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Cognitive abilities and adjustment with gabapentin: results of a multisite study☆

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Abstract

The cognitive and quality of life effects of gabapentin are not yet well explored. While preliminary work in the area has provided positive findings, a large double-blinded study has been needed to explore this area more thoroughly. From 24 sites in North America, 201 adults were studied who had uncontrolled complex partial seizures with or without secondary generalization. Attempts were made to convert each patient from one or two marketed antiepileptic drugs (AEDs) taken in baseline to gabapentin monotherapy (600, 1200, or 2400 mg/day). Tests of cognitive abilities and adjustment were administered at the end of the 8-week baseline period and at the end of the 26-week double-blind treatment period. Analyses of baseline to treatment period changes were conducted for each dose group in comparison with a reference group of placebo-treated patients from another study. In the area of cognitive functioning, no changes in any of the gabapentin groups were found in comparison with the reference group. In the area of adjustment and mood, however, improvement with gabapentin administration was noted on several variables pertaining to emotional and interpersonal adjustment. These results are consistent with findings from previous studies.

Keywords: Cognitive abilities; Adjustment; Gabapentin

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1. Introduction

Gabapentin is a relatively new antiepileptic drug whose mechanism of action is presently unknown. Gabapentin has now been shown in a series of studies to result in increased control of complex partial seizures (UK Gabapentin Study Group, 1990; US Gabapentin Study Group No. 5, 1993; Anhut et al., 1994; Baulac et al., 1998; Beydoun et al., 1998; Bruni, 1998; Chadwick et al., 1998). In these investigations, side-effects of this drug most commonly included somnolence, dizziness, ataxia, and fatigue. Occasionally, behavioral problems such as moodiness and emotional outbursts have occurred, which have disappeared when the drug was withdrawn (Wolf et al., 1995).

A review of the literature on the effects of this drug on neuropsychological performance and mood reveals four studies. In the first of these (Dodrill et al., 1992), 15 patients were evaluated in a randomized, double-blinded, and counterbalanced investigation in which the effects of gabapentin and carbamazepine were compared. Results showed that patients performed slightly better on gabapentin alone than on carbamazepine alone in cognition and mood/adjustment, but the difference was never statistically significant. The results of this study were complicated by the fact that seizure control was not as good with gabapentin as with carbamazepine with the relatively low dose of gabapentin (1200 mg/day) that was used. In the second investigation (Dimond et al., 1996), physicians and patient ratings of well-being with gabapentin were combined from five studies from the UK, USA, and Europe ($n = 705$). Randomized and blinded additions to drug regimens were made of either placebo or gabapentin (600, 1200, 1800 mg/day). Physicians' ratings of patient well-being improved with increasing doses of gabapentin and patient self-ratings also showed some improvement. In a third study (Leach et al., 1997), 21 patients had cognitive and mood testing under each of the following conditions added to their existing drug regimens: placebo, and 1200, 1800, and 2400 mg gabapentin. There was no effect of gabapentin upon psychomotor or memory test results, and the only mood or quality of life (QOL) measure showing any change was increased tiredness reported with 2400 mg gabapentin. Finally, in an open add-on study of 114 patients (Bruni, 1998), patients reported improved quality of life with gabapentin administration on the Quality of Life in Epilepsy Inventory-10.

The present study reports cognitive and adjustment/mood findings from a large multicenter, randomized, double-blind, parallel-group, dose-controlled study in which changes with gabapentin administration were compared to those seen in a reference group where there was repeat testing but no change in drug regimen.

2. Methods

This investigation represents the neuropsychological portion of a clinical study, the results of which are presented elsewhere (Beydoun et al., 1997). The one change to the study design was the addition of a reference group of patients from a published study of vigabatrin (Dodrill et al., 1993). In this vigabatrin study, the group had been treated with placebo and no changes in antiepileptic drug regimens had been made during the investigation. Patients were selected for the vigabatrin study in a similar manner to those in the present investigation (uncontrolled partial seizures with or without secondary generalization), the design was similar with randomly assigned subjects to parallel treatment groups, the neuropsychological battery used was exactly the same, and the test-retest interval was similar. Attention is drawn to the fact that the vigabatrin placebo group is not a control group, but is a reference group which was helpful in sorting out drug effects from retest or practice effects.

