controlled, prospective, randomized, double-blind, parallel group study of anticonvulsant withdrawal in a population of subjects taking a single anticonvulsant with completely controlled seizures. Outcomes of this study on cognitive measures from the California Computerized Assessment Package have recently been reported. To aid comparison with results of prior studies, we report outcomes here on several more standard measures of neuropsychological function. The major findings were that, in subjects with therapeutic drug levels at baseline, drug withdrawal was associated with significant improvement in performance on the Controlled Oral Word Association Test and the Stroop Color–Word Interference Test. Comparable results were achieved in the subgroup taking carbamazepine.
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Keywords: Antiepileptic drugs, AEDs, Neuropsychological side effects, Cognitive side effects, Carbamazepine

INTRODUCTION

Patients with epilepsy may receive anticonvulsant drugs (AEDs) throughout their lives and neuropsychological side effects of these drugs are an important management issue. Reduced attention and mental speed, psychomotor slowing, and impaired memory are side effects reported in studies of neuropsychological side effects (Aldenkamp et al., 1993; Craig & Tallis, 1994; Meador et al., 1991, 1993; Prevey et al., 1996; Thompson et al., 1981; Thompson & Trimble, 1981). Neuropsychological testing has been the major method of measuring cognitive function related to the use of AEDs. Many of the studies in the literature have several methodological problems (Baker & Marson, 2001; Brunbech & Sabers, 2002; Meador, 1998; Vermeulen & Aldenkamp, 1995). The most important of these problems are variable subject inclusion criteria, diverse test batteries, frequent absence of control groups and failure to randomize treatment, and inadequate statistical power. These factors make direct comparison between studies difficult (Cochrane et al., 1998). Consequently, much uncertainty still exists regarding the neuropsychological side effects of AEDs.

Studies of withdrawal of anticonvulsants in seizure-free epilepsy patients can be of particular value because they provide a means of assessing neuropsychological side effects of anticonvulsants in a subject group closely resembling clinical populations, and they provide the opportunity to use prospective, randomized, blinded, placebo-controlled parallel group designs. Hessen et al. (2006) reported the results of such a study using the California Computerized Assessment Package (CalCAP; Miller, 1990) in 139 subjects on drug monotherapy who had been seizure-free for more than 2 years. Cognitive function was assessed at baseline and 7 months after withdrawal of AEDs. The major finding was that discontinuation of major AEDs significantly improved performance on tests that require complex

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cognitive processing under time pressure like divided attention, rapid language discrimination, and rapid form discrimination. The difference in speed of cognitive processing between the two groups on these tasks was between 24 and 43 ms. There were no significant group differences on simple tests of attention and reaction time. Most of the subjects in the study were medicated with carbamazepine, and the results of discontinuation of carbamazepine were similar to those for the entire study population.

The CalCAP test battery incorporates a broad range of attention-related speeded cognitive measures with different levels of complexity that are sensitive to important treatment effects in both epileptic and other patient categories. To our knowledge, however, the CalCAP test battery has not previously been used in assessment of possible cognitive side effects of AEDs. Thus, it is difficult to make direct comparisons of the results of the CalCAP study (Hessen et al., 2006) with results from previous studies of cognitive effects of AEDs using standard neuropsychological tests.