2.1. Subjects

Eligible patients for the gabapentin study had refractory complex partial seizures with or without secondary generalization, both of which are hereafter referred to as 'study seizures'. Of the 275 subjects entered into the clinical gabapentin study (Beydoun et al., 1997), 74 were excluded from the

neuropsychological analyses reported in the present paper for the following reasons: 15 had either a Wechsler Adult Intelligence Scale-Revised (WAIS-R) Verbal IQ or Performance IQ less than 65; two were not English speaking; one was mute; two were children (< 16 years of age); 11 had no neuropsychological testing conducted at all; 11 had testing done at incorrect points during the study; 23 had only one testing (either baseline or treatment condition); and, nine were not included for a variety of additional reasons. It is noted that incomplete testing was most commonly due to administrative errors, scheduling difficulties, and drops from the study without retesting due to various factors. Thus, 201 patients from the gabapentin study contributed data to the neuropsychological evaluations. The reference group from the vigabatrin study (Dodrill et al., 1993) provided an additional 85 subjects who were brought into that study under guidelines similar to those in the present investigation of gabapentin.

The 201 patients from the gabapentin study were evaluated at 24 major medical centers in North America (23 in USA, one in Canada), and these individuals were entered into the same protocol. During baseline, every patient was taking one or two marketed antiepileptic drugs and no other experimental agents. Patients were excluded from the study for all of the following reasons: pregnancy; women of childbearing potential not practicing adequate birth control; progressive neurological disorder; history of drug abuse; history of status epilepticus within the last 2 years; idiopathic generalized epilepsy; previous exposure to gabapentin; use of investigational drugs, benzodiazepines, or phenobarbital for seizures within the 30 days prior to screening. A similar list of exclusionary criteria had been applied to the reference group of patients from the vigabatrin study (Dodrill et al., 1993), and that group had been obtained from 15 medical centers across the USA.

Descriptive information on all groups in this study is presented in Table 1. No statistically significant differences were found across the groups with respect to any of the variables noted in this table except for age (placebo group slightly younger, $P = 0.0481$) and number of AEDs at baseline (placebo group more often on polytherapy, Fisher's Exact $P = 0.0240$). It is not clear that these differences are of significance although it appears that patients in the reference group may have had seizures which were more difficult to manage.

2.2. Procedure

The gabapentin study consisted of an 8-week baseline phase, a 10-week conversion period, and a 16-week monotherapy period. Each patient kept a seizure diary recording the number and type of seizures experienced during baseline and double-blind treatment. To be included in the study, the patients had to have a minimum of four study seizures during the baseline phase with at least two seizures occurring in each of the two 4-week periods. They could have no more than five seizures on any one day, and could have no 28-day seizure-free interval. The complete Wechsler Adult Intelligence Scale-Revised (WAIS-R) was administered during the baseline. At the end of baseline, patients were randomized to either 600 mg/day gabapentin monotherapy ($n = 69$), 1200 mg/day gabapentin monotherapy ($n = 66$), or 2400 mg/day gabapentin monotherapy ($n = 66$). Double-blinded conditions were maintained from this point onward throughout the study.

After randomization of gabapentin patients, the conversion period began. During the first 2 weeks, gabapentin was titrated upwards to full dose. During the next 8 weeks, the baseline AED(s) were tapered and then stopped entirely. At the end of the conversion period, all patients remaining in the study were on gabapentin monotherapy, and they were maintained on gabapentin monotherapy through the 16-week monotherapy period. Details about discontinuation criteria and about drug titration and taper are presented elsewhere (Beydoun et al., 1997).

Reference group from the vigabatrin study (Dodrill et al., 1993) had a similar course of investigation. The patients were placed on placebo for a 16-week drug study period exactly as was the case for the gabapentin patients. They did not go through a titration/taper phase as did the gabapentin patients, but the length of the study is

nevertheless similar since only a portion of the gabapentin patients achieved gabapentin monotherapy ($n = 99$) and even fewer completed the entire 26-week period on gabapentin monotherapy ($n = 46$).

2.3. Psychological tests

At the end of baseline and again at the end of the drug treatment period (or at discontinuation if the patient did not complete the study), all patients were individually administered a battery of tests. The tests were of two types: (1) measures of abilities including a variety of cognitive skills; and (2) measures of adjustment including quality of life, mood, and psychosocial variables. This same battery of tests has been used in other studies of the effects of AEDs (Dodrill et al., 1993, 1995, 1998). The tests of abilities are described below.