The purpose of the present study is to address this problem by providing the results of widely used neuropsychological tests that were obtained in the course of the CalCAP study of Hessen et al. (2006). We used standard tests shown to be sensitive to neuropsychological effects of AEDs or probing cognitive functions thought to be of particular relevance (Dodrill, 1992). In a review of methodology and reporting standards of neuropsychological outcomes in randomized controlled trials of epileptic drugs, Cochrane et al. (1998) reported that a total of 87 tests have been used and concluded that there has been no uniform approach to the use of neuropsychological tests. Statistically significant neuropsychological effects have been detected for 20 of these tests. Four of the eight tests in the current study were chosen from this group: the Stroop Color–Word Interference test (Trenerry et al., 1989), the Trail Making Test (Reitan & Wolfson, 1985), Visual reproduction [Wechsler Memory Scale–Revised (WMS-R); Wechsler, 1987], and Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989). The Digit Vigilance Test (Lewis & Rennick, 1979) and the Grooved Pegboard Test (Kløve, 1963) were also included, as digit cancellation and pegboard tests have shown sensitivity to AED effects (Cochrane et al., 1998). Verbal learning and memory was assessed with the Rey Auditory and Verbal Learning Test (RAVLT; Rey, 1964; Schmidt, 1996) This test was the only one of 10 neuropsychological measures that showed statistically significant differences between anticonvulsant treatments in a study by Aldenkamp et al. (2000). The static steadiness test from the Kløve–Matthews Motor Steadiness Battery (Matthews & Kløve, 1964) is the only test for which we do not have data concerning anticonvulsant effects. All the described tests represent neuropsychological tests that meet the criteria of reliability, validity, and sensitivity to change. They cover areas of motor speed and coordination, attention and concentration, learning, memory, and executive functions that are the functions recommended by Cochrane et al. (1998) in their comprehensive review.

METHODS

Selection of Patients

The patients were selected from the epilepsy registry at the Akershus University Hospital and from six neurological outpatient clinics in the Oslo area. A total of 241 patients seemed to fulfill the inclusion criteria (Table 1) and were invited to participate in the study. Of these patients, 17 did not show up, 13 still had seizures, and 20 were dismissed on the basis of other exclusion criteria (Table 1). Of the remaining 191 eligible patients, 23 did not want to participate in the study primarily due to fear of seizure relapse. Thus, 168 patients were included in the study. Before randomization, another 18 patients left the study. Of these remaining patients, 12 changed their minds and withdrew. Two patients experienced seizures, three patients had generalized epileptiform activity on their electroencephalogram (EEG), and one patient had an acute illness. The remaining 150 patients went through randomization. Eleven of these patients had a seizure during the study. Of these, four belonged to the nonwithdrawal group and seven to the withdrawal group. We report baseline and retest results for the remaining 139 patients who completed the entire study.

Design

The study was prospective randomized controlled and double-blinded. Each patient was included in the study for 12 months or until seizure relapse. The randomization code was broken in cases of seizure relapse or acute illness. The neuropsychological assessments were done before and after intervention (withdrawal/not withdrawal). Both assessments were conducted by an experienced specialist in clin-

Table 1. Inclusion and exclusion criteria

Inclusion criteria:
Epilepsy (minimum two unprovoked seizures)
Freedom from seizures for > 2 years (5 years if prior unsuccessful withdrawal attempt)
Monotherapy
18–67 years of age
Exclusion criteria:
Juvenile myoclonus epilepsy
Polytherapy
Paroxysmal epileptiform activity in patients with primarily generalized epilepsy
Two previous withdrawal attempts
Pregnant or seeking pregnancy
Mental retardation
Progressive neurological disease
Other serious disease that could influence the health status in the study period
Comedication (except postmenopausal hormone substitution), aspirin, or thyroxin

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ical neuropsychology (E.H.). The investigator was blinded during the whole study period.

The patients were block-randomized to receive blindly either active medication or placebo in prepacked dispensers (Dosett), one for each of the 12 withdrawal weeks. Patients randomized to withdrawal had AED dose reduction by 20% the first 6 weeks and then 20% every second week until week 12. As the medication was reduced, it was replaced with placebo to maintain blinding throughout the study period. After complete withdrawal, no further changes in medication were made. By the time of the second neuropsychological testing 7 months after intervention, the patients were either on medication or placebo.

Seven months after withdrawal start, the patients were reassessed with the same neuropsychological tests. Twelve months after the start of withdrawal, the code was broken. Those who had not been withdrawn from medication were offered an ordinary withdrawal at the outpatient clinic. The Regional Committee for Medical Research Ethics approved the study protocol (Approval S-127/99-99044).

Neuropsychological Assessment

The patients were assessed with tests in the following categories:

1. Learning and memory: Rey Auditory and Verbal Learning Test (RAVLT; Rey, 1964; Schmidt, 1996) and Visual Reproduction I and II from the Wechsler Memory Scale–Revised (WMS-R; Wechsler, 1987).
2. Attention and psychomotor speed: Trail Making Test A (Reitan & Wolfson, 1985) and Digit Vigilance Test (Lewis & Rennick, 1979).
3. Aspects of executive functions: Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989), Trail Making Test B (Reitan & Wolfson, 1985), and the Stroop Neuropsychological Screening Test (SNST; Trenerry et al., 1989).
4. Motor coordination and steadiness: The Grooved Pegboard test (Kløve, 1963). A measure of steadiness was obtained from the static steadiness test from the Kløve–Matthews Motor Steadiness Battery (Matthews & Kløve, 1964). This is a test for tremor/fine motor control with dominant and nondominant hands.

Normative Data

Schmidt's (1996) metanorms were used to score data from the RAVLT. The original normative data for the WMS-R (Wechsler, 1987) was used to score Visual Reproduction I and II. Available normative data by Heaton and colleagues (1991) were used to score data from the Trail Making Test, Digit Vigilance Test, and the Grooved Pegboard test. Demographic norms by Gladsjo et al. (1999) were used to score the COWA. The normative data provided by Trenerry et al. (1989) were used for the Stroop Neuropsychological Screening Test. Scoring of the Kløve–Matthews Motor Steadiness Battery was done by the norms provided by Matthews and Kløve (1964).

Statistical Analysis

Three sets of statistical analyses were performed with the Statistical Package for Social Sciences for Windows (SPSS, version 11.0). First, descriptive statistics of the demographic, clinical, and cognitive characteristics of the patient population were computed. Then, a series of independent *t* tests were performed comparing mean differences between the cognitive variables measured before and after withdrawal of AEDs. Finally, correlations between the CalCAP subtests that showed significant improvement after discontinuation of AEDs and standard neuropsychological tests within the domains of attention/psychomotor speed and executive functions were performed. As there is no generally accepted approach to appropriately correcting for multiple comparisons in this type of study, no such corrections were made.

RESULTS

Baseline clinical data of the 139 patients who completed the study are shown in Table 2. The baseline test scores are given as raw scores in Table 3. There were no statistical differences between the test scores at baseline for the nonwithdrawal and the withdrawal group, except for the Digit Vigilance Test, on which the nonwithdrawal group had a mean of 4.6 errors ($SD = 5.9$) and the withdrawal group had a mean of 8.1 errors ($SD = 10.0$; $p = .014$).

Baseline tests scores were also converted to *T* scores. All mean group scores for the total study population as well as for the nonwithdrawal and the withdrawal groups were in the normal range. There were no statistical differences between the *T* scores for the nonwithdrawal and the withdrawal groups except on the error score of the Digit Vigilance Test where the nonwithdrawal group achieved a score of $T = 53.8$ ($SD = 11.8$) and the withdrawal group a score of $T = 48.8$ ($SD = 12.9$; $p = .021$). The only near-borderline test result was on the COWA, on which both groups scored close to 1 *SD* below the normative mean [nonwithdrawal group, $T = 41.8$ ($SD = 10.6$); withdrawal group, $T = 42.4$ ($SD = 9.4$)].

Changes in scores on the neuropsychological tests from baseline to 7 months after intervention are shown in Table 4 for the entire study group. The only significant differences associated with drug withdrawal were on the COWA ($p = .003$) and the Stroop Color–Word Interference Test ($p = .042$). The results for the carbamazepine subgroup (Table 5) were similar: significant differences associated with drug withdrawal were found only for the COWA ($p = .0001$) and the Stroop Color–Word Interference Test ($p = .013$).