2.3.1. Lafayette Grooved Pegboard

This test evaluates manual dexterity, visual-motor coordination, and motor speed. A pegboard is utilized into which 25 keyed pegs are placed only when each is turned into its appropriate orientation as indicated by the groove in the board. They are placed as quickly as possible using first the preferred and then the non-preferred hand. The score is the number of seconds required to do the task with each hand (120 maximum for each hand).

2.3.2. Stroop Test

A single color plate is used on which color names ('red', 'green', 'blue', 'orange') are printed in incongruous colors ('red' is printed in blue print, 'blue' is printed in orange print, 'orange' is printed in green print, etc.). The same test is part of the Neuropsychological Battery for Epilepsy

Table 1
Comparisons of patient characteristics across subject groups[a]

Variable		Reference (placebo) group ($n = 85$)	Gabapentin treatment groups		
			Gabapentin, 600 mg/day ($n = 69$)	Gabapentin, 1200 mg/day ($n = 66$)	Gabapentin, 2400 mg/day ($n = 66$)
Age	Mean	34.2	34.9	37.0	38.7
	S.D.	8.2	10.9	10.4	12.4
Gender	Female	45	31	28	42
	Male	40	38	38	24
WAIS-R Verbal IQ	Mean	88.53	89.99	89.65	91.48
	S.D.	12.72	14.34	14.87	13.62
WAIS-R Performance IQ	Mean	91.04	93.32	90.58	93.26
	S.D.	13.53	15.41	11.79	12.58
WAIS-R Full Scale IQ	Mean	88.69	90.72	89.21	91.64
	S.D.	12.94	14.77	12.83	12.80
Baseline CPS + sec gen t-c seiz/28 days	Median	8.3	8.6	8.0	7.5
Number of AEDs at baseline	1	39	45	37	45
	2	46	24	29	21
Common AEDs taken at baseline	CBZ	63	43	38	42
	PHT	22	25	31	20
	VPA	14	21	19	16

[a] No statistically significant ($P < 0.05$) differences were found across the groups for any variable except for age (reference group slightly younger, $F = 2.67$, $P = 0.0481$) and number of AEDs at baseline (placebo group more often on polytherapy, Fisher's Exact $P = 0.0240$). CBZ, carbamazepine; PHT, phenytoin; VPA, valproic acid; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

(Dodrill, 1978), except that only eight of the 16 lines of 11 words per line were used. On the first (reading speed) part of the test, the patient reads the words as quickly as possible, ignoring the colors, and on the second part (interference) the colors of print are read, ignoring the words. Time (150 and 300 s maximum for the first and second parts, respectively) and errors for both parts are recorded. Two forms of the test were used, with the order approximately counterbalanced for each patient.

2.3.3. Benton Visual Retention Test

A variant of the original version of this test (Benton, 1974) is used which has two forms. In Form F, for each of 15 items, a drawing is shown for 5 s. Then another card with four drawings is shown and the patient must pick out the drawing from the previous card. Form G has 15 items different from Form F which are shown for 10 s each with a 15-s delay before presenting the card with the choices. The score for each form is the number of items correctly recognized.

2.3.4. Controlled Oral Word Association Test

This is one subtest of the Multilingual Aphasia Examination (Benton and Hamsher, 1983). During a 60-s period, the patient says as many words as possible beginning with each of three letters (C, F, and L are used for one form of this test, and P, R, and W for the other form). The score is the total number of words correct for the three letters combined.

2.3.5. Symbol Digit Modalities Test (Smith, 1984)

This is similar to the Digit Symbol subtest of the WAIS-R except that numbers rather than symbols are written. Only the written part is used, and the number of items correct in 90 s is the score.

2.3.6. Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964)

A list of 15 words is read five separate times, and a recall is obtained after each reading. The total number of items correctly recalled for the five trials is recorded. Then a second list of 15 different words is read, and recall of this second list is obtained. The patient is then asked to recall the first list again. After 20 min, delayed recall and recognition of the first list are obtained.

2.3.7. Wonderlic Personnel Test (Wonderlic, 1977)

This is a written test of mental abilities which renders results closely approximating those of the WAIS Full Scale IQ (Dodrill, 1981). It requires 12 min for completion and results in both an IQ score and the number of items which are incorrect. Parallel forms of this test were used in a counterbalanced fashion.

2.3.8. Digit Cancellation

A page of random one digit numbers is presented and the patient cancels with a single stroke as many as possible of two target digits in a 4-min period. The variables resulting are number of items correct and number of items omitted. Form I ('0' and '7') and Form II ('1' and '6') were used in counterbalanced order.

2.4. Tests of adjustment and mood

The tests of adjustment and mood were as follows:

2.4.1. Profile of Mood States (POMS) (McNair et al., 1981)

This test provides scales of Tension-anxiety, Depression-dejection, Anger-hostility, Vigor-activity, Fatigue-inertia, and Confusion-bewilderment. A score is obtained from each scale, and a single overall score of 'mood disturbance' is also computed.

2.4.2. Washington Psychosocial Seizure Inventory (WPSI) (Dodrill et al., 1980)

This 132-item inventory of psychosocial adjustment in epilepsy provides indications of functioning in each of seven areas (Family Background, Emotional Adjustment, Interpersonal Adjustment, Vocational Adjustment, Financial Status, Adjustment to Seizures, Medicine and Medical Management). In addition, an index of overall adjustment is obtained as are two validity scales (Lie Scale, Rare Items Scale).

2.4.3. Mood Rating Scale

This visual-analogue procedure consists of 100-mm scales for 18 dimensions (e.g., alert...drowsy; tense...relaxed) commonly reported in the literature to be sensitive to drug effects (Dodrill, 1991). The distance in mm is measured from the unfavorable end of each scale to the patient's mark of mood during the last week. The average score for the 18 dimensions is the single measure arising from this test.

The order of test administration was as follows: POMS, WPSI, Lafayette Grooved Pegboard, Stroop, Benton Visual Retention, Controlled Oral Word Association, Mood Rating, Symbol Digit Modalities, Rey Auditory Verbal Learning, Wonderlic Personnel, and Digit Cancellation. To maximize the possibility of detecting a drug effect, the longest and most tedious of these were given last and with the examiner out of the room. Examiners were psychometrists or psychologists who had attended a comprehensive training session. A test manual and a training film were also used to ensure continued uniform administration of the tests. Parallel forms of the tests were used wherever possible in a counterbalanced fashion.

2.5. Data analysis

The analysis provided for a comparison of changes on the psychometric tests from baseline to gabapentin treatment for each gabapentin dose group with changes experienced by the reference group during a similar period of time. This was accomplished by computing baseline to treatment changes in test scores for each group of patients (reference group, and 600, 1200, and 2400 mg gabapentin) and by then running a one-way ANOVA across the groups (the Kruskal–Wallis non-parametric ANOVA was used in one case (Digit Cancellation, Number Omitted) when the homogeneity of variance assumption could not be met). This was done for each of the 19 variables in the area of abilities and each of the 18 variables in the area of adjustment and mood. A correction for multiple comparisons was made by adopting the 0.025 level of statistical significance instead of 0.05 so that the number of findings expected on the basis of chance from the entire study was less than one ($0.025 \times 37 = 0.925$). Where a statistically significant difference was detected for the overall ANOVA, the Newman–Keuls test (Winer, 1971) was used to determine which groups were statistically significantly different from one another.

3. Results

The results of the baseline to treatment period changes are presented in Table 2 for variables pertaining to mental abilities. This table shows no statistically significant differences. Thus, no changes in cognitive abilities were found with gabapentin administration. This is consistent with the findings from previous studies where tests of abilities were administered (Dodrill et al., 1992; Leach et al., 1997).

The results for measures of adjustment and mood are presented in Table 3. There were four statistically significant ($P < 0.025$) differences here, all of which were on measures of psychosocial adjustment and mood. On the POMS Total Mood Disturbance variable, the 600-mg gabapentin group improved relative to the 2400-mg gabapentin group. On both the WPSI Emotional Adjustment and Interpersonal Adjustment scales, the 600-mg gabapentin group improved more than did the reference (placebo) group while no significant changes were found in connection with the other groups. For the WPSI Medicine and Medical Management Scale, it was the 1200-mg gabapentin group which improved more than the reference group. No other comparisons between groups were significantly different from each other.