Correlations between the CalCAP subtests that showed significant improvement after discontinuation of AEDs and

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Table 2. Baseline clinical data of the patients that completed the study

	No withdrawal (n = 75)	Withdrawal (n = 64)
Mean age (range)	37.2 (18–67)	39.2 (19–64)
Female (%)	39 (52)	33 (52)
Epilepsy onset 0–18 years (%)	30 (40)	23 (36)
Epilepsy onset 18–61 years (%)	45 (60)	41 (64)
Seizure-free 2–5 years (%)	19 (25)	24 (38)
Seizure-free >5 years (%)	54 (72)	40 (62)
Known etiology (%)	22 (29)	17 (27)
MRI pathology (%)	21 (28)	14 (22)
Epileptiform activity on EEG (%)	32 (43)	21 (33)
Normal neurological examination (%)	69 (92)	61 (95)
Medication		
Carbamazepine (%)	49 (65)	41 (64)
Valproate (%)	17 (23)	11 (17)
Phenytoin (%)	5 (7)	4 (6)
Phenobarbital (%)	3 (4)	2 (3)
Lamotrigine (%)	1 (1)	5 (8)
Serum concentration within therapeutic range (%)	61 (81)	49 (77)
Mean dosage for each AED group (mg/day)		
Carbamazepine (*SD*)	584.08 (225.77)	566.46 (199.08)
Valproate (*SD*)	796.88 (331.89)	918.18 (386.28)
Phenytoin (*SD*)	340.00 (89.44)	331.25 (89.85)
Phenobarbital (*SD*)	100.00 (00.00)	87.50 (53.03)
Lamotrigine (*SD*)	100.00	140.00 (54.77)
Mean serum concentration for each AED group (μmol/L)		
Carbamazepine (*SD*)	25.47 (7.84)	24.78 (7.87)
Valproate (*SD*)	299.29 (118.80)	287.00 (146.15)
Phenytoin (*SD*)	30.20 (13.48)	24.25 (10.15)
Phenobarbital (*SD*)	68.00 (10.44)	18.00 (12.72)
Lamotrigine (*SD*)	9.00	7.40 (3.69)

Note. MRI = magnetic resonance imaging; EEG = electroencephalogram; AED, antiepileptic drug.

standard neuropsychological tests within the domains of attention/psychomotor speed and executive functions are shown in Table 6. A substantial and significant correlation was found between the Form Discrimination task on CalCAP and Trail Making Test A (.544**). Otherwise, medium size and small correlations were evident between the other CalCAP subtests and many of the traditional neuropsychological tests. Discriminant analysis using change scores with the two neuropsychological tests that showed significant improvement after discontinuation of AEDs (COWA and the Stroop-Color Interference Test) and the four sensitive CalCAP subtests showed that CalCAP Choice Reaction Time (digits) + COWA + CalCAP Language Discrimination did classify correctly two thirds of the patients as belonging to the withdrawal or placebo group, respectively.

DISCUSSION

The major findings of the present study were that, in epilepsy patients seizure-free for more than 2 years on monotherapy with therapeutic levels of carbamazepine, phenytoin, valproate, or phenobarbital, withdrawal of the anticonvulsant was associated with improved performance on a test of verbal fluency (the COWA) and a test of response inhibition under time pressure (the Stroop Color–Word Interference Test). Comparable results were achieved in the subgroup taking carbamazepine.

Correlations between the CalCAP subtests that showed significant improvement after withdrawal of AEDs and standard neuropsychological tests within the domains of attention/psychomotor speed and executive functions revealed mainly medium and small correlations. Discriminant analysis with the most relevant neuropsychological and CalCAP variables showed that both categories of variables contributed independently to characterizing the withdrawal group. The results indicate a substantial contribution of the CalCAP to the detection of neuropsychological improvement in the withdrawal group.

The two major strengths of the present study are that it fulfills the design criteria of a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients on monotherapy, tested after several months of steady-state treatment, and that the study includes a large sample of subjects and, therefore, has good statistical power.