4. Discussion

Neither of the two previous studies (Dodrill et al., 1992; Leach et al., 1997) of the cognitive effects of gabapentin showed any conclusive change with this drug, and the present study is clearly in support of this conclusion as well. It is true that patients sometimes reported to us that they felt more alert on gabapentin and that they

Table 2
Means and standard deviations of baseline and treatment performances across the four patient groups on tests of abilities[a]

Test/variable	Group								
	Placebo ($n = 85$)		600 mg Gabapentin ($n = 69$)		1200 mg Gabapentin ($n = 66$)		2400 mg Gabapentin ($n = 66$)		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	P
Lafayette Grooved Pegboard									
Preferred hand, s									
Mean	80.07	77.75	78.59	77.12	84.18	78.21	80.55	76.49	0.1013
S.D.	16.55	18.63	16.50	17.63	19.41	17.10	17.57	18.04	
Non-preferred hand, s									
Mean	87.31	84.05	84.84	82.79	89.62	86.02	87.77	84.80	0.9106
S.D.	18.22	18.94	17.42	19.34	21.24	20.99	20.20	19.49	
Stroop Test									
Reading speed, s									
Mean	54.30	57.95	50.82	55.43	57.32	62.29	52.05	55.49	0.9313
S.D.	16.59	24.33	14.92	19.94	22.43	26.58	15.33	20.65	
Reading speed, errors									
Mean	0.95	0.76	0.69	0.81	1.32	1.24	0.89	0.83	0.5958
S.D.	1.28	1.23	1.19	1.70	1.79	1.66	1.17	1.45	
Interference, s									
Mean	133.63	130.07	128.34	122.40	141.70	131.97	127.58	126.17	0.4286
S.D.	40.59	46.59	49.52	51.15	55.94	52.16	38.07	42.55	
Interference, errors									
Mean	4.17	4.20	4.75	4.12	5.30	4.39	4.88	4.42	0.3900
S.D.	3.36	3.88	3.81	4.54	3.89	3.83	4.36	4.85	
Benton Visual Retention									
Form F, number correct									
Mean	11.47	11.92	11.69	11.99	11.26	11.53	11.15	12.22	0.1551
S.D.	2.23	2.21	2.15	2.08	2.19	2.33	2.31	1.93	
Form G, number correct									
Mean	13.88	13.95	13.97	13.65	13.09	13.46	13.54	13.94	0.0441
S.D.	1.58	1.38	1.23	1.90	2.13	1.82	1.95	1.75	
Controlled Oral Word									
Total number right									
Mean	24.99	26.44	28.76	29.84	25.82	26.57	27.20	28.72	0.9303
S.D.	11.15	11.54	10.10	10.60	11.56	11.01	12.22	12.13	

Table 2 *(Continued)*

Test/variable	Group								
	Placebo ($n = 85$)		600 mg Gabapentin ($n = 69$)		1200 mg Gabapentin ($n = 66$)		2400 mg Gabapentin ($n = 66$)		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	P
Symbol Digit Modalities									
Number right (written)									
Mean	40.93	41.55	41.91	43.00	38.66	40.66	41.86	43.49	0.7257
S.D.	12.53	12.26	10.16	11.62	11.30	12.00	11.92	13.44	
Auditory Verbal Learning									
Trial 1–5, first list recall									
Mean	46.33	46.93	45.34	44.00	42.32	42.42	43.86	44.32	0.4741
S.D.	9.10	9.71	10.19	12.21	9.71	11.11	10.43	11.95	
Trial 6, second list recall									
Mean	5.47	5.31	5.09	4.94	5.05	4.88	5.23	5.12	0.9981
S.D.	1.94	2.13	1.79	2.04	1.97	1.85	1.88	2.47	
Trial 7, first list recall									
Mean	8.59	8.87	8.35	8.24	7.18	7.65	7.78	8.00	0.7515
S.D.	3.30	3.25	3.76	3.84	3.31	3.52	3.54	3.82	
Trial 8, first delay recall									
Mean	8.24	8.54	8.06	7.96	7.19	7.25	7.84	8.06	0.8506
S.D.	3.61	3.49	4.13	4.46	3.40	3.77	3.58	3.80	
Trial 9, first delay recognition									
Mean	13.35	13.88	13.43	13.18	13.22	13.11	13.30	13.20	0.0890
S.D.	2.00	1.64	2.09	2.20	2.34	2.30	1.97	1.96	
Wonderlic Personnel Test									
Items correct									
Mean	14.52	14.52	14.53	15.66	13.63	13.90	15.00	14.84	0.2605
S.D.	7.35	7.75	7.45	8.06	7.94	7.87	7.97	7.72	
Items wrong									
Mean	7.42	7.05	7.84	7.99	7.22	7.52	7.72	8.33	0.6094
S.D.	5.82	3.93	5.23	4.80	4.54	4.55	5.12	5.57	
Digit Cancellation									
Number right									
Mean	159.63	157.58	145.24	150.09	129.83	136.40	142.67	144.92	0.5940
S.D.	52.23	51.26	43.51	43.23	41.67	50.98	42.49	47.43	
Number omitted									
Mean	6.11	3.96	3.40	8.19	7.41	5.25	4.50	6.20	0.4261
S.D.	20.64	5.01	3.49	27.01	18.36	8.97	4.41	11.30	