The results of the study are relevant to patients that fulfilled the inclusion criteria: no seizures for at least 2 years, AED monotherapy, no epileptiform activity on EEG in patients with generalized epilepsy, and absence of juvenile

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Table 3. Baseline raw scores and standard deviations of the patients that completed the study

Rey Auditory Verbal and Learning Test (raw scores)	No withdrawal $N = 75$	Withdrawal $N = 64$	p values
RAVLT-A1 Word span (words)	6.1 (2.0)	6.0 (1.6)	.59
RAVLT-A5 Max acquisition (words)	11.4 (2.1)	11.0 (2.4)	.37
RAVLT-A 1–5 Total score (words)	47.1 (9.5)	46.5 (8.4)	.66
RAVLT-B Interference list (words)	5.6 (1.9)	5.5 (1.8)	.88
RAVLT-A6 Immediate recall (words)	10.0 (2.9)	9.7 (2.6)	.55
RAVLT-A7 Delayed recall (words)	9.9 (3.1)	9.4 (2.9)	.41
RAVLT-Delayed recognition (words)	13.9 (1.5)	13.4 (1.7)	.11
RAVLT-False-positive responses (words)	1.7 (3.0)	1.4 (2.4)	.46
Wechsler Memory Scale Revised-Visual recall (raw scores)			
Visual recall-1 Immediate recall (points)	32.7 (5.4)	33.0 (3.9)	.79
Visual recall-2 Delayed recall (points)	30.1 (7.2)	29.8 (5.6)	.78
Attention and psychomotor speed (raw scores)			
Digit Vigilance Test-time (s)	429.5 (144.7)	410.7 (146.3)	.45
Digit Vigilance Test-error (no)	4.6 (5.9)	8.1 (10.0)	.014
Trail Making Test A (s)	31.5 (13.9)	30.3 (11.5)	.61
Executive functions (raw scores)			
Trail Making Test B (s)	83.4 (63.0)	81.6 (60.3)	.87
COWA-Word fluency (words)	34.7 (13.1)	34.7 (11.0)	1.00
Stroop-Color–Word (words)	98.2 (17.7)	94.1 (19.0)	.19
Complex coordination and motor steadiness (raw scores)			
Grooved Pegboard-Dom. Hand (s)	67.7 (26.1)	63.7 (10.9)	.25
Grooved Pegboard-Nond. Hand (s)	70.7 (11.8)	74.2 (13.8)	.11
Steadiness Time-Dom. Hand (s)	2.3 (2.3)	2.5 (2.8)	.73
Steadiness Time-Nond. Hand (s)	3.4 (3.5)	3.8 (4.7)	.53
Steadiness Counter-Dom. Hand (no)	48.9 (43.0)	51.9 (53.2)	.72
Steadiness Counter-Nond. Hand (no)	61.5 (53.2)	66.1 (57.1)	.63

Note. COWA = Controlled Oral Word Association Test; Dom. = dominant; Nond. = nondominant.

Table 4. Changes in raw scores (*SD*) between baseline and 7 months after intervention

Rey Auditory Verbal and Learning Test (raw scores)	No withdrawal $N = 61$	Withdrawal $N = 48$	p values
RAVLT-A1 Word span (words)	.98 (1.91)	.92 (1.70)	.85
RAVLT-A5 Max acquisition (words)	.80 (1.87)	.73 (2.10)	.85
RAVLT-A 1–5 Total score (words)	4.25 (6.26)	3.46 (7.25)	.54
RAVLT-B Interference list (words)	.05 (1.81)	−.15 (1.64)	.56
RAVLT-A6 Immediate recall (words)	.85 (1.95)	.90 (1.95)	.91
RAVLT-A7 Delayed recall (words)	1.11 (1.84)	1.48 (1.81)	.30
RAVLT-Delayed recognition (words)	.44 (1.62)	.48 (1.40)	.90
RAVLT-False-positive responses (words)	−.38 (3.00)	.60 (2.52)	.07
Wechsler Memory Scale Revised-Visual recall (raw scores)			
Visual recall-1 Immediate recall (points)	.46 (3.22)	.06 (3.00)	.51
Visual recall-2 Delayed recall (points)	.74 (3.52)	.71 (3.76)	.97
Attention and psychomotor speed (raw scores)			
Digit Vigilance Test-time (s)	−12.95 (45.54)	−19.87 (48.03)	.45
Digit Vigilance Test-error (no)	−1.02 (4.66)	−2.02 (6.91)	.37
Trail Making Test A (s)	−2.11 (10.83)	−.87 (12.12)	.58
Executive functions (raw scores)			
Trail Making Test B (s)	−6.92 (25.60)	−6.45 (39.24)	.94
COWA-Word fluency (words)	.98 (5.97)	4.92 (7.48)	.003
Stroop-Color–Word (words)	2.75 (8.63)	6.90 (12.35)	.042
Complex coordination and motor steadiness (raw scores)			
Grooved Pegboard-Dom. Hand (s)	−1.67 (9.45)	−1.91 (6.54)	.88
Grooved Pegboard-Nond. Hand (s)	−2.68 (7.32)	−5.00 (8.84)	.14
Steadiness Time-Dom. Hand (s)	.94 (2.68)	1.09 (3.06)	.78
Steadiness Time-Nond. Hand (s)	−.09 (2.62)	.12 (2.79)	.69
Steadiness Counter-Dom. Hand (no)	−3.72 (37.23)	−1.62 (44.95)	.79
Steadiness Counter-Nond. Hand (no)	3.62 (41.65)	3.60 (44.43)	.99

Note. Patients on lamotrigine and patients with subtherapeutic levels of other anticonvulsants excluded. Dom. = dominant; Nond. = nondominant.

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Table 5. Changes in raw scores (*SD*) from baseline to 7 months after intervention for patients on carbamazepine with serum concentration within therapeutic range

Rey Auditory Verbal and Learning Test (raw scores)	No withdrawal $N = 46$	Withdrawal $N = 41$	*p* values
RAVLT-A1 Word span (words)	1.00 (1.98)	.88 (1.75)	.76
RAVLT-A5 Max acquisition (words)	.72 (1.63)	.71 (2.17)	.98
RAVLT-A 1–5 Total score (words)	3.89 (5.44)	3.34 (7.29)	.69
RAVLT-B Interference list (words)	−.04 (1.86)	−.05 (1.61)	.99
RAVLT-A6 Immediate recall (words)	.67 (1.54)	.85 (1.97)	.63
RAVLT-A7 Delayed recall (words)	.85 (1.63)	1.54 (1.82)	.06
RAVLT-Delayed recognition (words)	.43 (1.47)	.29 (1.01)	.61
RAVLT-False-positive responses (words)	−.09 (3.14)	.68 (2.70)	.23
Wechsler Memory Scale Revised-Visual recall (raw scores)			
Visual recall-1 Immediate recall (points)	.33 (3.13)	.02 (3.13)	.60
Visual recall-2 Delayed recall (points)	.33 (3.62)	.85 (4.02)	.52
Attention and psychomotor speed (raw scores)			
Digit Vigilance Test-time (s)	−13.24 (49.89)	−19.64 (46.22)	.55
Digit Vigilance Test-error (no)	−1.33 (5.11)	−2.05 (6.92)	.59
Trail Making Test A (s)	.00 (8.48)	−1.17 (12.62)	.61
Executive functions (raw scores)			
Trail Making Test B (s)	−4.61 (22.14)	−7.73 (30.66)	.59
COWA-Word fluency (words)	.80 (5.68)	5.49 (7.31)	.001
Stroop-Color–Word (words)	2.02 (7.51)	7.66 (12.75)	.013
Complex coordination and motor steadiness (raw scores)			
Grooved Pegboard-Dom. Hand (s)	−1.74 (10.34)	−1.10 (6.10)	.73
Grooved Pegboard-Nond. Hand (s)	−2.93 (8.10)	−6.10 (8.70)	.08
Steadiness Time-Dom. Hand (s)	.60 (2.59)	1.03 (3.26)	.50
Steadiness Time-Nond. Hand (s)	.27 (2.50)	.18 (2.80)	.87
Steadiness Counter-Dom. Hand (no)	−3.77 (39.70)	−.98 (47.26)	.77
Steadiness Counter-Nond. Hand (no)	9.25 (47.71)	6.37 (46.35)	.77

Note. Dom. = dominant; Nond. = nondominant.

myoclonic epilepsy. There is reason to believe that the selected group is representative for the majority of seizure-free epilepsy patients (Kwan & Brodie, 2000; Lossius et al., 1999). The findings, however, cannot be extrapolated to all epilepsy patients, including patients with intractable epilepsy.