[a] Significance levels utilize one-way analysis of variance based upon difference scores (baseline minus treatment) for each group except for the Digit Cancellation, Number omitted variable which was based upon the Kruskal–Wallis non-parametric ANOVA due to a lack of homogeneity of variance.

Table 3
Means and standard deviations of baseline and treatment performances across the four patient groups on tests of mood and adjustment[a]

Test/variable	Group								
	Placebo ($n = 85$)		600 mg Gabapentin ($n = 69$)		1200 mg Gabapentin ($n = 66$)		2400 mg Gabapentin ($n = 66$)		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	P
POMS									
Tension-anxiety									
Mean	10.84	10.26	12.59	10.76	12.03	11.77	12.55	13.61	0.0771
S.D.	5.95	5.72	5.75	6.45	6.36	6.67	5.82	7.65	
Depression-dejection									
Mean	11.29	10.05	13.53	10.85	12.21	12.61	13.02	13.98	0.0729
S.D.	8.95	8.98	10.27	9.87	8.98	11.30	11.26	10.78	
Anger-hostility									
Mean	8.35	7.71	10.16	7.66	9.77	9.21	10.20	9.58	0.3209
S.D.	7.35	7.09	8.04	7.83	7.07	8.52	8.03	8.27	
Vigor-activity									
Mean	15.78	16.74	15.31	16.41	15.32	15.55	17.58	15.92	0.0312
S.D.	5.28	5.45	5.76	5.58	6.21	6.48	6.63	7.05	
Fatigue-inertia									
Mean	8.49	7.86	10.12	7.78	9.85	9.36	9.84	9.91	0.1294
S.D.	5.68	5.17	6.08	6.03	5.64	7.45	5.51	6.05	
Confusion-bewilderment									
Mean	8.25	8.00	9.46	7.79	9.26	8.70	9.94	10.38	0.1165
S.D.	4.53	4.26	5.03	4.87	5.71	5.17	6.42	5.47	
Total mood disturbance									
Mean	31.45	27.13	40.54	28.44	37.33	36.11	36.27	41.53	0.0048
S.D.	28.78	27.06	32.39	33.20	31.11	38.05	29.34	34.94	
Mood Rating Scale									
Average score									
Mean	59.08	64.17	57.31	61.20	56.21	58.25	59.80	58.81	0.1703
S.D.	17.02	14.98	15.78	16.05	19.79	17.45	15.78	17.50	
WPSI									
Family Background									
Mean	2.18	2.07	2.61	2.28	2.83	2.53	1.94	2.17	0.0576
S.D.	2.18	1.90	2.39	2.34	2.47	2.34	1.75	1.76	
Emotional Adjustment									
Mean	11.17	10.88	13.36	10.99	13.08	11.36	13.19	11.94	0.0223
S.D.	5.28	5.15	6.36	5.42	6.39	5.81	5.44	4.94	
Interpersonal Adjustment									
Mean	5.14	5.19	6.00	4.54	5.70	5.02	5.60	4.87	0.0235
S.D.	3.48	4.25	4.24	3.90	4.46	4.06	3.97	4.03	