As reported by Cochrane et al. (1998), several other tests within areas of motor speed and coordination, attention and concentration, learning, memory, and executive functions, have also shown sensitivity to the effects of anticonvulsants. On this basis, we acknowledge that the use of several

Table 6. Correlation between the CalCAP subtests showing significant improvement after discontinuation of AEDs and standard neuropsychological tests within the domains of attention/psychomotor speed and executive functions

	Choice Reaction Time digits	Language Discrimination	Response reversal words	Form Discrimination
Attention/psychomotor speed				
Digit Vigilance (s)	.381**	.328**	.331**	.343**
Digit Vigilance (errors)	.030	.109	.152	.242**
Trail Making A (s)	.297**	.368**	.430**	.544**
Executive functions				
Trail Making B (s)	.267**	.417**	.439**	.454**
Stroop Color–Word (words)	−.380*	−.391**	−.497**	−.487**
COWA (words)	−.113	−.282**	−.161	−.338**

Note. CalCAP = California Computerized Assessment Package; AEDs = antiepileptic drugs; COWA = Controlled Oral Word Association Test.
*$p < .05$.
**$p < .01$.

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other tests, including Symbol Digit Modalities Test or paragraph memory tests, may have revealed equal or possibly greater sensitivity to the effects of anticonvulsants as the tests used in the present study.

Analysis of change from baseline to retest after 7 months was done only for the patients with AED blood levels within the therapeutic range, as patients with subtherapeutic levels would be unlikely to show any neuropsychological change related to AED withdrawal. Patients on lamotrigine were also excluded from the analysis, as this drug has been shown to have few cognitive effects (Meador et al., 2001).

As research design and patient population have been somewhat different from most of the other reported studies, it is difficult to make direct comparison of the present results with results from many other studies of neuropsychological influence of major AEDs. Two earlier withdrawal studies of AEDs in children have revealed the following results: In an unblinded and nonrandomized withdrawal study of AEDs in epileptic children with seizure freedom more than 2 years (Chen et al., 2001), no improvement in IQ or on any of the subtests from the Wechsler Intelligence Scale for Children–Revised were found. However, it was found that P300 latencies (auditory event-related potentials) were significantly increased in children receiving phenobarbital but not in children receiving carbamazepine or valproate. In another withdrawal study of seizure-free epileptic children (Aldenkamp et al., 1993), no cognitive AED effects were revealed, compared with healthy controls. The children in this study used a mixture of AEDs, but mainly carbamazepine.

It is interesting that Meador et al. (1991, 1993) in direct comparison of 1-month exposure to phenytoin and carbamazepine found that carbamazepine impaired performance on tasks of response inhibition (Stroop test) and memory (Story recall). In another study of healthy volunteers, Meador et al. (2001) found that subjects on carbamazepine performed poorer than subjects on lamotrigine and subjects off AEDs on measures of attention, cognitive speed, memory, and graphomotor coding. A 12-week, randomized, double-blind, parallel group study of carbamazepine and gabapentin in healthy volunteers revealed effects of both drugs on measures of graphomotor coding and response inhibition (Salinsky et al., 2002). It is our view that these findings are well matched with the results of the present study. However, these findings are challenged by studies by Thompson et al. (1981) with normal volunteers and the mentioned study by Aldenkamp et al. (1993), both of which found no cognitive effects of carbamazepine.

The potential clinical impact of the modest anticonvulsant-associated decrements in COWA and Stroop performance demonstrated here is difficult to determine. Significant improvement was seen on some, but not all, tasks requiring speeded cognitive performance under time pressure. The improvement from baseline after withdrawal was 4.9 words in the verbal fluency test and 6.9 words in the response inhibition test. As these cognitive processes are necessary in many daily activities, even a subtle reduction in processes that are repeated many times during the day may have a significant functional impact.

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