Table 3 *(Continued)*

Test/variable	Group								
	Placebo ($n = 85$)		600 mg Gabapentin ($n = 69$)		1200 mg Gabapentin ($n = 66$)		2400 mg Gabapentin ($n = 66$)		
	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	Baseline	Treatment	P
Vocational Adjustment									
Mean	6.96	6.93	6.21	5.94	6.63	6.80	6.25	6.24	0.6795
S.D.	2.85	2.87	3.16	3.35	3.09	2.85	3.22	3.20	
Financial Status									
Mean	2.35	2.29	2.52	2.24	3.00	2.77	2.73	2.54	0.8485
S.D.	2.10	2.02	2.12	1.99	2.15	2.11	2.07	2.28	
Adjustment to Seizures									
Mean	5.50	5.26	6.10	5.60	6.09	5.36	5.71	5.22	0.8041
S.D.	3.35	3.53	3.75	3.64	3.93	3.44	3.38	3.70	
Medicine and medical management.									
Mean	1.38	1.48	1.85	1.81	2.08	1.52	1.76	1.68	0.0192
S.D.	0.96	1.11	1.17	1.36	1.61	1.32	1.25	1.35	
Overall Functioning									
Mean	18.35	17.76	20.16	16.63	20.05	17.98	19.17	17.87	0.0517
S.D.	8.28	8.70	9.99	8.87	10.32	9.22	8.15	8.18	
Lie									
Mean	2.42	2.40	2.13	2.37	2.44	2.58	2.21	2.29	0.7476
S.D.	1.88	1.88	1.76	1.91	2.32	2.30	1.97	2.09	
Rare Items									
Mean	1.20	1.13	1.21	1.24	1.47	1.56	1.17	1.54	0.2411
S.D.	1.19	1.11	1.12	1.12	1.62	1.44	1.39	2.09	

[a] Significance levels utilize one-way analysis of variance based upon difference scores (baseline minus treatment) for each group.

were better able to function cognitively. While this could possibly be true in selected cases, the more likely explanation is that there is some improvement in mood and adjustment and that it is this improvement which convinces some patients that they are thinking more clearly.

In the area of mood and adjustment, two of the previous studies (Dimond et al., 1996; Bruni, 1998) have pointed to improved well-being with gabapentin administration. Our results agree with those findings with less anxiety, discouragement, and general mood disturbance with gabapentin administration relative to our reference group. Changes were seen on both the POMS and the WPSI. In addition, there were fewer reports of interpersonal concerns (WPSI Interpersonal Adjustment) as well as at least slightly improved rapport with physicians (WPSI Medicine and Medical Management). The findings on the WPSI are of particular interest as the items on the WPSI scales are empirically anchored in performances in life (Dodrill et al., 1980) and changes on these scales are not commonly seen in drug studies of this type (Dodrill et al., 1993, 1995, 1998), presumably because changes in life performances are difficult to make over relatively short periods of time. In this case, however, there were improvements in the core areas of emotional and interpersonal functioning. In fact, if the three gabapentin groups are combined and compared with the reference group, statistically significant improvements on the key WPSI scales become more prominent (Emotional Adjustment, $P = 0.004$; Interpersonal Adjustment, $P = 0.010$). Thus, the results do support the contention of improved function with gabapentin administration across the dosages included in this study.

Of interest is the fact that the improvements in adjustment and mood are seen most notably seen in patients taking lesser rather than greater amounts of gabapentin. Why this is the case is not clear, but it is notable that exactly the same finding appeared with respect to tiagabine in a similar conversion to monotherapy study (Dodrill et al., 1998). In that investigation, improvement in mood and adjustment was clearly in evidence in those patients who could be successfully converted from one standard antiepileptic drug to tiagabine monotherapy at only 6 mg/day. Patients converted to 36-mg/day tiagabine monotherapy did not show that improvement at all. In the present study, the findings were not quite as striking, but they are similar. The underlying reason for these findings is not clear. One is tempted to note that both drugs are associated with increased GABA (tiagabine definitely, gabapentin not as prominently), but one cannot press this argument too far as improvement in mood and adjustment was not associated with vigabatrin when the same test battery was used (Dodrill et al., 1993, 1995).

Attention is again drawn to the fact that our reference group treated with placebo is not a true control group. Data on this group were not collected at the same time as those collected during the rest of the study. Because of this, interpretation of the findings has been done with care. At the same time, after much work with the data, it was evident that the inclusion of this group was of real value in interpreting the changes noted in the gabapentin groups, and that without such a group it would not have been possible to sort out retest effects from drug effects.

Overall, no cognitive effects of gabapentin were found in this study, either favorable or unfavorable. This is consistent with existing literature. However, an improved sense of well-being was noted with gabapentin administration. This is also consistent with existing literature. Future studies will be needed to sort out the relative contributions to this favorable change of the removal of the baseline medications when gabapentin was instituted, the effects of a decrease in seizures as noted in the clinical report of the study (Beydoun et al., 1997), and to gabapentin itself.

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